To my mentors and colleagues—Bill Grossman and Donald Baim—recognizing their charismatic vision and persistence in creating and then sustaining this textbook over the past 30 years, and in training and mentoring multiple generations of cardiologists.

And to my wife Adriana and my children, Alessandra and Matteo, for their understanding, for their love and support, and for adapting their life to the many months of night and weekend work that were required to create this Eighth Edition.
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Preface to the Eighth Edition

My personal experience with Grossman's Cardiac Catheterization, Angiography, and Intervention textbook started with the fourth edition, during my cardiac catheterization rotation in 1991 as a cardiology fellow at the University of Chicago. That rotation, working under the mentorship of John Carroll and Ted Feldman, was sensational and led to a major change in my career. For the next 6 months, Grossman’s textbook became my evening reading, cover to cover, and I made the decision that interventional cardiology was going to be the future of my career. One year later, I moved to the Beth Israel Hospital in Boston for further training in interventional cardiology under the mentorship of Donald Baim and William Grossman. The richness of the Beth Israel Hospital program, the quality of the training both from a clinical and research perspective, and the charismatic leadership of Don Baim became unforgettable. Those two additional training years further shaped my professional development, and the friendships that I developed with many colleagues and with Don became a highlight for the next two decades. Beginning with the fourth edition and all the way through the seventh edition of the textbook, I did not miss a single edition and I was delighted to see the evolution of the textbook through the years.

The publication in 2006 of the seventh edition of Grossman's Cardiac Catheterization, Angiography, and Intervention was a milestone. After 30 years of shaping the textbook through six editions, William Grossman had stepped down as coeditor and Don Baim had taken the new duty as the lead editor. Unfortunately, the unexpected and premature death of Don Baim in 2009 was a major loss for the interventional community and a personal loss for me.

I was thrilled to be asked to become the editor of the eighth edition of the textbook, which represents a new milestone. Dr. Grossman's and Dr. Baim's legacy remains and the title has been modified to Grossman and Baim's Cardiac Catheterization, Angiography, and Intervention, to further reflect that legacy.

Returning readers will find the addition of color as a major, exciting new change in the textbook and will be pleased to find that the basic structure has been retained. Furthermore, to address the tremendous growth that has occurred in cardiac catheterization and interventional cardiology, the total number of chapters has increased from 34 to 46, and every chapter from the prior edition has been updated where needed and expanded with further emphasis on hemodynamic data, hemodynamic tracings, interventional procedures, and the addition of new tables and images.

Section I—General Principles includes a new chapter on Integrated Imaging Modalities in the Cardiac Catheterization Laboratory and a separate chapter on Complications. Recognizing the expanding adoption and value of radial artery access, a new chapter dedicated to this topic has been added to Section II—Basic Techniques. In addition, the chapter on brachial artery cutdown has been expanded with the inclusion of other open cutdown vascular access approaches, which have recently received enhanced interest due to the development of percutaneous aortic valve replacement.

The acquisition and interpretation of hemodynamic data require a full understanding of the pathophysiology of cardiovascular disease, of acquisition protocols of hemodynamic data, and knowledge of potential pitfalls that could lead to misinterpretation of the data acquired. Recognizing the importance of potential pitfalls leading to erroneous interpretation of hemodynamic data, Section III—Hemodynamic Principles has been expanded with the inclusion of a new chapter entitled Pitfalls in the Evaluation of Hemodynamic Data. We hope that returning and new readers will find this chapter helpful.

The anatomic classification of coronary artery anomalies has critical implications from a management perspective. General textbooks on cardiovascular disease provide limited information on coronary artery anomalies, as well as on the evaluation and management of patients who have been identified as having a coronary artery anomaly. Section IV—Angiographic Techniques includes a new chapter on Coronary Artery Anomalies. Likewise, the evaluation of pericardial disease and the differential diagnosis of constrictive versus restrictive physiology continue to be a challenging area in cardiology. Therefore, in this new eighth edition, the topic of pericardial disease has been expanded across three chapters. Section V—Evaluation of Cardiac Function includes a new chapter entitled Evaluation of Tamponade, Constrictive, and Restrictive Physiology. Section VII—Interventional Techniques includes a new chapter on
Pericardial Interventions covering pericardiocentesis, balloon pericardiotomy, and epicardial approach to cardiac procedures. In addition, the valuable chapter on Profiles in Pericardial Disease in Section VIII has been retained and updated with a new case.

Since the seventh edition was published, there has been a tremendous growth in interventions for structural heart disease, peripheral vascular disease, and cardiac arrhythmias, while primary PCI for ST segment Elevation Myocardial Infarction has become the standard of care for patients with acute myocardial infarction, and cell therapies have emerged as a new exciting and promising option for patients with cardiovascular disease. Five new chapters addressing these exciting developments have been added to the eighth edition in Section VII—Interventional Techniques. Chapter 30 outlines interventions for acute myocardial infarction. Chapter 32 provides a general overview of intervention for structural heart disease and Chapter 36 introduces the readers to the new field of interventions with cell therapies. Chapter 37 provides an overview of aortic endovascular grafting, while interventions for cardiac arrhythmias including epicardial access for ventricular arrhythmias are outlined in Chapter 39. In addition, all the other chapters in this section have been updated and expanded according to the tremendous growth that has occurred in this field.

Throughout the textbook, particular effort has been made in referring the reader to available guidelines, providing summary tables, illustrations, and images, while maintaining the overall structure and historical character of the textbook and a focus on how the field of cardiac catheterization has evolved since the first invasive human cardiac catheterization was performed by Werner Forssmann on himself in 1929.

I hope that this eighth edition of the textbook will go beyond providing just an update, and that it will elicit in new and returning readers the same excitement that I developed for this field during my reading of the fourth edition more than two decades ago. Finally, I hope that all the work of the contributing authors and the long weekends and nights that went into this endeavor will ultimately benefit our patients.

Mauro Moscucci, MD, MBA
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The current (eighth) edition of Grossman and Baim’s provides a companion website that contains 171 cases covering a broad range of classic findings, specific procedures (including percutaneous valve and other new therapies), and anomalies and complications. Following the structure of the prior edition, the cases include a summary of important teaching points and references to the particular chapters in the printed textbook. Most cases from the prior edition have been retained, and the contributions of Donald Baim and Jeffrey Popma in providing several of those cases are kindly acknowledged. The new cases reflect the new chapters and the updates to other chapters that have been included in this eighth edition. I believe that from a learning perspective there is nothing more valuable than the ability to review real images of procedures, complications, and bailout techniques. Thus, the readers are encouraged to review these cases to enhance their learning experience from this eighth edition.

Readers should also feel free to use the material included in the website for educational purposes such as teaching conferences and presentations at meetings, with acknowledgment of the source.

Mauro Mosucci
First and foremost, I would like to thank Dr. Donald Baim and Dr. William Grossman for their charismatic mentorship and guidance during my 2 years of training at the Beth Israel Hospital in Boston in the early 1990s, and for their continued friendship and support during the following decades. I would also like to thank Fran DeStefano, who in her role as the Acquisitions Editor of prior editions provided incredible support while we were shaping and planning this eighth edition; in addition, I would like to thank Julie Goolsby, who following Fran's retirement has continued to provide the same enthusiastic support in her role as Acquisitions Editor, and Leanne Vandetty for her outstanding assistance and patience as the Product Manager. Finally, I am extremely grateful to all the authors and to the many colleagues and friends who have contributed to this textbook during the past three decades.
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Our concepts of heart disease are based on the enormous reservoir of physiologic and anatomic knowledge derived from the past 80 years of experience in the cardiac catheterization laboratory. As Andre Cournand remarked in his Nobel lecture of December 11, 1956, “the cardiac catheter was … the key in the lock.”¹ By turning this key, Cournand and his colleagues led us into a new era in the understanding of normal and disordered cardiac function in humans.

According to Cournand,² cardiac catheterization was first performed (and so named) by Claude Bernard in 1844. The subject was a horse, and both the right and left ventricles were entered by a retrograde approach from the jugular vein and carotid artery. In an excellent review of the history of cardiac catheterization, angiography, and interventional cardiology, Mueller and Sanborn³ describe and cite references for experiments by Stephen Hales and others whose work antedates that of Claude Bernard. It is Stephen Hales who perhaps can be credited with the first invasive hemodynamic assessment, as he measured the blood pressure of a horse by inserting a brass rod in the femoral artery and observing the column of blood rising in a 9-foot glass tube connected to the brass rod. In further experiments, which he published in 1733, he proceeded toward identifying how much blood goes through the heart in one minute and determining the capacity of the left ventricle.⁴

Although Claude Bernard may not have been the first to perform cardiac catheterization, his careful application of scientific method to the study of cardiac physiology using the cardiac catheter demonstrated the enormous value of this technical innovation and provided the inspiration for the future development of cardiac catheterization. In 1861, Chaveau and Marey published their work on the measurement of intracardiac pressure. They were able to determine that ventricular systole and apical beat are simultaneous, and they were able to perform the first simultaneous measurement of left ventricular (LV) and central aortic pressures. An era of investigation of cardiovascular physiology in animals then followed, resulting in the development of many

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¹ William Grossman and Donald Baim authored this chapter in previous editions and contributed much of the historical information and the overall structure.
important techniques and principles (pressure manometry, the Fick cardiac output method), which awaited direct application to the patient with heart disease.

Werner Forssmann is credited with performing the first cardiac catheterization of a living person—himself. At age 25, while receiving clinical instruction in surgery in Germany, he passed a 65 cm catheter through one of his left antecubital veins, guiding it by fluoroscopy until it entered his right atrium. He then walked to the radiology department (which was on a different level, requiring that he climb stairs), where the catheter position was documented by a chest roentgenogram (Figure 1.1). During the next 2 years, Forssmann continued to perform catheterization studies, including six additional attempts to catheterize himself. Bitter criticism, based on an unsubstantiated belief in the danger of his experiments, caused Forssmann to turn his attention to other concerns, and he eventually pursued another catheter-related career as a urologist. Nevertheless, for his contribution and foresight he shared the Nobel Prize in Medicine with Andre Cournand and Dickinson Richards in 1956.

Forssmann’s primary goal in his catheterization studies was to develop a therapeutic technique for the direct delivery of drugs into the heart. He wrote:

If cardiac action ceases suddenly, as is seen in acute shock or in heart disease, or during anesthesia or poisoning, one is forced to deliver drugs locally. In such cases the intracardiac injection of drugs may be life saving. However, this may be a dangerous procedure because of many incidents of laceration of coronary arteries and their branches leading to cardiac tamponade, and death. … Because of such incidents, one often waits until the very last moment and valuable time is wasted. Therefore I started to look for a new way to approach the heart, and I catheterized the right side of the heart through the venous system.

Others, however, appreciated the potential of using Forssmann’s technique as a diagnostic tool. In 1930, Klein reported 11 right heart catheterizations, including passage to the right ventricle and measurement of cardiac output using

Figure 1.1 The first documented cardiac catheterization. At age 25, while receiving clinical instruction in surgery at Eberswalde, Werner Forssmann passed a catheter 65 cm through one of his left antecubital veins until its tip entered the right atrium. He then walked to the radiology department where this roentgenogram was taken. (Klin Wochenschr 1929;8:2085. Springer-Verlag, Berlin, Heidelberg, New York.)
With rapidly evolving technology and expanding indications, cardiac catheterization was developed by Seldinger in 1953 and was soon applied to coronary angiography. Selective coronary arteriography was elaborated by the use of this pulmonary artery wedge position and reported that the pressure measured at this position was a remarkable excellence over the ensuing years.

Subsequent studies from Dexter’s laboratory and by Werko elaborated the use of this pulmonary artery wedge position and reported that the pressure measured at this position was a good estimate of pulmonary venous and left atrial pressure. During this exciting early period, catheterization was used to investigate problems in cardiovascular physiology by McMichael and Sharpey-Shafer in England, Lenègre and Maurice in Paris, and Warren, Stead, Bing, Dexter, Courand, and others in the United States.

Further developments came rapidly in the 1950s and 1960s. Retrograde left heart catheterization was first reported by Zimmerman and others and Limon-Lason and Bouchard in 1950. The percutaneous (rather than cutdown) technique was developed by Seldinger in 1953 and was soon applied to cardiac catheterization of both the left and right heart chambers. Transseptal catheterization was first developed by Ross and Cope in 1959 and quickly became accepted as a standard technique. Selective coronary arteriography was reported by Sones and others in 1959 and was perfected to a remarkable excellence over the ensuing years. Coronary angiography was modified for a percutaneous approach by Ricketts and Abrams in 1962 and Judkins in 1967. In 1970 Swan and Ganz introduced a practical balloon-tipped, flow-guided catheter technique enabling the application of catheterization outside the laboratory, and in 1977, Andreas Gruntzig introduced the technique of balloon angioplasty, generally known as percutaneous transluminal coronary angioplasty (PTCA), thus expanding the use of cardiac catheterization to therapeutic interventions and spearheading its future exponential growth.

**INTERVENTIONAL CARDIOLOGY**

The most significant change in the last 30 years has been the evolution of the therapeutic potential of the cardiac catheter. With rapidly evolving technology and expanding indications, PTCA grew to equal stature with coronary artery bypass grafting (CABG) as the number of annual PTCA procedures grew to 300,000 by 1990. Encouraged by the success of PTCA but challenged by its shortcomings, physician and engineer inventors have developed and introduced into clinical practice a panoply of new percutaneous interventional devices over the past decade. This includes various forms of catheter-based atherectomy, bare metallic stents, and drug-eluting stents, which together have largely solved earlier problems relating to elastic recoil, dissection, and restenosis of the treated segment (see Chapters 28 through 31). These newer techniques are usually subsumed (along with conventional balloon angioplasty) under the broader designation of percutaneous coronary intervention (PCI). Similar techniques have also developed in parallel for the treatment of peripheral arterial atherosclerotic disease, which is a common cause of morbidity and even mortality in patients with coexisting coronary disease (see Chapters 19, 34, and 37).

The evolution of PCI has also stimulated the development of other techniques for the treatment of structural heart disease (see Chapter 32). Catheter devices developed to close intracardiac shunts in pediatric patients have now been adopted to close adult congenital and acquired defects (see Chapter 35). Balloon valvuloplasty was developed in the mid-1980s and remains successful for the treatment of rheumatic mitral stenosis. Due to early recurrence, balloon aortic valvuloplasty is now used as a treatment for aortic stenosis only in patients who are not candidates for aortic valve replacement surgery or in preparation for percutaneous aortic valve replacement. Newer technologies for percutaneous aortic valve replacement and percutaneous reduction of mitral regurgitation are now available as alternative therapies to open heart surgery in selected patient populations (see Chapter 33).

In essence, these new procedures have made interventional cardiology a new field in cardiovascular medicine, whose history is well summarized by Spencer King and the interested reader is referred there for further historical details. But it is thus clear in the 21st century that interventional cardiology—by virtue of its new technologies, potent adjunctive drug therapies, expanding indications, and improving results—has blossomed. In many ways, these therapeutic modalities (rather than purely diagnostic techniques) have now become the centerpiece within the broad field of cardiac catheterization. Although the emphasis thus lies appropriately on this dynamic field of catheter-based intervention, we can ill afford to lose sight of the basic principles of catheter insertion, hemodynamic measurement, high-quality angiography, and integration of catheterization findings with the overall clinical scenario as the foundations on which all current interventional techniques are built and from which future evolution of cardiac catheterization will proceed.

**INDICATIONS FOR CARDIAC CATHETERIZATION**

As performed today, cardiac catheterization is a combined hemodynamic and angiographic procedure undertaken for diagnostic and often therapeutic purposes. As with any invasive procedure, the decision to perform cardiac catheterization
must be based on a careful balance of the risk of the procedure against the anticipated benefit to the patient. Indications for the use of catheterization and coronary intervention in the management of stable angina, unstable angina, and ST-elevation myocardial infarction (MI) have been developed by the American College of Cardiology (ACC) and the American Heart Association (AHA),37-39 and are available online at <http://www.cardiosource.org/ >.

The basic principle is that cardiac catheterization is recommended to confirm the presence of a clinically suspected condition, define its anatomic and physiologic severity, and determine the presence or absence of associated conditions when a therapeutic intervention is planned in a symptomatic patient. The most common indication for cardiac catheterization today thus consists of a patient with an acute coronary ischemic syndrome (unstable angina or acute MI) in whom an invasive therapeutic intervention is contemplated. The goal of cardiac catheterization in such patients is to identify the culprit lesions and then to restore vessel patency via PCI. In a few such patients, the diagnostic portion of the catheterization procedure may reveal other features (e.g., complex multivessel or left main coronary disease, severe associated valvular disease), which provide critical information for the decision and planning of open heart surgery.

Although few would disagree that consideration of heart surgery is an adequate reason for the performance of catheterization, clinicians differ about whether all patients being considered for heart surgery should undergo preoperative cardiac catheterization and coronary angiography. According to the most recent update of the ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease, “Coronary angiography is not indicated in young patients undergoing nonemergency valve surgery when no further hemodynamic assessment by catheterization is deemed necessary and there are no coronary risk factors, no history of CAD, and no evidence of ischemia. (Level of Evidence: C)” 40 Thus, many young patients with echo-proven valvular disease and no symptoms of myocardial ischemia are sometimes operated on using only noninvasive data. However, the risks of catheterization in such patients are extremely small, particularly compared to the risk of embarking on cardiac surgery on a patient for whom an incorrect clinical diagnosis or the presence of an unsuspected additional condition greatly prolongs and complicates the planned surgical approach. Therefore, the current guidelines still recommend cardiac catheterization in patients who might be at higher risk of coronary artery disease independent of age, or in patients for whom additional information might be required. By providing the surgical team with a precise and complete road map of the course ahead, cardiac catheterization can permit a carefully reasoned and maximally efficient operative procedure. Furthermore, information obtained by cardiac catheterization may be invaluable in the assessment of crucial determinants of prognosis, such as LV function, status of the pulmonary vasculature, and the patency of the coronary arteries. For these reasons, we recommend cardiac catheterization (or at least coronary angiography) in nearly all patients for whom heart surgery is contemplated, even if the severity of valve disease and ventricular function have been determined by preoperative echocardiography.

Catheterization data can also inform other nonsurgical therapeutic considerations. For example, the decision for pharmacologic intervention with heparin and/or a thrombolytic agent in suspected acute pulmonary embolism, the use of high-dose beta-blocker and/or calcium antagonists in suspected hypertrophic obstructive cardiomyopathy (versus catheter-based alcohol septal ablation) might well be considered of sufficient magnitude to warrant confirmation of the diagnoses by angiographic and hemodynamic investigation prior to the initiation of therapy. Although a clinical diagnosis of primary pulmonary hypertension can often be made by echocardiography, cardiac catheterization is usually required (a) to confirm the diagnosis and (b) to assess potential responsiveness to pharmacologic agents. Catheterization can also be used to optimize pharmacologic therapy for advanced congestive heart failure.

Another broad indication for performing cardiac catheterization is to aid in the diagnosis of obscure or confusing problems, even when a major therapeutic decision is not imminent. A common instance of this indication is presented by the patient with chest pain of uncertain cause, when there is confusion regarding the presence of obstructive coronary artery disease. Both management and prognosis of this difficult problem can be greatly simplified when it is known, for example, that the coronary arteries are widely patent. However, more recently CT angiography (CTA) has emerged as a new imaging modality and has been replacing invasive coronary angiography as a diagnostic tool to rule out coronary artery disease in this setting. Another example within this category is the symptomatic patient with a suspected diagnosis of cardiomyopathy. Although some may feel satisfied with a clinical diagnosis of this condition, the implications of such a diagnosis in terms of prognosis and therapy are so important that we feel it worthwhile to be aggressive in ruling out potentially correctable conditions (e.g., hemochromatosis, pericardial effusive-constrictive disease) with certainty, even though the likelihood of their presence may appear remote on clinical grounds.

Research

On occasion, cardiac catheterization is performed primarily as a research procedure. Although research is conducted to some degree in many of the diagnostic and therapeutic studies performed at major medical centers, it usually relates to the evaluation of new therapeutic devices (e.g., new stent designs) in patients who would be undergoing diagnostic and therapeutic catheterization in any event. All such studies require prior approval of the Food and Drug Administration (FDA) in the form of an Investigational Device Exemption, of the local Committee on Human Research at the institution (Institutional Review Board, or IRB), and attainment of informed consent after the details of the risks and potential
bene fits of the procedure and its alternatives have been thor­
oughly explained. Doing such research also requires meticu­
lous attention to protocol details, inclusion/exclusion criteria, 
data collection, and prompt reporting of any complications.

Even so, this is quite different from a catheterization that 
is performed solely for the purpose of a research investigation 
(as a 6-month follow-up angiogram after a new stent might 
be). Such studies should be carried out only by or under 
the direct supervision of an experienced investigator who is 
expert in cardiac catheterization, using a protocol that has 
been carefully scrutinized and approved by the IRB (Human 
Use Committee) at the investigator’s institution.

Contraindications

Although it is important to carefully consider the indications for 
cardiac catheterization in each patient, it is equally important to 
discover any contraindications. Over the years, our concepts of 
contraindications have been modified by the fact that patients 
with acute MI, cardiogenic shock, intractable ventricular 
tachycardia, and other extreme conditions now tolerate cardiac 
catheterization and coronary angiography surprisingly well.

At present, the only absolute contraindication to cardiac 
catheterization is the refusal of a mentally competent patient 
to consent to the procedure. But a long list of relative contra­
indications must be kept in mind, including all intercurrent 
conditions that can be corrected and whose correction would 
improve the safety of the procedure. Table 1.1 lists these rela­
tive contraindications. For example, hypertension increases 
predisposition to ischemia, pulmonary edema, or bleeding 
and should be controlled before and during catheterization. 
Other conditions that should be controlled before elective 
catheterization include intercurrent febrile illness, decomp­
ensated left heart failure, active bleeding, digitalis toxicity, 
and hypokalemia. Unexplained increases in creatinine or 
worsening renal function are strong indications to postpone 
cardiac catheterization, given the associated high risk of acute 
renal failure following administration of radiographic con­
trast in this context. Allergy to radiographic contrast agent is 
a relative contraindication to cardiac angiography, but proper

<table>
<thead>
<tr>
<th>Condition</th>
<th>Increased Risk</th>
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<tr>
<td>Hyperkalemia, Hypokalemia or digitalis toxicity</td>
<td>Arrhythmias</td>
</tr>
<tr>
<td>Uncontrolled Hypertension</td>
<td>Bleeding, hemorrhagic stroke following anticoagulation, heart failure and myocardial ischemia during angiography</td>
</tr>
<tr>
<td>Febrile illness</td>
<td>Infection</td>
</tr>
<tr>
<td>Ongoing anticoagulation with warfarin (INR &gt;1.5 commonly used as a cutoff)</td>
<td>Bleeding</td>
</tr>
<tr>
<td>Severe thrombocytopenia. The general consensus is that a platelet count of 40,000/mL to 50,000/mL is sufficient to perform major invasive procedures with safety, in the absence of associated coagulation abnormalities.</td>
<td>Bleeding</td>
</tr>
<tr>
<td>History of severe allergy to contrast media</td>
<td>Life-threatening anaphylactoid reactions</td>
</tr>
<tr>
<td>Decompensated heart failure</td>
<td>Pulmonary edema following contrast administration. Inability to lay flat during the procedure</td>
</tr>
<tr>
<td>Severe renal insufficiency and or anuria, unless dialysis is planned to remove fluid and as renal replacement therapy</td>
<td>Volume overload and pulmonary edema, nephropathy requiring dialysis</td>
</tr>
<tr>
<td>Worsening renal function: unexplained or following radiocontrast administration</td>
<td>Acute renal failure requiring dialysis</td>
</tr>
<tr>
<td>Active bleeding including gastrointestinal bleeding</td>
<td>Major bleeding secondary to administration of anti-platelets and antithrombotic agents</td>
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</table>


premedication and use of low osmolar contrast agents can substantially reduce the risks of a major adverse reaction, as discussed in Chapters 2 and 4. Even so, severe allergic reactions or even anaphylaxis can occur, and the operator and catheterization laboratory staff should be well versed in managing the procedure.

Anticoagulant therapy is more controversial as a contraindication. Heparin (unfractionated or low molecular weight), direct thrombin inhibitors (bivalirudin), and antiplatelet agents such as aspirin, ADP receptor blockers, or the platelet glycoprotein IIb/IIIa receptor blockers are widely used in the precatheterization management of acute coronary syndromes and are part and parcel of any coronary intervention. But the use of heparin for simple diagnostic coronary angiography, once felt to lower the incidence of thromboembolic complications during coronary angiography, is now uncommon except when the radial artery approach is used. These agents may be continued through and after the catheterization, particularly with the use of vascular closure devices, with only a small increase in the risk of local bleeding. If a complication arises, these agents can often be reversed (protamine, platelet transfusion) or allowed to wear off. But the view regarding oral anticoagulants (e.g., warfarin) that it is best to reverse the prolonged prothrombin time to an international normalized ratio (INR) of <2 (and in most labs to <1.5) before cardiac catheterization represents a more complex problem. This is best done by withholding warfarin for 3 to 5 days before the procedure, potentially switching to subcutaneous low-molecular-weight heparin or intravenous heparin for a strong anticoagulant indication (e.g., atrial fibrillation, a mechanical heart valve). If more rapid reversal of oral anticoagulation is required, fresh-frozen plasma (FFP) is commonly used. We reserve its use only to clinical conditions where urgent reversal is indicated, as administration of FFP requires a high volume load and it is associated with a low though not insignificant risk of infections and of transfusion-related acute lung injury (TRALI). More recently, prothrombin complex concentrates (PCC) have been introduced as a new option to reverse anticoagulation in patients receiving warfarin. They have the advantage of rapid reversal, no association with TRALI, and require administration of a significantly lower volume when compared with FFP. However, the major drawback with PCC has been the risk of thrombotic complications. Their use in reversing oral anticoagulation prior to cardiac catheterization has not been assessed.

Factors Influencing Choice of Approach

Certain approaches to cardiac catheterization have only historical interest (transbronchial approach, posterior transthoracic left atrial puncture, suprasternal puncture of the left atrium). In this book, we discuss in detail catheterization by percutaneous approach from various sites (including femoral or radial arteries, femoral or internal jugular veins, transseptal catheterization of the left heart, and apical puncture of the left ventricular apex; Chapter 6). Although it has largely been supplanted by the percutaneous approach, we also discuss catheterization by direct surgical exposure of the brachial artery and vein (the so-called Sones technique, Chapter 8). In addition, the need for using larger catheters for percutaneous valve replacement or endovascular aortic stenting is leading to a resurgence of the femoral artery and subclavian/axillary artery surgical exposure technique, and a shift of the paradigm toward a multidisciplinary team approach including interventional cardiologists, vascular surgeons, and cardiac surgeons (Chapter 8).

The great vessels and all cardiac chambers can be entered in nearly all cases by any of these approaches; thus the choice depends on patient issues (aortic occlusion, morbid obesity), procedural issues (need for use of larger bore catheters), and patient/operator preference. Ideally, the physician performing cardiac catheterization should be well versed in several of these methods (at least one upper extremity approach as well as the femoral approach). More recently, the radial artery approach has become the preferred approach of many operators (Chapter 7). It appears to have a lower complication rate when compared to femoral artery access and allows early ambulation. In general, the radial artery is our preferred approach in any setting that might increase the risk of bleeding, including, among others, morbid obesity or the need to resume anticoagulation following a diagnostic or therapeutic procedure.

**DESIGN OF THE CATHETERIZATION PROTOCOL**

Every cardiac catheterization should have a protocol, that is, a carefully reasoned sequential plan designed specifically for the individual patient. This protocol may be so common (e.g., left heart catheterization with coronary angiography, annual transplant evaluation) that the operator and support staff are already in sync with the plan. If anything beyond this approach is planned, it is helpful to map this out, even preparing and posting a written protocol in the catheterization suite so that all personnel in the laboratory understand exactly what is planned and anticipate the needs of the operator.

Certain general principles should be considered in the design of a protocol if it includes hemodynamic measurements. First, hemodynamic measurements should generally precede angiographic studies, so that crucial pressure and flow measurements may be made as close as possible to the basal state. Second, pressures and selected oxygen saturations should be measured and recorded in each chamber “on the way in,” that is immediately after the catheter enters and before it is directed toward the next chamber. If a problem should develop during the later stages of a catheterization procedure (atrial fibrillation or other arrhythmia, pyrogen reaction, hypotension, or reaction to contrast material),
it will be beneficial to have the pressures and saturations already measured in advance, rather than waiting until the time of catheter pullback. Third, measurements of pressure and cardiac output (using true Fick, Fick with estimated oxygen consumption, or thermodilution, Chapter 11) should be made as simultaneously as possible.

Beyond these general guidelines, the protocol will reflect differences from patient to patient and factor in changes when unexpected findings are encountered (e.g., finding an unexpected marked elevation of LV end diastolic pressure may cause addition of a right heart catheterization to the protocol). It is important to be selective about the inclusion of angiographic studies beyond the coronaries to limit total contrast volume for the study (the upper limit is 3 to 5 mL/kg divided by the serum creatinine). In a patient with an elevated creatinine in whom coronary intervention is anticipated, the LV angiogram should be replaced by a noninvasive evaluation of ventricular function and even the number of baseline coronary injections should be limited. With regard to angiography, it is important to keep Sutton’s law in mind (When asked why he robbed banks, Willie Sutton is reported to have replied, “because that’s where the money is.”), and limit contrast injections to the most important diagnostic considerations in a given patient.

The Checklist

Checklists are commonly used (and are often a necessity) in several industries and professions. They allow a detailed breakdown of the process in each individual component and prevent skipping key steps, which could result in an adverse outcome. More recently, there has been an enhanced interest in the application of checklists to medicine and particularly to surgical procedures. It has been shown that routine use by hospitals of surgical checklists can result in improved survival and lower complications rates. The field of interventional cardiology, with its evolution toward the execution of more complex procedures requiring the expertise and interaction of multiple subspecialties, is an ideal area for an effective use of checklists. Figures 1.2 and 1.3 illustrate two simple checklists currently in use in our institution for all patients referred for invasive procedures and for patients referred for transcatheter aortic valve implantation.

Informed Consent

It goes without saying that both the medical and the emotional preparation of the patient for cardiac catheterization are the responsibility of the operator. This includes a full explanation of the proposed procedure in such terms that the patient can give truly informed consent. This should include a candid but general discussion of the potential risks, particularly if the patient’s condition or the nature of the procedure increases them above the boilerplate information in the preprinted consent form. The consent process should be viewed as an opportunity to set expectations and as a tool to manage risk. In general, adequate informed consent discussions should include a description of the proposed procedure and alternatives, including risks and benefits. In addition, we try to accurately state the moderate amount of discomfort involved, the duration of the procedure, and the postprocedure recovery—failure to do so risks one’s credibility.

In general, the expectation is that the physician performing the procedure or proposing the therapy has the duty to provide informed consent and that such duty is “nondelegable.” The consent process should be documented in a standardized consent form and in a contemporary note in the patient’s chart. The note in the patient’s chart should document that a discussion on risks, benefits, and alternatives to the procedures has occurred between the physician performing the procedure and the patient. A study of psychological preparation for cardiac catheterization found that patients who received careful psychological preparation had lower levels of autonomic arousal both during and after cardiac catheterization than did control subjects. A more recent study has also shown that the use of visual aids enhances the patient’s understanding of the procedure and future retention of the information provided.

Preparation and Premedication of the Patient

It is our practice to have the patient fasting (except for oral medications) after midnight, but some laboratories allow a light tea and toast breakfast without ill effects. The guidelines by the American Society of Anesthesiologists currently recommend a minimum of 2 hours fasting period after clear liquids, and 6 hours after a light meal. Complete vital signs should be recorded before the patient leaves the floor (for inpatients), or shortly after arriving at the Ambulatory Center (for outpatients), so that the procedure may be reconsidered if a change has occurred in the patient’s condition since he or she was last seen.

Once the question of indications and contraindications has been dealt with and the patient’s consent obtained, attention can be directed toward the matter of premedications. We do not administer antibiotics prophylactically before cardiac catheterization, and we know of no controlled studies to support their use, but antibiotic prophylaxis should be considered if there have been any breaks in sterile technique, in immunocompromised patients, or if a vascular closure device is being used in a patient with diabetes mellitus. Antibiotic prophylaxis is also commonly used prior to implantation of certain devices, such as atrial septal or ventricular septal defect occluders and percutaneous aortic valves. A single dose of a cephalosporin administered 30 to 60 minutes prior to the procedure is adequate in providing suitable tissue concentrations for several hours. As an alternative, vancomycin can be used although the recommendation is that it should be given 120 minutes prior to the procedure. For a comprehensive review on infection control in the cardiac catheterization
Section I General Principles

PRE·PROCEDURE CHECKLIST

<table>
<thead>
<tr>
<th>Patient Arrival to Holding Area / T-S. Time:</th>
<th>Completed</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time-out Done (Correct info/identifiers/orders)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physician Pre-procedure Orders Completed/Done</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procedure Consent Signed and in Chart</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H&amp;P Completed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nursing Assessment Done</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nursing Notes Sheet In Chart</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-Sedation Assessment Form Completed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication Reconciliation Completed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV Access Started / Checked / Patent / IVF Infusing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient Clipped / Prepped</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre Cath/ EPS/ Pacer / AICD Orders Completed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post Cath/ EPS/ Pacer/ AICD Orders in Chart</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post PTCA Orders in Chart</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anesthesia Consent in Chart</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood Refusal Consent in Chart</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Labs (BP7/CBC/PT/PTT/Type &amp; Screen) Done, Results in Chart</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EKG Done and in Chart</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physician Post Procedure Orders Forms in Chart</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observation Orders for Outpatients in Chart</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Printed Physician Progress Notes in Chart</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensis Documentation Completed and in Chart</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PACU Report Form in Chart/Post Gen. Anesthesia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physician Preliminary Report Form in Chart</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procedures Charges Sheet in Chart</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Report given to Procedure RN. Time:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Checklist/Chart Reviewed by both RNs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Holding Area/7-S RN Signature: __________________________
Receiving CCL RN Signature: __________________________

University of Miami Hospital
1400 NW 12th Avenue, Miami, Florida 33136

Figure 1.2 Example of a simple nursing checklist for patients referred for cardiac catheterization or any other invasive procedure. The checklist can be easily included in the workflow when using either paper charts or a full electronic medical record (courtesy of the University of Miami).

laboratory, the reader is referred to the guidelines of the Society for Cardiovascular Angiography and Interventions.35

Various sedatives have been used for premedication. We no longer routinely order premedication to be given before the patient is sent to the catheterization laboratory, but instead assess the patient’s state of alertness and need for sedation once he or she is on the catheterization table. Per conscious sedation guidelines, we usually administer small repeated doses of midazolam (Versed) 0.5 to 1.0 mg intravenously and/or fentanyl 25 to 50 mg intravenously to maintain a comfortable but arousable state. Premedication of patients with prior history of allergic reactions to contrast media is listed in Chapter 4. With appropriate prior counseling, good local anesthesia, and a reassuring presence by the operator and team throughout, a cardiac catheterization should be an easily tolerated procedure.

THE CARDIAC CATHETERIZATION FACILITY

In the past, the cardiac catheterization suite required ~ 500 square feet of space. With the advent of multimodality imaging and the growth of interventions for structural heart disease, interventional procedures today require the contribution and presence of multiple subspecialties, as well as the presence in the cardiac catheterization suite of additional equipment ranging from anesthesia equipment to echocardiographic consoles and LV assist devices. Thus, the modern cardiac catheterization laboratory has been evolving toward the new concept of the “hybrid suite” and today requires an area ranging from 850 to 1,000 square feet, within which will be housed a conglomeration of highly sophisticated
**Clinical TAVR Pre Procedure Checklist**

Patient Name: ________________________________

_____ Cardiac Interventionist: Dr(s) ________________________________

_____ Valve Size # ________ mm

_____ Valve available in CCL

_____ Same size 2nd valve available

_____ Procedure approach: _______ Trans Apical _______ Trans Aortic _______ Trans Femoral __________ Right _______ Left

_____ Physicians:  
- Cardio Thoracic Dr
- Vascular Dr
- Anesthesia Dr

_____ Perfusionists:  
- Bypass Machine
- IABP Operator
- Impella

_____ TEE manage by:  
- Anesthesiologist Dr
- Cardiologist Dr
- Echo Tech

_____ 4 Units of PRBC’s Blood in cath lab before procedure starts

_____ OR Team:  
- RN OR Circulator
- OR Scrub Tech

_____ CCL Team:  
- RN CCL Circulator
- Scrub CCL Tech
- Monitor CCL Tech

---

**Figure 1.3** Checklist for patients referred for transcatheter aortic valve replacement. As an example, the checklist ensures that a minimum of two valves of the planned size are available in the inventory (courtesy of the University of Miami).

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Electronic and radiographic equipment (Figures 1.4 and 1.5). Reports of the Inter-Society Commission for Heart Disease Resources on optimal resources for cardiac catheterization facilities have appeared in 1971, 1976, 1983, and 1991. The American College of Cardiology (ACC) and the Society of Cardiac Angiography and Interventions have published clinical consensus documents of cardiac catheterization laboratory standards in 2001 and in 2012. These reports deal with issues regarding lab construction, staffing, quality assurance, and more controversial topics such as the following:

1. Traditional versus nontraditional settings for a cardiac catheterization laboratory; location within a hospital versus freestanding
2. Ambulatory cardiac catheterization: indications and contraindications
3. Ethical issues related to self-ownership of laboratories, self-referral of patients, self-reporting, unnecessary services and advertising
4. Optimal annual caseload for physicians and for the laboratory
5. Safety issues during conduct of the procedure (sterile technique, heparin)
6. Physical arrangements and space requirement
7. Radiation safety and radiologic techniques

**Location within a Hospital versus Freestanding**

The issue of whether cardiac catheterization laboratories should be hospital based, freestanding, or mobile has been the subject of much debate. Performance of catheterization in a freestanding or mobile unit should be limited to diagnostic procedures in low-risk patients. In its 1991 report, the ACC/AHA (American Heart Association) Task Force "generally found that in freestanding catheterization laboratories, access to emergency hospitalization may be delayed and appropriate
oversight may be lacking. Additionally, opportunities for self-referral may be fostered and the perception of commercialism and entrepreneurial excess in practice created.56 Immediately available cardiac surgical backup is particularly critical for laboratories that perform diagnostic catheterization on unstable or high-risk patients, as well as for those that perform coronary angioplasty, endomyocardial biopsy, or transseptal catheterization. Some states, however, have recently allowed performance of acute MI and even elective coronary intervention in hospitals without on-site cardiac surgery as long as it is performed by operators active at other sites and with a formal plan for transfer within 1 hour to a facility with cardiac surgery on site (e.g., an ambulance standing by, and an agreement with a nearby surgical facility to provide timely backup if needed).

**Outpatient Cardiac Catheterization**

Outpatient cardiac catheterization has been demonstrated by a variety of groups to be safe, practical, and highly cost efficient, and is now widely practiced throughout the world. Outpatient catheterization can be accomplished by the radial, brachial, or femoral approaches, which allow the patient to be ambulatory within minutes of the completion of the catheterization study.59-62 For femoral procedures, hemostasis can be obtained by manual compression for 10 minutes over the femoral artery, followed by bed rest for 2 to 4 hours, or use of a femoral closure device (see Chapter 6) with 1 to 2 hours of bed rest before discharge. More recently, it has been suggested that outpatient PCI with same day discharge might be both feasible and safe in selected patients.

**TRAINING STANDARDS**

Training in the performance and interpretation of hemodynamic and angiographic data derived from cardiac catheterization is an important part of fellowship training in Cardiovascular Disease. The current Accreditation Council for Graduate Medical Education (ACGME) training guidelines call for a minimum of 4 months of diagnostic catheterization experience (100 cases, Level 1), with an additional 8 months of catheterization experience (200 additional cases, Level 2) for individuals wishing to perform diagnostic catheterization in practice, within the basic 3-year Cardiovascular Disease fellowship.63-64 Level 3 advanced training in interventional cardiac catheterization requires 12 months of additional training and the performance of 250 PCI as primary operator. Although many cardiologists in the past were jacks-of-all-trades performing office evaluation, noninvasive imaging, pacemaker implantation, and diagnostic cardiac catheterization, the current trends toward ad hoc coronary intervention as an adjunct to diagnostic catheterization make it less likely that new practitioners will be seeking to establish practices that are limited to diagnostic cardiac catheterization.

As the field continues to evolve, it is thus increasingly likely that an invasive cardiologist (one who performs cardiac catheterization) will also be an interventional cardiologist (one who performs PCI). In the first 20 years of coronary intervention (1977–1997), one’s designation as an interventional cardiologist was at first based on an expressed interest in the field and attendance at one or more informal training symposia. Subsequently, most interventional cardiologists completed a
1-year fellowship at a center that performed interventional procedures.

In 1999, however, the ACGME established the structural, content, and faculty requirements for creating an accredited fellowship in interventional cardiology, requiring an additional 12 months beyond the 3-year general cardiovascular training period, during which at least 250 interventional procedures should be performed. As of 2005, there were 116 accredited interventional programs with 231 positions. By 2011, the number of ACGME-accredited training programs had grown to 137 with 300 active positions.

In parallel, the American Board of Internal Medicine (ABIM) recognized the body of knowledge subsumed by interventional cardiology by offering a voluntary one-day proctored examination to individuals who met certain eligibility requirements—documented prior performance of 500 coronary interventions (the practice pathway, no longer open after 2003), or completion of an ACGME-approved interventional fellowship (the fellowship pathway). Candidates able to pass this examination receive Board Certification via a Certificate of Additional Qualification in Interventional Cardiology. An example of the type of content tested in this exam is given in Table 1.2. At this writing, 5,337 interventional cardiologists held a valid Certificate of Additional Qualification in Interventional Cardiology, which now also includes the performance of computer-simulated procedures for both training and certification. On the other hand, several thousand individuals continue to perform interventional procedures without the benefit of such certification, or do not recertify after expiration of the initial certification. However, many hospitals today require active certification for renewal of privileges.

As the field of interventional cardiology expands, it is increasingly recognized that knowledge and skill in coronary intervention do not necessarily confer the ability to safely perform peripheral vascular intervention. Some content relating to peripheral vascular procedures is tested in the interventional exam, but individuals interested in performing complex lower extremity or carotid intervention are increasingly undertaking an additional training period after their interventional fellowship to gain the necessary skills and experience. As outlined in Table 1.3, this training should occur under the proctorship of a formally trained vascular interventionalist and includes some degree of training in vascular medicine and noninvasive testing for peripheral vascular disease. Certifications by a general examination in vascular medicine and an endovascular specialty examination are available through the American Board of Vascular Medicine. Details on eligibility criteria and the examinations can be found at: http://www.vascularboard.org/cert_reqs.cfm. (access date: May, 16, 2013).

As is evident from the range of topics discussed in the remainder of this text, the knowledge and experience base that is now required to perform invasive and interventional cardiology procedures is quite extensive and changes continuously with the serial introduction of new devices and procedures.
**Table 1.2 Medical Content, Sample Topics, and Relative Percentage Included in the Interventional Board Exam**

<table>
<thead>
<tr>
<th>Case Selection and Management</th>
<th>25%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Topics:</strong> Chronic ischemic heart disease and acute coronary syndromes: catheter-based interventions (angioplasty, stent, IVUS, other devices, pressure wire/FFR assessment, thrombectomy; treatment modality (interventional, surgical, medical); recognition, and management of hemodynamic compromise: pharmacologic agents, devices, and procedures (balloon counterpulsation, emergency pacing, pericardiocentesis, stent placement, and therapeutic hypothermia); catheter-based management in valvular disorders (mitral, aortic, and pulmonary) and in hypertrophic cardiomyopathy, including clinical, invasive, and noninvasive findings that differentiate patients who require surgical versus percutaneous approaches. Catheter-based management of adult congenital heart disease and interventional approaches to peripheral vascular disease, focusing primarily on diagnosis and patient selection.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Procedural Techniques</th>
<th>25%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Topics:</strong> Planning and execution of interventional procedures, selection and use of equipment (guiding catheters, guidewires, balloon catheters, coronary stents, atherectomy, thrombectomy, embolic protection devices, ventricular support devices), antithrombotic agents, complications.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Basic Science</th>
<th>15%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Topics:</strong> Vascular biology, including plaque formation, vascular injury, vasoreactivity, vascular healing, restenosis, reperfusion injury, microvascular angina, clotting cascade, platelet function, thrombolysis, coronary and peripheral anatomy, coronary physiology and myocardial function, alterations in coronary flow, assessment and effect of flow dynamics on myocardial perfusion, function of collateral circulation, arterial spasm or microembolization on coronary flow, left ventricular function, including stunning and hibernation, arterial pressure evaluation, right ventricular infarction, and shunt quantification.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pharmacology</th>
<th>15%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Topics:</strong> Effects and appropriate use of vasoactive drugs, antiplatelet agents, thrombolytics, anticoagulants, antiarrhythmics, lipid-lowering agents, sedating agents, DES compounds, device-related pharmacology, local anesthetic agents, angiographic contrast agents.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Imaging</th>
<th>15%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Topics:</strong> Applications of imaging to interventional cardiology, including identification of anatomic features; visualization of lesion morphology by angiography and by intravascular and intracardiac ultrasonography; structural cardiac and peripheral vascular imaging (including echocardiography, MRI, and OCT), radiation physics, radiation risks and injury, and radiation safety, methods to control radiation exposure for patients, physicians, and technicians, equipment operation and imaging techniques.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Miscellaneous</th>
<th>5%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ethical and legal issues, as well as risks associated with diagnostic and therapeutic techniques. Patient consent and patient safety, statistics, epidemiologic data, and economic issues related to interventional procedures.</strong></td>
<td></td>
</tr>
</tbody>
</table>

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**Physician and Laboratory Caseload**

Use levels and optimal physician caseload are important issues in invasive cardiology. Earlier reports have recommended 300 diagnostic catheterization cases per year for the laboratory and 150 cases per year for each operator to maintain cost-effectiveness, skills, and favorable outcome. While there are no data supporting these minimum volume standards, it is generally accepted that high-volume laboratories tend to have better outcomes. In addition, low-volume laboratories might be associated with the risk of inadequate equipment and staffing due to financial limitations. At the same time, a cardiologist
should not have such an excessive caseload that it interferes with proper precatheterization evaluation of the patient and adequate postcatheterization interpretation of the data, report preparation, patient follow-up, and continuing medical education. More recent guidelines, however, have pointed out the exceptionally low incidence of complications from diagnostic catheterization and questioned the need for minimum individual operator volumes as long as outcome data collection and quality assurance programs are in place (see below).\textsuperscript{57,67}

For interventional cardiology, the guidelines call for the laboratory to perform a minimum of 200 procedures (more than 400 being ideal), and each operator to perform a minimum of 75 cases per year, to remain proficient.\textsuperscript{67,70} In actuality, these numbers are generally not enforced except at the level of hospital privileging (compliance with minimal volumes is required in some states, however), and a segment of the interventional community still performs as few as 25 to 50 interventions per year. Outcome data suggest that higher-volume operators working in higher-volume interventional centers do have greater procedural success and fewer adverse complications. However, other data suggest that while the trend between operator and outcomes continues to exist with contemporary PCI, some lower-volume operators can still practice safely (Figure 1.6).\textsuperscript{71} and particularly if they work side by side with more-experienced operators in high-volume centers and if they limit the complexity of the procedures they attempt. With the current very low rate of major complications associated with interventional procedures and the difficulties in accurately adjusting outcomes for differences in case complexity, it would be very difficult to draw statistically valid conclusions about this issue. All that said, as in other areas of procedural medicine, there is a compelling truth to the adage that “practice makes perfect.”

### The Catheterization Laboratory Director and Quality Assurance

An important check on the appropriateness of procedural indications, the safety of procedural outcomes, and the quality of catheterization lab report documentation, is the existence of a qualified director in each functioning catheterization laboratory.

The director should have at least 5 years of post fellowship experience in procedural performance and should be board certified in both cardiology and interventional cardiology (i.e., the Certificate of Additional Qualification as described above). Important roles of the director include selection and upkeep scheduling of all equipment, oversight of device ordering systems and procedural policies, training supervision of ancillary personnel (nurses, cardiovascular technicians, and radiographic technicians), and development of an equitable case scheduling methodology. The director usually also has fiduciary responsibilities to the hospital for the safe and efficient use of catheterization lab time, personnel, and supplies, as well as oversight of the hospital billing activity for catheterization procedures. In exchange, the director often receives partial salary support from the hospital to cover time taken away from remunerative clinical practice.

### Alternative Route to Achieve Competence in Peripheral Catheter-Based Interventions

<table>
<thead>
<tr>
<th>Common requirements</th>
<th>Procedure requirements for competency in all areas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completion of required training within 24-month period</td>
<td>Diagnostic peripheral angiograms—100 cases (50 as primary operator)</td>
</tr>
<tr>
<td>Training under proctorship of formally trained vascular interventionalist competent to perform full range of procedures</td>
<td>Peripheral interventions—50 cases (25 as primary operator)</td>
</tr>
<tr>
<td>Written curriculum with goals and objectives</td>
<td>No fewer than 20 diagnostic/10 interventional cases in each area, excluding extracranial cerebral arteries</td>
</tr>
<tr>
<td>Regular written evaluations by proctor</td>
<td>Extracranial cerebral (carotid/vertebral) arteries—30 diagnostic (15 as primary operator), 25 interventional (13 as primary operator)</td>
</tr>
<tr>
<td>Documentation of procedures and outcomes</td>
<td>Percutaneous thrombolysis/thrombectomy—5 cases</td>
</tr>
<tr>
<td>Supervised experience in inpatient and outpatient vascular</td>
<td>Supervised experience in a noninvasive vascular laboratory</td>
</tr>
<tr>
<td>Consultation settings</td>
<td></td>
</tr>
<tr>
<td>Supervised experience in a noninvasive vascular laboratory</td>
<td></td>
</tr>
</tbody>
</table>

*The fulfillment of requirements via an alternative pathway is only appropriate if the candidate physician has the cognitive and technical skills and is competent to perform either coronary intervention, interventional radiology, or vascular surgery.*

One of the most important roles (if not the most important) of the catheterization laboratory director is the systematic collection of outcomes data and a fair assessment of the quality of care provided by individual operators. In addition to clinical outcomes, data collection should include comorbidities and procedure variables. This can be achieved by participation in a regional or national registry, or through the use of homegrown databases. Participation in a regional registry (Northern New England, Michigan BMC2, New York State, Massachusetts, Washington State, and other regional registries), or in the national American College of Cardiology CathPCI registry provides the added value of comparative risk-adjusted data that can be used for benchmarking and for quality improvement. Outcome data of interest usually include periprocedural death, MI, stroke, emergency CABG, peripheral vascular/access site complications (pseudoaneurysm, arteriovenous (AV) fistula, loss of pulse, need for vascular surgery, or significant hematoma), pericardial tamponade, the occurrence of contrast-induced nephropathy, and blood transfusion.

These are best presented to the clinical cardiology and cardiac surgery staff in a joint conference, during which laboratory-wide solutions to certain problems can be introduced and their effectiveness monitored in subsequent conferences (Continuous Quality Improvement methodology). The director should also organize didactic conferences for the fellows and faculty as well as a periodic “cath conference” in which interesting cases, complications, and cases performed with new technologies are presented. In addition, an assessment of the appropriateness of procedure performed according to available guidelines should be included in the quality assurance program. In short, the director is responsible for overseeing the safe, effective, and up-to-date operation of the laboratory, with the commitment to provide the best and most appropriate patient care.

PERFORMING THE PROCEDURE

Having carefully considered indications and contraindications, chosen a method of approach, designed the catheterization protocol, and prepared the patient, the next step is to perform the cardiac catheterization itself and thereby gain the anatomic and physiologic information needed in the individual case. Benchmarking from 82,548 procedures across 53 catheterization laboratories in 1997–1998 showed that the average left heart catheterization took 64 minutes of lab time, including 25 minutes of procedure time. Adding a right heart catheterization increased lab time to 84 minutes and procedure time to 32 minutes. Interventional procedures averaged 117 minutes, with a procedure time of roughly 70 minutes. Of course, the actual procedure time varies with operator experience and patient complexity, but these data serve as useful benchmarks.

In individual cardiac catheterization procedures, the choice of procedure components draws selectively on the techniques that are described throughout this text. Detailed descriptions of catheter insertion and hemodynamic measurements are contained in Section II (Chapters 6 through 8) and Section III (Chapters 10 through 14), with description of angiographic and interventional techniques in Section IV (Chapters 15 through 19) and Section VII (Chapters 28 through 39). Methods for evaluation of cardiac function and special catheter techniques used only in selected situations are described in Section V (Chapters 20 through 23) and VI (Chapters 24 through 27). Our readers should note that the techniques that are described throughout this text are not proposed as the only correct approaches to cardiac catheterization (many laboratories and operators take different approaches, and still obtain excellent results). Rather, they are the methods that
have consistently been found to be safe, successful, and practical. Moreover, their strengths and weaknesses are well characterized, and they therefore constitute an excellent point of reference as one’s personal practice continues to evolve based on new clinical trial data and individual preference.

REFERENCES


Section I General Principles


Interventional cardiologists must have a sufficient working knowledge of radiation safety, the science of x-ray imaging, and the technology of fluoroscopic equipment. All of the major US cardiology societies (ACC, AHA, HRS, SCAI) have published relevant clinical competency statements, guidelines, and educational materials.\textsuperscript{1–9} This body of knowledge defines the minimal acceptable knowledge base for which interventional cardiologists and electrophysiologists are accountable. Radiation competence is included in the examination for a Certificate of Additional Qualification in Interventional Cardiology. This expectancy is reinforced both by institutional privileging standards and by regulatory requirements.

Patient safety is more than a theoretical concern because fluoroscopic radiation injuries ranging from inconsequential to devastating continue to occur.\textsuperscript{10–22} Necessary images need to be obtained while protecting both patients and staff from unnecessary radiation. It is essential to include radiation usage statistics and case reviews in the laboratory's formal quality process. In simplest terms, radiation should be used and monitored in the same manner as contrast-agents or drugs.

This chapter includes brief reviews of basic x-ray physics, radiation biology, patient radiation management, staff radiation safety, and iodinated contrast agents. These materials are current as of the time of writing but will certainly evolve over time. Those seeking more detailed information can start with existing publications, recommendations, and textbooks\textsuperscript{1,6–9,23–26} and use these as a springboard to the evolving literature.

### BASIC X-RAY PHYSICS

X-rays are a form of electromagnetic radiation similar to visible light and radio waves. The x-ray beam is often described as a stream of photons (i.e., discrete packets of electromagnetic radiation, each containing a defined amount of energy). Each x-ray photon contains thousands of times the energy of a photon of visible light. This explains why different and more potent biologic effects occur when an x-ray photon is absorbed by or scattered from living tissue.

X-rays are predominantly produced when high-energy electrons are decelerated by interaction with a metallic target (in our case tungsten). This is called \textit{bremstrahlung} (breaking radiation). The resulting x-ray beam contains a spectrum of photon energies ranging from approximately 20 KeV up to the maximum voltage applied to the x-ray tube. Characteristic x-rays are also produced when the incoming electrons interact with the orbital electrons of the target's atoms. The x-ray spectrum emitted toward the patient is modified by filters placed between the x-ray tube and the patient. The shape of the x-ray spectrum strongly affects both image contrast and patient dose. Too "soft" a spectrum needlessly increases patient dose; too hard a spectrum decreases image contrast.

This chapter uses those radiation quantities and units needed to describe the use of x-rays in the interventional laboratory (Table 2.1). These derive from the SI system of measurement (\textit{Système international d'unités}), their use in the publications of the International Commission on Radiological Units (ICRU),\textsuperscript{27} the International Commission on
### Table 2.1 Clinically Important Dosimetric Definitions

<table>
<thead>
<tr>
<th>Quantity</th>
<th>Description</th>
<th>SI Unit</th>
<th>Related Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure $K_{air}$</td>
<td>The radiation present at a point in space. It is currently described as air kerma (kinetic energy released in matter) in units of gray. At fluoroscopic energies, air kerma is the dose delivered to air. By itself, exposure gives no information regarding how much radiation energy is delivered to tissue or the biologic effects that that irradiation might have.</td>
<td>gray (Gy) <em>\text{In air}</em></td>
<td>Roentgen (R)  $100 , R = 0.87 , G_{\text{air}}$</td>
</tr>
<tr>
<td>Dose $D_{\text{material}}$</td>
<td>The local concentration of energy absorbed by a small volume of a specified material (e.g. air) or specified tissue (e.g. myocardium) from the x-ray beam. Tissue dose is usually stated in units of gray (1 Gy = 1 joule/kilogram) or milligray (mGy). The dose delivered to different portions of a patient from an initially uniform x-ray beam is always nonuniform because of x-ray beam size limits, x-ray absorption, and x-ray scatter. It is incorrect to describe the physical dose distribution in a patient or staff member using a single number. 1 Gy (specific substance) = 1 joule (absorbed)/kg (specific substance)</td>
<td>gray (Gy) *\text{In soft tissue or another specified material}</td>
<td>RAD  $100 , \text{RAD} = 1 , \text{Gy}$</td>
</tr>
<tr>
<td>Peak Skin Dose PSD</td>
<td>The highest dose received by any portion of the patient’s skin from a procedure. Presently, there is no commercially available technology to map skin dose distribution while a procedure is in progress. However, real-time skin mapping is anticipated in the near future. Several film-based technologies are available to produce a skin dose map after the patient has been removed from the table.</td>
<td>gray (Gy)</td>
<td>Includes backscatter from patient</td>
</tr>
<tr>
<td>Effective Dose $(E)$</td>
<td>A calculated quantity that was introduced by the ICRP for managing stochastic radiation risks experienced by large populations. This usage has also been adopted by the NCRP. The calculation includes a complex convolution of radiation type and organ sensitivity in a hypothetical standard person. Effective dose is not intended to characterize the radiation risk experienced by any individual. Its use for such purposes is specifically rejected by both the ICRP and NCRP. Effective dose is a useful metric for generally comparing different types of procedures or different protocols. $ED , (Sv) = \sum [\text{Dose to a volume of tissue (Gy)}] \times \text{Radiosensitivity of that tissue}$</td>
<td>sievert (Sv)</td>
<td>100 REM = 1 Sv</td>
</tr>
<tr>
<td>Air Kerma Area Product $P_{\text{KAP}}$</td>
<td>A measure of the total x-ray energy in a beam. In simple terms, it is the product of the dose measured at a point in the center of the beam and the cross sectional area of the beam at that point. Following this definition, dose area product (DAP) is usually stated in units of Gy cm$^2$. $P_{\text{KAP}}$ has the same value anywhere between the x-ray tube and the patient’s entrance surface. DAP and anatomical information can be combined to estimate effective dose using conversion factors derived from Monte-Carlo simulations. $P_{\text{KAP}}$ is the best dose metric for estimating patient stochastic risk and the amount of scatter in the procedure room.</td>
<td>Gy cm$^2$</td>
<td>See Figure 2.1</td>
</tr>
<tr>
<td>Reference Point Air Kerma $K_{\text{r}}$</td>
<td>The total air kerma accumulated at an internationally defined reference point during a procedure. For an isocentric fluoroscope, the reference point is located 15 cm from the isocenter along a line from the isocenter to the x-ray tube’s focal spot. This point approximates the skin location for a nonmoving beam. $K_{\text{r}}$ is the best currently available dose metric for managing the possibility of skin injury.</td>
<td>Gy</td>
<td>See Figure 2.1</td>
</tr>
<tr>
<td>Fluoroscopic Time</td>
<td>This is not a useful dose metric because fluoroscopic time does not reflect patient size, beam orientation, or the use of cine. The use of fluoroscopic time as a dose metric or equipment that can only display fluoroscopic time for interventional procedures is strongly discouraged.</td>
<td>Minutes</td>
<td>See Figure 2.1</td>
</tr>
</tbody>
</table>
Radiological Protection (ICRP), the International Atomic Energy Agency (IAEA), and the US National Commission on Radiological Protection and Measurements (NCRP). Table 2.1 also includes key conversion factors between current SI units and related older units.

**CLINICAL MEASUREMENT OF PATIENT IRRADIATION**

Clinical radiation dose measurements in the interventional fluoroscopic laboratory are used as practical indicators of patient risk. Clinical concerns include patient skin injury as well as patient and staff cancer risk. Available measurements furnish sufficient real-time information so that the operator can include radiation use in ongoing benefit-risk assessment as a procedure progresses.

Radiation can be measured in many ways and at many locations (Figure 2.1). Of these, the image-receptor entrance point is best for assessing image noise and the patient entrance point is best for assessing the risk of skin injury. Image-receptor measurements are available from many current fluoroscopes. Real-time patient-entrance measurements are not currently commercially available. The reference point air kerma \( (K_{ar}) \) is an available reasonable surrogate for predicting skin damage. Cancer risk is related to the dose received by each of the organs in the body and its radiosensitivity. Organ dose is not directly measurable. However, kerma area product \( (P_{KAP}) \) can be used to estimate cancer risk. Fluoroscopy time, although available, provides an extremely imprecise indicator of either risk. Because of this limitation, potentially high radiation dose procedures should not be done using equipment that can only display fluoroscopic time.

Measuring and tracking radiation during a fluoroscopic procedure provides critical safety information to the operator. Interventional fluoroscopes conforming to the International Electrotechnical Commissions 60601–2-43 standard incorporate mandatory instrumentation to monitor \( K_{ar} \), \( P_{KAP} \), and fluoro time. All fluoroscopes sold in the United States since 2006 must at a minimum incorporate displays of \( K_{ar} \) and fluoro time. According to both standards, all available data must be displayed at the operator's working position as well as on the fluoroscope's control panel. The Joint Commission (JC) considers a skin dose of 15 Gy to be a reportable sentinel event. Facilities should be able to demonstrate their ability to detect such an occurrence during a JC survey.

**IMAGE FORMATION**

Image Contrast

An x-ray beam that totally passes through a patient or is totally absorbed by the patient carries no clinical information (Figure 2.2). Images are formed when different structures in the body absorb different amounts of radiation from the beam. The x-ray beam leaving the patient is modulated by differential absorption. It is detected and converted into a useful image by an image receptor. A structure in the patient can only be seen if its detected signal is sufficiently different from the surrounding structures. The visibility of the primary signal is degraded by scattered radiation and obscured by image noise.

The primary signal is produced by differences in x-ray absorption attributable to differences in thickness, physical density (gm/cc), or atomic number \( (Z) \) between the target

![Figure 2.2](image-url)
and its surrounds (Figure 2.3). Natural differences between structures are enhanced by the use of a contrast agent. These materials have markedly different x-ray absorption than the unenhanced target or its background. Contrast media is either mechanically delivered or biologically concentrated in the target. The contrast agents used in the catheterization laboratory (cath lab) usually contain iodine (atomic number 53). The K-shell absorption edge of iodine is 31 KeV. It is a strong absorber of x-ray photons in the range from 31 to 70 KeV. This property allows visualization of small vessels when the iodinated contrast agent displaces blood during angiography. The pharmacological effects of contrast agents are discussed later in this chapter.

The word “contrast” has several overlapping meanings in the context of interventional fluoroscopy. Subject contrast describes the modulation of the incident x-ray spectrum by the patient’s tissues and injected contrast agents. Display contrast describes the intensity range in the modulated x-ray beam between black and white on the monitor. Radiographic contrast includes both of these factors. An observer needs appropriate radiographic contrast to see clinical structures. Increasing subject contrast by adjusting the x-ray factors often increases patient dose.

X-ray production is automatically controlled by most fluoroscopes by changing factors including the voltage applied across the x-ray tube and beam filtration. For long tissue paths (due to patient size and/or beam angulation), the x-ray spectrum is displaced above the photon energy range that produces optimum visibility of iodine or steel (e.g., stents or guidewires). This produces less beam modulation and is one of the reasons why the visibility of contrast media and devices vary from view to view and from patient to patient.

Image Noise

The radiographic image of a totally uniform object has random variations in brightness from point to point and over time. These random fluctuations are called image noise. Noise reduces the ability to detect low-contrast structures. Image noise includes an avoidable component attributable to the imaging system itself (structural noise) and a second component unavoidably attributable to the physics of the x-ray beam (quantum mottle). There is a minimum of structural noise in a well-constructed and well-maintained imaging system. Quantum mottle is caused by the statistical photon nature of the x-ray beam. Fewer detected x-ray photons results in a noisier image (Figure 2.4). A higher dose image such as a single cine frame is produced using about 10 times more x-ray photons than a corresponding low-dose single fluoroscopic frame. The desire for low-noise imaging must always be balanced against its cost of increased patient exposure.
Cardiologists will substantially decrease patient (and their own) dose if they can perform procedures using noisier fluoroscopic and cine images. Increasing display contrast will increase the observer's perception of noise.

### Image Sharpness

The primary sharpness of an object in a fluoro image is affected by interactions between (a) the size of the x-ray tube's focal spot; (b) the position of the object between the x-ray tube and the image receptor; (c) the object's motion; (d) the spatial resolution properties of the image receptor. Visual sharpness is also influenced by several of the image-processing methods discussed in a later section.

The nominal x-ray tube focal spot ranges from $0.3 \times 0.3 \text{ mm}$ to over $1.0 \times 1.0 \text{ mm}$. Larger focal spots are needed for high-power imaging. The effect of focal spot size is determined by the location of the target relative to the gantry (geometric magnification) with greater loss of sharpness in the x-ray image from large focal spots at high geometric magnification. This is called geometric unsharpness or blur (Figure 2.5). Geometric magnification increases target sharpness if primary sharpness is limited by the image receptor. As discussed below, zooming an image intensifier increases its resolution and increases overall primary sharpness. However, the intrinsic resolution of most flat-panel detectors (FPDs) is not changed by zooming.

Large focal spots are commonly used in cine to handle the power needed to quickly produce a high-dose image. Figure 2.6 demonstrates the effects of focal spot size and magnification for a stationary test pattern. Coronary arteries are moving targets. Shorter x-ray pulses result in less movement blur than longer pulses. If a small focus is used to reduce geometric blur, the pulse width may be prolonged to avoid melting the x-ray target. This increases movement blur (Figure 2.7). Some fluoroscopes automatically switch the focal spot based on patient size and beam geometry. The resulting run-to-run changes in vessel sharpness might be clinically confusing if this is not known.

### Scattered Radiation

Scattered radiation is produced when the x-ray beam interacts with the patient or other objects and is redirected rather than absorbed completely. When scattered radiation reaches the image receptor, it reduces contrast by reducing primary beam modulation. Scattered radiation is the principal source of exposure of the patient's body parts outside of the direct beam. It is also the primary source of exposure of laboratory staff. The
The amount of scatter is proportional to the intensity of the x-ray beam and the size of the x-ray field (i.e., proportional to $P_{KA}$).

**OPTIMIZING PATIENT EXPOSURE AND IMAGE QUALITY**

Producing an x-ray image involves balancing many factors including image contrast (needed to detect an object), spatial and temporal sharpness (needed to characterize the object), image noise, and patient exposure. Improving performance in any of these areas usually degrades performance in one or more of the other areas. For example, fluoroscopic image noise can be reduced by either increasing the fluoroscopic dose rate or by integrating multiple fluoroscopic frames. All else being equal, an increased dose rate produces a corresponding increase in patient exposure. Integrating many frames will blur moving objects and thereby reduce their visibility. Increasing x-ray tube voltage to image through long tissue path lengths changes the x-ray spectrum and thus the visibility of iodine-filled blood vessels or guidewires. Decreasing the image receptor input dose rate reduces patient exposure but increases image noise.

Most modern fluoroscopes contain a large set of pre-programmed technique sets intended to provide an optimal balance between patient size, image quality, and patient exposure for a large number of different imaging tasks. Programming also includes image-processing and display parameters that further affect image appearance. Dozens to hundreds of these sets are initially installed when the fluoroscope is manufactured. They are often modified to meet local requirements during the installation process. In some cases, hospitals have the capability to make further persistent changes to these sets. Most fluoroscopes provide controls to modify sets for a single procedure or run. Selecting an inappropriate set, or inappropriately modifying a set, may substantially degrade image quality, increase patient dose, or both. Routinely used technique sets should be reviewed and approved by the laboratory director. The configuration of technique sets is a clinical decision that will profoundly affect all of the patients examined using that set.

**THE CINEFLUOROGRAPHIC SYSTEM**

Chest fluoroscopy has evolved since its beginnings in the 19th century (Figure 2.8). The purpose of an x-ray cinefluorographic system is to produce fluoroscopic and fluorographic optimized images of relevant anatomy at minimum patient exposure. The technical means to do this include the production of a collimated x-ray beam of appropriate quality and intensity, projection of that beam through the patient at the required angle, detection of the modulated x-ray beam after it passes through the patient, processing and storing the resultant images, and last but not least, displaying these images to the operator. The principle components needed for these tasks are illustrated in Figure 2.9.

Fluoroscopically guided interventional procedures are clinically demanding and potentially dangerous. The International Electrotechnical Commission (IEC) maintains a safety standard with minimum requirements for interventional fluoroscopes. Major fluoroscopic procedures should only be performed on well-maintained equipment that is purchased as IEC-60601-2-43 compliant and maintained at that level of safety. Equipment quality assurance is discussed later in this chapter.

**Radiation Production and Control Generators**

The cinefluorographic x-ray generator delivers controlled amounts of electrical power to the x-ray tube. One circuit selects the appropriate x-ray tube filament and heats that filament to produce an electron beam at a current ranging between 1 and 1,000 milliamperes (mA). A second circuit supplies a voltage ranging from 50 to 125 kilovolts peak (kVp) to accelerate the electrons toward the anode of the x-ray tube. X-rays are usually produced as a series of pulses. This is accomplished by electrically switching the electron beam on and off to produce the pulses.
Figure 2.8 Chest fluoroscopy at Boston City Hospital c 1898. This photo was taken within 3 years of Roentgen’s first report on x-rays. The x-ray tube on the floor and the fluoroscopic screen on the patient were used to minimize patient dose. To obtain any image visibility, fluoroscopic rooms were always very dark when fluoroscopic screens were used. The x-ray tube is connected to the electrostatic generator by exposed high-voltage tubes.

X-ray generators use large amounts of power, particularly when producing cine. Interventional fluoroscopes are usually connected to hospital emergency power and to uninterruptable power supplies (UPS). Backup power may be limited. The interventionist needs to be aware of what time and operating mode restrictions are imposed when the system is operated on emergency power (the system may have a limited available fluoroscopic time until backup energy is exhausted; cine may not be available at all.). It is not advisable to perform nonemergency cases using backup power unless this has been cleared in advance by the hospital’s technical staff.

Figure 2.9 Block diagram of a medical fluoroscope. Fluoroscopic systems consist of components needed to produce x-rays, detect the modulated beam passing through the patient, process and display images to the operator, and store images for later use. The automatic dose rate control system (ADRC) stabilizes the image-receptor signal against changes in path length in the patient. The operator can profoundly influence both patient irradiation and image appearance by changing examination sets or irradiation mode.
X-Ray Tubes

The x-ray tube is a device that converts electrical energy into x-rays. It consists of an evacuated glass or metal housing. Its key components are one or more tungsten filaments (housed in a focusing cup) and an anode disk (tungsten alloy, 100 to 200 mm in diameter), which rotates at more than 10,000 rpm (Figure 2.10 illustrates a medium power tube). Electrons are emitted from the selected filament by thermionic emission. The number of emitted electrons, and thereby the tube current (mA), is controlled by adjusting the filament temperature. These electrons are accelerated toward the anode by the electric field (50–125 kV) supplied by the generator. X-rays are produced when the electrons hit the anode.

Because of basic physical principles, less than 1% of the electrical energy applied to the tube is converted into x-rays. The remainder is deposited in the anode as heat. Too much heat delivered in too short a time will melt the focal track or the entire anode. Present tube designs include active anode cooling. Twenty years ago, tube overload often limited procedures and thereby patient dose. Today this is seldom the case. A tube heat warning occurring during a procedure is a secondary clinical indicator that substantial amounts of radiation may have been delivered to a patient.

For sharpest imaging, the point of impact of the electron beam on the anode should be as small as possible, so that x-ray emission appears to come from a single “point” focal spot. The actual size of the focal spot represents a balance between the requirements for sharp imaging and the need to avoid melting the target. X-ray tubes have two filaments and hence two focal spots. The smaller (typically 0.3–0.5 mm) is used for fluoroscopy. The larger focal spot (typically 0.8–1.0 mm) accommodates the higher power requirements of adult cine. The thermal capability of the target is increased by rotating the anode; this spreads the heating over a long focal track instead of concentrating it on a small point.

Spatial and Spectral Shaping of the X-Ray Beam

The x-ray beam contains a spectrum of photon energies. These range from the maximum determined by the peak voltage supplied by the generator (kVp) to a lower energy determined by the filters in the beam. Images are mainly formed by photons of intermediate energies. Higher energy photons strongly penetrate both tissue and iodine; this reduces contrast. Low-energy x-ray photons are easily absorbed by the patient’s tissues; they contribute to risk but not to image formation. Regulations require permanent placement of a minimum thickness of aluminum filter in the beam to absorb these nonproductive photons from the beam before they enter the patient.

Many modern fluoroscopes offer various thicknesses of copper or similar atomic-number element filters in addition to the mandatory aluminum filter. These are used in conjunction with high-powered x-ray tubes and specific generator programming to concentrate more of the x-ray beam just above the K absorption edge of iodine. In some systems, filter selection is determined by the selected operating mode. In other systems, the filter is dynamically selected by the system’s automatic dose-rate control, with thinner filters typically used for longer tissue paths.37 The appropriate use of spectral filtration increases the visibility of contrast media and guidewires while simultaneously reducing patient exposure. The availability and use of spectral shaping has been a major contributor to dose-rate reduction over the past two decades.

The extent of the x-ray beam is spatially limited so that at a maximum it is confined to the active field of view (FOV) seen by the operator. Although current regulations permit a slightly oversized field, most systems can be permanently adjusted to confine the maximum field within the FOV. Setting systems to achieve a small unilluminated margin on all four sides is strongly recommended. Loss of beam alignment is easily seen if this is done.

The size of the x-ray beam can always be reduced by the use of the collimator control. Actively confining the beam to the area of immediate clinical interest as a procedure progresses reduces both patient and staff irradiation while simultaneously improving image contrast (by limiting scatter).

Many systems also have movable semitransparent copper shutters (also called wedge filters) that can be positioned over the lung fields up to the heart border in each projection. These improve the visibility of vessels and devices as well as overall image quality by reducing excessive image brightness in the lung fields.

Imaging Modes

Dedicated cardiac fluoroscopes have two principal modes of operation: Fluoroscopy (Fluoro) and Cinefluorographic Acquisition (Cine). Multipurpose units have an additional Digital Subtraction Acquisition (DSA) mode. One of the ways
that these modes differ from each other is that a single cine frame delivers about as much dose to the patient as 10 fluoro frames; a single DSA frame delivers as much as 10 cine frames (100 fluoro frames). Figure 2.4 illustrates the differences in image appearance between fluoro and cine.

In the 1990s, systems had separate imaging channels for Fluoro, Cine, and DSA. As of this edition, most systems use the same digital imaging channel for all modes. System settings determine the irradiation and imaging parameters used for any particular run. Many systems now exploit this common imaging channel to provide retrospectively stored fluoroscopy. This “mode” allows the last 10–30 seconds of fluoroscopy to be stored as if it was a cine run. No additional radiation is needed for this purpose. Whenever possible, the use of retrospectively stored fluoro instead of cine (e.g., documenting balloon inflation during an angioplasty) can significantly reduce patient and staff exposure.

Current systems also provide digital gap-fill between individual fluoro and cine frames. Images presented to an observer above the critical flicker frequency appear continuous. Acquired images are therefore shown multiple times before being refreshed to avoid flicker. This facility is routinely provided by all digital image monitors (including desktop computers). Gap-fill is also applied when reviewing stored images (from PACS or a CD).

**Fluoroscopy**

Fluoroscopy provides a real-time x-ray image with adequate quality for observing motion and guiding device manipulations. The single fluoroscopic frame seen using Last Image Hold (LIH) (Figure 2.4) was produced using a low dose and therefore contains a great deal of noise (quantum mottle). Live fluoroscopy (or the replay of stored fluoroscopic runs) appears less noisy due to the integration of images over a few hundred milliseconds. The visibility of noise can be further reduced by the use of recursive filters in the image processor. However, physiological or digital averaging will blur the appearance of moving objects and may produce artifacts such as the doubling of the right coronary artery (RCA) at systole. The “ghost” wires seen in Figure 2.7 were produced by recursive filtering.

Current fluoroscopic systems have two or more operator-selectable fluoroscopic dose rates and often several operator-selectable frame rates. A higher dose rate provides less image noise at the expense of greater patient and operator exposure. In the United States, the regulatory maximum table-top fluoroscopic dose rate is an air kerma rate of 88 mGy/min when measured under FDA-specified conditions. Many systems have a low dose rate mode capped at 44 mGy/min. Some systems have a special fluoroscopic mode that can be used up to 176 mGy/min (such modes are required to produce an audible alert when they are active). The actual patient entrance dose rate varies from moment to moment. It is a function of the selected operating mode of the fluoroscope, system programming, tissue path length, focal spot to skin distance, and focal spot to image receptor distance. For most fluoroscopes, the maximum legal patient entrance air kerma rate can be at least twice that observed under FDA testing conditions.

At present, the most common US frame rate in adult coronary angiography is 15 frames per second (many European operators work at somewhat lower frame rates). Decreasing frame rate saves dose at the expense of visual smoothness of the transition between frames. The required dose rate scales against the square-root of the frame rate for equal visual perception of noise.

**Acquisition (Cine)**

Cine requires images of sufficient quality for single-frame viewing. Higher x-ray input dose rates are therefore needed to reduce noise and optimize clinical visualization. Most systems are calibrated such that a single “normal dose” cine frame is generated at approximately 10 times the dose needed to generate a single fluoroscopic frame. It is therefore worthwhile to remember that a minute of cine is essentially equivalent to 10 minutes of fluoroscopy.

Many current systems also provide a choice of cine dose rates. Experience has shown that the cine image quality needed for critical diagnostic studies may be excessive for some diagnostic studies and for many interventional procedures. Low dose-rate cine should be used whenever it does not reduce the clinical value of the images. Routine use of low dose-rate cine will reduce overall patient and staff dose exposure by 10% to 25%.

Because each cine frame contains sufficient information to be read by itself, eye integration cannot be relied on to reduce dose. Therefore, the cine dose rate is directly proportional to the cine frame rate.

**Digital Subtraction Angiography (DSA)**

The DSA process begins with the acquisition of a series of images of the same anatomical area. Typically, contrast media is injected during this acquisition. The first image in the series is usually used as a mask. The mask is digitally subtracted from the remaining images in the series. The remainder shows the difference between the mask and the target image (usually a faint image of contrast plus artifacts due to motion). Display contrast is increased to improve visibility. Quantum noise is not removed by the subtraction process because it is random. Thus, all of the images in the original series must be acquired at high dose to reduce their noise content. As noted above the dose needed for a single DSA frame is approximately 10 times higher than that needed for a cine frame. Because of the high dose per frame, DSA images should be acquired at the lowest clinically usable frame rate and for the shortest possible time.

**Automatic Dose Rate Control (ADRC)**

The x-ray beam is attenuated as it passes through tissue. The degree of attenuation varies with the beam's path length in tissue (patient size and beam angulation), the nature of the
tissue, and x-ray generation factors. Attenuation affects the radiation dose at the image receptor. The radiation level at the image receptor is also geometrically influenced by the source to image receptor distance. Fluoroscopic systems use ADRC to monitor the dose at the image receptor and automatically adjust x-ray production to produce the requisite receptor level. The normal function of this circuit has a profound influence on patient skin dose. X-ray intensity is increased if the detector measures too dim a signal and decreased if it measures too bright a signal. This means that the patient’s entrance port skin dose increases substantially for heavy patients and when compound projection angles are used. Increasing the tissue path length from 10 to 40 cm will increase patient’s skin dose rate by more than a factor of 10 for fluoroscopy and more than a factor of 100 for cine (Figure 2.11).

ADRC’s primary goal is to maintain the programmed image receptor dose rate irrespective of patient size. Competing goals include optimizing the visibility of iodinated contrast as well as minimizing patient irradiation. The wide variety of ADRC algorithms available to the user on most modern systems provide different trade-offs between these goals.

The ADRC can control the tube voltage (kV), tube current (mA), pulse width (expressed in milliseconds), and beam filtration. It may also influence the image processor. An improper setting can lead to suboptimum images. Different makes and models of fluoroscopes will often have different ADRC strategies. In addition, most machines offer different ADRC modes of operation. Thus, system response might be very different when the same fluoroscope is in coronary or electrophysiology (EP) mode. As a second example, when the system is set to cine coronary arteries, the ADRC remains functional throughout the entire cine run. When the same system is set to left ventricular (LV) lock, the ADRC establishes a level early in the run and then maintains that level during the contrast injection phase of the ventriculogram. Quantitative calculations can be distorted if the quantitative coronary angiography (QCA) algorithm is not aware of the details of the ADRC control strategy.

In most fluoroscopes, responding to increased tissue path length requires an increase in the kVp. This moves the x-ray spectrum away from the region of maximum iodine absorption. The primary x-ray contrast is further reduced because the same opaque vessel produces less modulation against a long tissue path than in a short path. In addition, more scattered radiation is generated in long-path situations. Some of this scatter reaches the image receptor and further degrades the visibility of vessels and devices by reducing both net beam modulation and the signal-to-noise ratio of the entire image.

### CLINICAL PROGRAMS AND PROGRAMMING

Most if not all interventional fluoroscopes are configured to perform a specific type of procedure (e.g., coronary angiography; EP mapping) by selecting a preprogrammed examination set. A multipurpose laboratory offers many dozens of such sets. Each set transforms the fluoroscope into a highly specialized imaging tool by configuring its x-ray acquisition and image display properties. An incorrect selection can result in excessive radiation use, substandard images, and other inconveniences. For example, using the low dose and frame rate EP configuration for performing PCI will seldom be successful. Conversely using the angiographic settings for EP mapping will produce very high quality images at the cost of unnecessary irradiation of patients and staff.

Users have the ability to modify some parts of the configuration (e.g., frame rate or dose rate) while the procedure is in progress. Using these controls can be advantageous if it does not distract from patient care.

### IMAGE DETECTION, PROCESSING, AND RECORDING

The x-ray image formed by the interaction of the x-ray beam and the patient must be detected and transformed into a usable format. The fluoroscopic screen was the original x-ray detector used by Roentgen. It was the only fluoroscopic...
When a specific magnification is selected, the electronics brightness gain to be viewed by the light-adapted eye, expose coronary angiography because it provided enough light to expose cine film. In the last 10 years, the image intensifier itself has been substantially replaced by solid-state detectors (commonly called flat-panel detectors (FPDs)).

The resolution of an image intensifier tube is limited by the characteristics of its output screen. In most cases, decreasing FOV (increasing zoom) increases the spatial resolution of the image intensifier tube. The downside is the additional radiation needed for small FOVs. Patient dose can be minimized by working at the largest FOV consistent with seeing clinically relevant structures. Visibility can sometimes be improved in heavy patients by increasing the FOV and collimating the beam to the region of interest. This maneuver relies on the greater gain of the larger FOV and scatter reduction due to collimation.

Image intensifiers degrade over time. Routine service adjustments can compensate for these losses for about 5 to 10 years. Eventually the end of the adjustment range is reached and additional radiation is needed to supply adequate brightness.

No film-based cine systems are currently being produced and few older systems remain in service. Interested readers are referred to the older literature for descriptions of cine cameras, analog video, and the associated optics. Almost all current image-intensifier systems use a digital CCD video camera to handle both fluoroscopy and cine. An optical diaphragm provides compensation for image intensifier degradation. More importantly, adjusting the diaphragm’s aperture provides constant brightness to the CCD while allowing different dose rates for fluoro and cine.

The structure of a single-mode image intensifier is shown in Figure 2.12. The modulated x-ray beam emerging from the patient enters the image intensifier and is detected and converted to visible light by a cesium iodide (CsI) fluorescent layer. This visible light image is converted into an electron image by a photocathode. Focusing electrodes in the tube accelerate and minify the electrons onto a small output screen. The output screen converts the electron image back into a smaller and brighter visible light image. The combination of acceleration of the electrons and minifying of the output image relative to the input image size produces enough brightness gain to be viewed by the light-adapted eye, expose cine film, or to activate a video camera.

Image intensifiers offer several magnification modes. When a specific magnification is selected, the electronics focuses a larger or smaller portion of the input screen onto the fixed-size output screen. The minifying gain of the tube (ratio of selected input screen area to fixed output screen area) decreases as the tube is zoomed. Therefore, smaller FOVs require higher input dose rates than do larger FOVs. Vascular image intensifiers remain available with FOVs exceeding 40 cm. These devices require substantially higher dose rates than cardiac image intensifiers when they are used at the typical 17 cm cardiac FOV. In addition, the larger bulk of vascular tubes limits beam angulation. Moving the image intensifier away from the patient to obtain the necessary angles further increases patient dose rate.

The imaging behavior of a flat-panel system differs from an image-intensifier system in two important respects: the optical diaphragm between the image intensifier and the video camera delivers the same light level to the camera for both fluoro and cine. Thus, the camera noise is the same for both modes. Because there is no diaphragm inside the flat panel, the electronics must use a greater degree of amplification during fluoro relative to cine. Flat panels require a somewhat higher fluoroscopic entrance dose rate to overcome patient dose. However, flat-panel systems are usually furnished as part of a new fluoroscopic system. In newer systems, better dose-management algorithms, spectral shaping, and reduced frame rates for both fluoro and cine have combined to substantially reduce the overall dose required to perform a procedure.

Figure 2.12 X-ray image intensifier. See text for discussion.

Over the past decade, the image intensifier and its video camera have been replace by integrated image receptors (FPDs). Most of these use a CsI x-ray detector that is similar in performance to the CsI found in image intensifiers. Some systems use a selenium layer to directly convert x-rays into an electron signal. Both designs generate a digital image with fewer stages than those needed for an image intensifier–video chain. Figure 2.13 schematically illustrates the structure of both FPDs.

The x-ray detection capabilities (dose efficiency) of flat-panel systems are similar to those of the latest generation of image intensifiers. The FPD by itself will not appreciably affect patient dose. However, flat-panel systems are usually furnished as part of a new fluoroscopic system. In newer systems, better dose-management algorithms, spectral shaping, and reduced frame rates for both fluoro and cine have combined to substantially reduce the overall dose required to perform a procedure.
Indirect and direct flat-panel image receptors. The indirect (left) detector uses a CsI scintillator, virtually identical to that in an image intensifier, to convert the x-ray signal into light. A photodetector converts the light into an electron signal. This signal is then digitized. The direct detector (right) uses a selenium layer to directly convert the x-ray signal into an electrical charge distribution. This signal is then digitized.

Figure 2.13

Indirect and direct flat-panel image receptors. The indirect (left) detector uses a CsI scintillator, virtually identical to that in an image intensifier, to convert the x-ray signal into light. A photodetector converts the light into an electron signal. This signal is then digitized. The direct detector (right) uses a selenium layer to directly convert the x-ray signal into an electrical charge distribution. This signal is then digitized.

Digital images are always highly processed before they are displayed. Processing techniques include gray-scale transformations (changes overall contrast level and the relative contrast of objects of different brightness), edge enhancement (improves the visibility of small high-contrast structures such as stents at the expense of increasing the visibility of noise), smoothing (reduces the effect of noise in a single frame at the expense of edge sharpness), and temporal averaging. This last function provides a time-weighted average of several image frames. This reduces noise by averaging while maintaining the sharpness of nonmoving structures. The selections of the types of image processing used in a study are among the parameters included in the preprogrammed examination set. Most fluoroscopes provide user controls (typically on the x-ray control console) that allow the interventionalist to modify some of the parameters.

The output of an image intensifier is the same size irrespective of the magnification mode. Thus, the (uncollimated) image always fills the entire digital matrix produced by the CCD camera. Each pixel represents a larger or smaller area of the input screen depending on the current magnification mode. However, the intrinsic spatial resolution of the II-CCD chain is often limited by the output screen. Thus, spatial resolution usually increases with increasing magnification because each area on the output screen represents a smaller area of the patient at higher magnification.

Most FPDs have a fixed total matrix size. In these systems, fewer pixels are used to capture the image in magnification mode. The resulting image is secondarily processed and magnified to fill the entire viewing monitor. In such systems, spatial resolution is independent of magnification mode. Some large-format FPDs have a large number of small pixels. For most magnification modes, four of these pixels are digitally averaged. Intrinsic resolution is independent of magnification in this domain. The pixels are unbundled for large magnifications (small FOVs). This increases intrinsic spatial resolution at the expense of increased dose and noise. Even when the limiting resolution is constant, digitally magnified images shown on the monitor may provide better detail coupling to the observer’s eye and can improve clinically usable resolution.

**IMAGE PROCESSING AND DISPLAY**

Digital images are always highly processed before they are displayed. Processing techniques include gray-scale transformations (changes overall contrast level and the relative contrast of objects of different brightness), edge enhancement (improves the visibility of small high-contrast structures such as stents at the expense of increasing the visibility of noise), smoothing (reduces the effect of noise in a single frame at the expense of edge sharpness), and temporal averaging. This last function provides a time-weighted average of several image frames. This reduces noise by averaging while maintaining the sharpness of nonmoving structures. The selections of the types of image processing used in a study are among the parameters included in the preprogrammed examination set. Most fluoroscopes provide user controls (typically on the x-ray control console) that allow the interventionalist to modify some of the parameters.

Interventional and other fluoroscopes have an increasingly rich array of playback and storage options. Last-image-hold is now an FDA regulation. There may also be looped replay of the last fluoroscopy run as well as the more conventional replay of cine runs. Many systems offer the ability to store the current fluoroscopy loop as if it were a cine run. This does not require irradiating the patient. Stored fluoroscopy runs will have more noise than cine runs because they were acquired with less dose per frame. When clinically possible (e.g., documenting a balloon inflation), the use of retrospectively stored fluoroscopy instead of cine is an excellent dose reduction technique.

**DIGITAL IMAGING AND COMMUNICATION IN MEDICINE (DICOM) AND PICTURE ARCHIVING AND COMMUNICATION SYSTEM (PACS)**

Within the fluoroscopic system, displayed digital cardiac images are usually formatted to a nominal 1,024 × 1,024 pixel matrix. The internal bit depth of each pixel is usually 10–12 bits (1,024–4,096 potential shades of gray). In the laboratory, these images are usually stored and displayed at full resolution. Cardiac studies are usually down-sampled and archived in a 512 × 512 × 8 bit image format. This format was specified in the 1995 DICOM standard so that most studies would fit onto a single CD-ROM disk. This standard has proven to be acceptable for most purposes over the past two decades. Higher resolution storage is available and is used for specific purposes such as “spot films.” The DICOM standard supplies details.
How big a matrix is needed? The effective spatial resolution at the patient's heart is affected by the x-ray tube's focal spot, geometric magnification, anatomical motion, and image receptor characteristics. For example, changing from a $1,024 \times 1,024$ matrix to a $512 \times 512$ matrix does not substantially change effective resolution when the large focal spot is used for cine with typical geometric magnification. Differences can be seen when the small focal spot is used with a small geometric magnification.

The number of bits defining each pixel determines the number of possible shades of grey in the image. The fluoroscope's transformation software maps the larger acquisition bit depth down to the most useful eight bits while preserving the modulation of the recorded image. The exact mapping algorithm varies from system to system. The effect of this transformation can easily be seen by reviewing a case on the fluoroscope's console while adjusting window width and window level (display contrast). Improper adjustments can result in images that are too flat for optimum viewing or very high contrast with clipping of the black, white, or both ends of the scale. A clipped image will have regions that are either totally black or totally white. No structures can be seen in clipped regions.

Historically, Cardiology and Radiology maintained separate PACS for technical reasons. Nuclear and ultrasound images were stored on still other servers. Networked access to each of these systems is common but may require different interface software. This is evolving toward integrating all forms of PACS with the Electronic Medical Record (EMR). This will provide a single access point for all images and other patient records.

One terabyte (TB) can store about 2,500 coronary artery studies using the DICOM ($512 \times 512 \times 8$ bit) format and proportionally smaller numbers at higher matrix sizes and bit depths. Digital storage devices are currently available with capacities exceeding a few TB in pocket-size portable drives to hundreds of TB in large clinical archives. The cost of large-scale storage is now only several tens of dollars per TB and is still declining. Online storage of all of a laboratory’s archives is both technically and economically achievable.

Image monitor performance can strongly affect the ability to use images clinically. Primary diagnostic workstations require periodic formal testing to assure minimum performance. If the monitors directly attached to a fluoroscope are tested as part of the laboratory’s QA program, they should be acceptable. Monitors found elsewhere in the hospital may or may not have acceptable performance and should be tested or used with care.

**THE ANGIOGRAPHIC ROOM**

The angiographic room must have sufficient space to house the fluoroscope, an increasing array of ancillary equipment (e.g., IVUS, IABP), work, and storage areas. Larger rooms can increase working efficiency while providing staff space away from tableside. A visually and acoustically isolated electronic area provides space for the numerous generator and control cabinets without distracting from procedures. Unimpeded access between the electronics area and procedure room is necessary for efficient installation and service. The control room should be large enough to accommodate working staff, physiological monitors, and an increasing number of computer workstations. Ideally, all individuals whose duties do not require them to be in the procedure room itself, should be comfortably accommodated in the control room. The scattered radiation field around the fluoroscope is complex and changes with beam angles (Figure 2.14). Whenever possible, staff required to be in the procedure room should work at a distance from the x-ray table and be positioned behind fixed or mobile x-ray shielding, unless delivering direct services to the patient.

Hybrid rooms are integrated laboratories that meet the requirements and standards of both an advanced cardiac cath lab and a state-of-the-art operating room. Careful design and equipment selection is needed to achieve a laboratory that optimally fulfills its roles as a cath lab, an operating room, and as a combined facility. Some items that need to
be considered are mechanical conflicts between permanently installed components such as the x-ray gantry and operating-room lighting; the need for additional mobile equipment during hybrid procedures; and space for two potentially large teams to work.

Room lighting must be sufficient to facilitate each of the many tasks associated with an interventional procedure. However, the lighting should not interfere with optimum viewing of the fluoroscopic and other monitors in the room. One design goal is to avoid having the operators see reflections of any of the lights in the monitors. This can be accomplished by a combination of lighting placement, light intensity, and control of monitor reflectivity. The older technique of dimming the lights when the x-ray beam is on has no impact on image visibility when reviewing stored x-ray images on the fluoroscope's monitors or while using other imaging devices.

The angiographic room requires structural and movable radiation shielding. One example: The scatter field is highly asymmetric and dependent on beam angulation (Figure 2.14). To assure optimum protection, a qualified medical physicist or health physicist will design the shielding based on the laboratory's anticipated equipment and workload, the occupancy of adjacent areas (including above and below), and local regulatory requirements. The NCRP has recently made several recommendations in this respect, including elimination of x-ray interlocks on the doors, a specific x-ray disable switch to prevent irradiation unless a procedure is in progress, additional task-specific shielding in the procedure room, and x-ray "active" indicators in the procedure room.

The centerpiece of the cardiac cath lab is the gantry that holds the x-ray tube and image receptor in correct alignment while providing a full range of two-dimensional rotation (left to right anterior oblique) and skew (cranial to caudal) of the direction with which the x-ray beam passes through the patient. The two axes of rotation meet at a single point called the isocenter. An object, such as the patient's heart, placed at isocenter will remain centered on the screen as the beam direction is changed. The patient is supported on an adjustable-height flat-top table. The tabletop can be panned in the left-right or head-foot direction to move the patient relative to the x-ray beam. Ceiling suspended gantries can be moved as well if additional panning range is needed. Some tables feature a tilt capability to put the patient into Trendelenburg or reverse Trendelenburg positions. Robotic base systems provide further extension and integration of gantry and table motions.

A second complete imaging chain is provided in some laboratories to provide simultaneous viewing from two angles. Biplane imaging is indispensable for certain patients and procedures, but is not required for most invasive cardiology procedures.

Physiological monitors and their displays are indispensable. These are increasingly integrated into the laboratory's clinical information system such that physiological data, event logs, and other information are time-stamped and recorded while the procedure is in progress (Chapter 3). Many such systems offer structured reporting enabling generation of a complete report as soon as the procedure is completed. Some of these clinical systems integrate with the patient's EMR and PACS; this facilitates immediate access to reports and images of many types.

Each piece of equipment in the laboratory must meet specific patient electrical safety requirements if there is any possibility that it could come in contact with the patient under either normal or emergency circumstances. These include non-x-ray imaging devices (e.g. ultrasound), emergency equipment (e.g. defibrillator), interventional devices (e.g. rotoblator), physiological monitors, etc.

### Imaging Equipment Quality Assurance

Imaging equipment (radiation output, image quality, and functionality) must be appropriately evaluated. Any new room requires both a radiation safety survey and an equipment acceptance test to assure compliance with regulatory requirements and conformance to the manufacturer's specifications. Commissioning tests should be done after the fluoroscope is configured to meet its local clinical requirements. Testing is also required after service activities (e.g. replacing an x-ray tube or image receptor) that might affect x-ray output or image quality. Periodic quality testing is needed to maintain quality and safety. The regulatory minimum test set is often set by regulations based on generic gastrointestinal fluoroscopy requirements; appropriate additional tests are essential to assure appropriate performance for invasive cardiology.

The video monitors that are used to view clinical images range from dedicated in-laboratory displays through desktop workstations to smartphones. Basic performance testing of all monitors is appropriate. As discussed above, any monitor used for clinical decision making (especially procedure and control-room monitors) must be included in the laboratory's quality assurance protocol.

Fluoroscopes are delivered from the manufacturer with a default array of examination sets. These are initially programmed into the fluoroscope during manufacturing and are often reconfigured at installation and during the life of the system. Laboratory personnel may make additional program changes. Reconfiguration can lead to major differences in system operation for the same nominal setting in different laboratories or even for different fluoroscopes in the same laboratory. An initial and periodic inventory and review of available settings and their frequency of clinical use should be part of the laboratory's QA program.

Safety and quality testing of the fluoroscope, along with an audit of its configuration, should be done by a qualified medical physicist (this is a regulatory requirement in some states). Testing needs to be done after installation and before first clinical use, after major repairs (e.g. replacement of an x-ray tube or image receptor), and on a periodic basis.
Radiation injuries are induced by one of two mechanisms. The \textit{stochastic} mechanism of action is triggered by unrepaired radiation damage to the DNA of even a single viable cell. In contrast, \textit{tissue reactions} are caused by radiation killing large numbers of cells (\textit{deterministic} mechanism). Radiation management differs for these two mechanisms.

### Stochastic Effects

The word \textit{stochastic} implies chance or probability. Stochastic effects are presumably induced when a single photon causes unrepaired injury to the DNA of a single viable cell. Radiogenic cancer is the principal stochastic risk in the interventional laboratory. Because clinical disease requires cellular proliferation, radiogenic cancer will take years to decades before it becomes clinically apparent.

Radiation may be the best studied of all environmental “pollutants” because it is so easy to measure.\textsuperscript{62–67} Every person is irradiated by a variety of natural and human-made sources (Figure 2.15). In the United States, the typical annual effective dose from natural background is around 3 mSv.\textsuperscript{68} The actual amount of natural background varies depending on where individuals live, housing construction, and other factors. The natural background rate in Denver is about 1 mSv per year higher than in New York City.

![Figure 2.15](image-url) **Annual per capita effective dose (E) in the United States for 2006. About 48% of the population’s dose came from medical sources. The main contributors are computed tomography, nuclear cardiology, and interventional fluoroscopy.**\textsuperscript{68}

Almost all human-made exposure (approximately 3 mSv/year in the United States) comes from medical exposure.\textsuperscript{68} Presuming that each imaging procedure is clinically justified and technically optimized, the expected clinical benefits of using radiation almost always outweigh the radiogenic risks of the procedure.\textsuperscript{7} This is not true for unnecessary procedures and may not be true for procedures performed using too much radiation. The goal is to use as little radiation to accomplish a goal as low as is reasonably achievable (ALARA).

### Radiogenic Cancer

Most dose-risk models used for radiation protection purposes predict an increase in cancer with increased procedural and lifetime dose.\textsuperscript{23,24,69} For all models, the severity of the subsequent radiogenic cancer is independent of the dose delivered to the patient by the procedure that started the process.

Epidemiological evaluation of the actual risk at background levels or those corresponding to most imaging procedures is a statistical impossibility. Low dose risks are estimated by extrapolating from the effects high-level irradiations (i.e. atomic bomb survivors) back to the low dose region. The commonly used linear non-threshold (LNT) model is an example of such an extrapolation. Other models, such as the linear-quadratic, are possible and are used to model specific cancers.\textsuperscript{63} Epidemiological validation of LNT or any other model at cath-lab dose levels (E < 100 mSv) is unlikely.

LNT is a pragmatic safety model. Using LNT, the nominal risk coefficient for fatal cancer induction in working age adults is 5% per Sv of effective dose (BEIR,\textsuperscript{63} ICRP).\textsuperscript{18} The risk is substantially higher in young children and declines over life.

Effective dose is far too imprecise to be predictive of individual patient risk. Both the NCRP and ICRP strongly recommend against any such usage. Effective dose is of value in comparing different kinds of procedures and evaluating the radiogenic risk for the entire population.

Effective dose can be used to estimate the order of magnitude of radiogenic risk. For example, a typical adult diagnostic coronary angiogram will result in a calculated \( E \) in the range from 5 to 10 mSv\textsuperscript{70–73}. The resultant cancer risk is likely to be in the order of magnitude of 0.1%. By way of comparison, a 60-year-old cancer-free male with no special risk factors has a 16% probability of being diagnosed with cancer in the next 10 years of his life.\textsuperscript{73} One can conclude that the stochastic risk of neoplasm from an adult diagnostic coronary angiogram is small in comparison with the natural incidence of cancer in the typical patient population receiving this procedure.

Radiation risk management in children is different from that for adults. Radiogenic neoplasm is related to age at exposure and is gender dependent.\textsuperscript{63} Females are more susceptible than males because of greater breast sensitivity. Additionally, because of a smaller body, a greater portion of a child’s radiosensitive tissues is in close proximity to the x-ray beam during cardiologic procedures. Fortunately, because of
small body size, pediatric dose rates and total doses are relatively low. Caution is indicated when working with almost-adult-size children as these individuals retain pediatric risk factors and are irradiated using adult-size doses.\textsuperscript{74}

**The Pregnant Patient**

Radiation risks associated with pregnancy are thoroughly reviewed elsewhere.\textsuperscript{7,75–78} At low fetal dose, the principal risk is radiation-induced cancer. The lifetime radiogenic risks induced by an in utero exposure are likely to be similar to the newborn’s radiogenic risk. Fetal dose >50 mGy place the child at risk for deterministic effects such as central nervous system damage, growth retardation, malformation, or miscarriage. The specific risks are determined by actual fetal dose and gestation age. Fetal dose in this range seldom happens unless the uterus is heavily irradiated.

Fluoroscopic procedures on pregnant women may be justifiable in an emergent situation. Procedures that involve structures above the diaphragm are unlikely to induce fetal deterministic effects if direct irradiation of the fetus is minimized. However, the fetus will still receive scattered radiation from the irradiated area. The carcinogenic risk to the child is the principal concern, and this risk must be weighed in relation to the anticipated clinical benefits to the mother. Minimizing the total use of radiation, applying good collimation, and avoiding unnecessary direct irradiation of the uterus during pregnancy contribute to minimizing fetal injury. Protective measures including avoiding extreme cranial angulations and using a radial approach reduce fetal radiation risk. A consultation with a medical physicist regarding fetal dose management prior to the procedure can be very helpful.\textsuperscript{7}

**Radiation-Induced Heritable Effects**

Genetic risk is applicable only to individuals who become future parents. Thus, the main concerns for radiation-induced genetic damage should be focused on pediatric patients and younger adults. Patient risk can be managed by reducing total patient dose while minimizing gonadal irradiation. Staff risk is reduced by most actions taken to reduce staff dose. Even though there are no epidemiologically documented effects, the nominal risk for all radiation-induced heritable effects over baseline is estimated to be about 0.5% to 1.0% per Gy of gonadal dose.\textsuperscript{23} Supporting this estimate is the failure to detect cases in the Atomic Bombing Survivor Study and in other investigations.\textsuperscript{67,79–81}

**Tissue Reactions**

**Deterministic** effects occur when a significant number of existing cells are sufficiently damaged so as to cause observable injury.\textsuperscript{10,23,26,81–89} Acute injury occurs when there is massive immediate cell killing (extremely uncommon under fluoroscopic conditions) or there is a physiological response to dose levels that may produce serious injury in the subsequent months. Skin and subcutaneous tissue injuries appear when damaged cells die off and are not adequately replaced.\textsuperscript{23} Such injuries manifest a few weeks after irradiation and may take a year or more to fully mature. The time and dose thresholds for injury and recovery are shown in Table 2.2. The boundaries between the cells in the table are vague as a reflection of clinical variability. At higher doses, microvasculature is denuded and subcutaneous necrosis can occur. Biopsies of such injuries frequently result in nonhealing tracks resulting in increased risk of infection.

The patient’s state of health may modify the normal response of skin or other organs to radiation,\textsuperscript{7,10,24,81,90} with collagen vascular disease, diabetes mellitus, and hypothyroidism making the patient more susceptible to injury. Various chemical agents and pharmaceuticals have also been associated with increased risk for skin injury.

Radiation-induced skin injury is the most common tissue reaction occurring after fluoroscopically guided cardiac procedures.\textsuperscript{10,13,91} Hair loss is usually associated with neurointerventional procedures and occasionally with dynamic CT studies. A severe skin injury obtained from the FDA web site is illustrated in Figure 2.16. Major debilitating injuries from cardiac procedures continue to occur, but are rare. Based on anecdotal reports and FDA information, in round numbers, one major injury case per month currently enters the US legal system. Unfortunately, in many of these cases, the operators were seldom aware that their radiation use caused the injuries.

Table 2.2 presumes that the entire irradiation occurred in less than a day and that the skin was not previously irradiated. Tissue will tolerate a higher total dose if the irradiation is divided over several sessions with enough time between sessions for DNA repair. In general, skin will require about 2 months to recover from a dose high enough to cause any visible injury. At least 1 month is needed for the affected cells to die and at least a second month for tissue regeneration. At higher doses, subcutaneous microvasculature is damaged and regeneration is incomplete. The injury threshold for visibly damaged skin is lower than that of pristine skin.

The skin at the site where the fluoroscopic beam enters the patient receives the largest radiation dose and is therefore at greatest risk. This usually occurs on the patient’s back because of the geometry of most interventional fluoroscopies. If the beam angles are not changed during prolonged portions of the procedure, the lesion will be a well-demarcated square or rectangle of several centimeters on a side.\textsuperscript{17} Major injuries extend into subcutaneous tissues to a depth of several centimeters and may result in radionecrosis of an underlying rib.\textsuperscript{22} The appropriate management of several major injuries was delayed because the tissue reactions were mistaken for a defibrillator or electrocautery pad mark. Such mistakes are hard to understand since most devices applied to the patient’s skin are visible on fluoroscopy and cine.

It is not uncommon to hear of major injury cases in which the operator was unaware that a substantial amount of radiation was used and that the patients were unaware of any radiation use. A dermatologist is often consulted when...
Table 2.2  Skin Injury: Local Skin Dose and Time of Onset

<table>
<thead>
<tr>
<th>Band</th>
<th>Single-Site Acute Skin-Dose Range (Gy)*</th>
<th>NCI Skin Reaction Grade†</th>
<th>Approximate Time of Onset of Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Prompt</td>
</tr>
<tr>
<td>A1</td>
<td>0–2</td>
<td>NA</td>
<td>No observable effects expected</td>
</tr>
<tr>
<td>A1</td>
<td>2–5</td>
<td>1</td>
<td>Transient erythema</td>
</tr>
<tr>
<td>B</td>
<td>5–10</td>
<td>1–2</td>
<td>Transient erythema</td>
</tr>
<tr>
<td>C</td>
<td>10–15</td>
<td>2–3</td>
<td>Transient erythema</td>
</tr>
<tr>
<td>D</td>
<td>&gt;15</td>
<td>3–4</td>
<td>Transient erythema; after very high doses, edema and acute ulceration; long term surgical intervention likely to be required</td>
</tr>
</tbody>
</table>

Note.—Applicable to normal range of patient radiosensitivities in absence of mitigating or aggravating physical or clinical factors. Data do not apply to the skin of the scalp. Dose and time bands are not rigid boundaries. Signs and symptoms are expected to appear earlier as skin dose increases. Prompt is <2 weeks; early, 2–8 weeks; midterm, 6–52 weeks; long term, >40 weeks.

*Skin dose refers to actual skin dose (including backscatter). This quantity is not the reference point air kerma described by Food and Drug Administration (21 CFR § 1020.32 [2008]) or International Electrotechnical Commission (57). Skin dosimetry is unlikely to be more accurate than ±50%. NA = not applicable.

†NCI = National Cancer Institute

†Refers to radiation-induced telangiectasia.Telangiectasia associated with area of initial moist desquamation or healing of ulceration may be present earlier.

Skin reactions of “unknown etiology” such as the radiation reactions appear a month or more after a fluoroscopic procedure. Skin biopsies are likely to be performed in the absence of a radiation history. At high dose levels, the resulting nonhealing biopsy puncture provides a path that may result in subsequent major infection of already damaged skin and subcutaneous tissue. With proper information about the possible etiology, dermatologists experienced in treating radiotherapeutic skin toxicity should be able to appropriately manage fluoroscopic injuries.

Patient Radiation Management

The amount of radiation used in a simple diagnostic study performed on an average-sized adult cardiac patient is highly unlikely to cause either a skin injury or a late cancer. Radio-
tion use increases with increasing patient size and clinical complexity. These factors may increase risks to a level of clinical significance. A population of pediatric patients is at increased stochastic risk relative to an adult population who received the same nominal effective dose.

The risk of a radiation-induced injury is only one of the hazards of invasive cardiology. Radiation use should be managed as well as the use of other hazardous materials such as drugs or contrast materials. Questions to be included in the overall and ongoing benefit-risk evaluation process include the following: How much radiation can be safely used before stopping? What are the risks to the patient attributable to staging a procedure in comparison to time mitigation of radiation and contrast use? Am I making enough progress on this patient to justify continuing? Answering these and related questions requires knowledge of the patient's clinical situation, the pathophysiology of radiation, appropriate patient consent, and information on prior or other planned irradiation. Published guidelines and formal laboratory policy should be used as key baselines for patient radiation management.

The operator has total control of the amount of radiation delivered to the patient and therefore the intensity of scattered radiation in the cath lab. For example, radiation should never be produced unless the operator's eyes are on the live x-ray monitor.

The operator is expected to reduce the amount of fluoroscopy and cine to the clinically required minimum. Equipment features, preprogrammed examination sets, and user selections provide the operator with a great deal of control over x-ray dose rates and beam sizes. This envelope usually includes settings that are inappropriately low for many clinical purposes up to those that produce radiation in excess of any clinical need. Operators should thus know the location and function of all available dose management controls on each piece of equipment that they use. These controls should be used to obtain clinically acceptable image quality with minimal patient and staff irradiation.

Because most cardiac fluoroscopes are routinely used in an automatic mode, appropriately configuring programmed examination sets when a fluoroscope is installed or upgraded is a clinical decision of great importance. The laboratory director should personally sign off on the sets to meet the laboratory's needs. The operator has the responsibility of selecting the appropriate examination set at the start of each procedure and applying modifications as needed. This is especially important for those laboratories that perform a variety of procedures (e.g., both cath and EP).

Images generated at lower dose per frame and at lower frame rates can be of lesser absolute quality but may still be sufficient for clinical needs. The appropriate use of retrospectively stored fluoroscopy in place of selected cine documentation runs is a good example of such a situation. However, too low a dose or frame rate may paradoxically increase total dose. This is because increased beam-on time is needed to allow the operator to comfortably make clinical decisions. Conversely, the routine use of cine in place of fluoroscopy yields high-quality images, often with little added clinical value. The goal is to select the lowest total dose operating conditions that meet specific procedural requirements.

Different types of imaging equipment are available in most laboratories. The operator should have sufficient knowledge of the equipment's dosimetric characteristics to select...
the most appropriate room for each procedure. For example, a laboratory equipped with a large FOV image receptor (needed for peripheral procedures) is less dose efficient at cardiac FOVs than a dedicated cardiac laboratory. Rooms offering state-of-the-art dose monitoring and dose management capabilities should be selected if the planned procedure is likely to require substantial amounts of radiation.

Imaging geometry matters. This includes both gantry configuration and placement of the gantry relative to the patient. For example, when the heart is placed in the fluoroscopy unit’s isocenter, it appears to rotate without moving as the gantry is rotated and skewed. This minimizes the need to reposition the patient when the x-ray projection angle is changed.

The best general advice is to position the table height to a level comfortable for the primary operator. This should help reduce overall patient (and staff) dose by facilitating efficiency. However, when clinically possible, it is prudent to increase the x-ray tube to patient-skin distance when the beam-port has already been highly irradiated. This step helps reduce patient entrance dose rate in this small area.

Minimizing the gap between the patient and the image receptor will reduce patient irradiation and scatter in the laboratory. This should be checked and done every time the gantry or table is moved. Some fluoroscopes have the facility to do this automatically. It is to be noted that at high source-to-image receptor distances (SIDs), fluoroscopic patient entrance dose rates can substantially exceed the nominal FDA limit of 88 mGy/min. This is legal for an interventional system based on FDA compliance testing procedures. In many systems, the maximum tabletop rate exceeds 200 mGy/min when measured using a PA projection along with minimum table height and maximum SID.

Collimating the x-ray beam within the working FOV is an important radiation management tool that is often neglected by interventionalists. Although collimation does not reduce skin dose per se, it decreases the total radiation load on the patient and facilitates beam motion without field overlap. In addition, less scatter is produced in a collimated beam in comparison to an uncollimated beam (Figure 2.17). This has two beneficial effects: image contrast is improved because less scatter reaches the image receptor; and reducing scatter production in the patient reduces scatter irradiation of the operator and staff.

As a minimum, all systems should be set up by the equipment’s service provider to have a small irradiated margin on all sides of the “fully opened beam” for all FOVs and SIDs. This assures that all of the radiation reaching the patient produces clinically useful information. Collimator shifts, visible during routine clinical procedures, should be promptly corrected.

Moving the beam should be considered when clinically practicable, especially if $K_{fs} > 3,000 \text{ mGy}$. Changing beam angulation during the procedure reduces peak skin dose provided the beam-ports do not overlap. Smaller input field sizes at the patient’s entrance skin require smaller minimum changes in beam angle to be effective. Larger changes provide a margin of safety.

Clinical Dose Monitoring

Any form of radiation used inside or outside the cath lab must be justified. To do so requires documentation of clinical appropriateness and quantitative radiological data. The operator has sole control of the amount of radiation administered during a fluoroscopic procedure. Tracking radiation use while a procedure is in progress is therefore the operator’s responsibility. This is of increasing importance at dose levels where skin injuries are possible.

Intraprocedural radiation monitoring is a necessary tool to help the operator avoid unintentional skin injuries. The hope of a widely available real-time map of the dose distribution on the patient’s skin is coming but has not yet been achieved. At present, reference point air kerma ($K_{rpa}$) is the best available metric for managing skin injury, while $P_{stt}$ is the metric for estimating late cancer risk. Most, if not all, interventional fluoroscopes currently in service are required to measure $K_{rpa}$, $P_{stt}$, or both. Both the FDA and the IEC require the data to be displayed at the operator’s working position.

For interventional fluoroscopes, $K_{rpa}$ is defined at a point on the beam axis 15 cm from isocenter toward the x-ray tube. Depending on table height and patient size, this point is seldom exactly on the patient’s skin and may be either inside or outside the patient. Furthermore, the reference point moves with the gantry as the beam is rotated or skewed. For these reasons, $K_{rpa}$ is not a precise measurement of skin dose. It tracks well enough for clinical use to serve until accurate real-time...
skin dose maps are available. The laboratory's medical physicist should be consulted for further information on this topic.

Unfortunately, many laboratories continue to rely on fluoroscopic time as a primary dose measure. Fluoro time is a poor predictor of radiogenic risk because it does not account for the effects of patient size and beam orientation, cine usage, and other factors. As shown in Figure 2.18, there is an order of magnitude range of $K_{d}$ at almost any fluoro time.

Similar noncoronary plots have an almost two order of magnitude span due to both the wide range in tissue thicknesses in different procedures and the relative use of fluoroscopy versus acquisition in such procedures.

It is recommended to have the physiological monitoring person (or another designated individual) track radiation and remind the operator when preset milestones are passed. A positive response from the operator acknowledging this information is expected. These reminders are simply another way to facilitate the inclusion of radiation use into the operator's ongoing benefit-risk assessment.

Postprocedural documentation of radiation should be as universal a requirement as is documentation of drug and contrast medium use. All available dose metrics should be documented in the procedure report and medical record. This should be done automatically where possible or manually when necessary. Radiation documentation is among the operator's responsibilities. For substantial-dose procedures, an immediate postprocedural note documenting and justifying radiation use provides important information for the quality process.

Including radiation reviews in the laboratory's continuous quality improvement (CQI) program is always important for patient safety as well as increasingly becoming accredita-

![Fluoroscopic time is a poor predictor of dose. The plot illustrates the relationship between fluoro time and clinical dose. For most fluoro times, there is an order of magnitude range of different clinical doses (arrow).](image)

**Figure 2.18** Fluoroscopic time is a poor predictor of dose. The plot illustrates the relationship between fluoro time and clinical dose. For most fluoro times, there is an order of magnitude range of different clinical doses (arrow).

**Staged and Multiple Procedures**

Staging a procedure allows time for DNA repair and tissue regeneration. A few months are required for skin and subcutaneous tissue regeneration to complete at skin doses above a few Gy. The required time interval increases with increasing skin dose. In addition, increasing skin dose results in losses of the local microvasculature and other forms of incomplete repair. Previous skin dose, time between stages, and beam angles need to be carefully considered when planning a follow-on intervention.

Patients who have previously undergone fluoroscopically guided procedures or radiation therapy may have a lower threshold for radiation injury in subsequent procedures. Extreme caution is needed when reirradiating a known radiogenic skin injury. By definition, repair is incomplete in an active injury. Substantial reirradiation of such regions can be catastrophic. Chronic skin changes are also associated with multiple procedures irradiating the same portion of the patient's skin.

Radiogenic cancer may also be a consideration: decreases in radiosensitivity with age and the years to decades between irradiation and clinical cancer can be important. In addition, the LNT model states that an individual's radiogenic cancer risk depends on the total effective dose (E) accumulated over a lifetime. However, according to the LNT model, the carcinogenic risk of a procedure is independent of the patient's past radiation history. Thus, the anticipated radiation use in a planned procedure is the quantity of importance for use for preprocedure benefit-risk assessment.

**Patient Education, Consent, and Follow-up**

The possibility of late radiogenic cancer or skin injury should be appropriately included in the informed consent process. The informed consent process should be enhanced for a patient who is at increased risk for one or more reasons. Radiogenic cancer is the primary risk for small (<50 Kg) pediatric patients. Skin injury is a risk for patients who are expected to undergo a particularly long and complex procedure, have had multiple recent procedures, have received or are scheduled to receive radiotherapy to the chest, or who are extremely obese (>150 Kg).

Appropriate postprocedure patient education and a follow-up plan are necessary for all patients where a substantial amount of radiation was used. The basics are informing
the patient that radiation was used and to have his or her
back examined by a family member approximately 2 and
4 weeks after the procedure. The laboratory is to be called if
a red area “the size of a hand” is seen. Any reported reaction
should be presumed to be radiogenic until proven otherwise.
The patient should be instructed to avoid abrading or other­
wise damaging the affected skin. They should also tell other
health-care providers that the lesion is of possible radiogenic
etiology. The operator is responsible for follow-up for a year
after the procedure.7 Patients with suspected radiation inju­
ries should be seen in the operator’s clinic for evaluation and
referral if necessary.

**Staff Radiation Safety**

Staff radiation safety differs from patient radiation safety.7
Patients have the expectation of a direct health benefit from
their irradiation. Irradiation of staff is one of the risks of the
job. Providers have a social obligation to provide care even
if there is some risk.9,10 Nevertheless, available protective
measures reduce all forms of radiogenic risks to low levels.
Other occupational hazards in the cath lab such as infection,
muscular-skeletal damage, etc., are also of concern.101,102

**Staff Tissue Reaction**

Staff skin injury should never happen in an interventional
setting. Nevertheless, there are reports of hair loss on the legs
of interventional cardiologists (below the lead apron) after
many years of practice.9 There are also reports of chronic skin
changes and basal cell carcinoma in practitioners,8,103 Unnece­
ssary hand irradiation is often seen in the interventional car­
diology laboratory; this is particularly disturbing when it is
recorded on cine.

There has been a great deal of evidence collected in the
past few years documenting radiation-induced opacities in
the eyes of interventionalists and support staff.104–106 Based on
this evidence, the ICRP has recommended reducing the dose
limit for the eyes from 150 mSv/y to 20 mSv/y. The new rec­
ommended limit can be exceeded by a busy interventionalist
who does not use supplemental eye protection. Appropriate
protective measures are discussed below.

**Staff Cancer Risk**

Cancer induction is a topic of real concern to staff members.
Multiple studies of radiation workers of all types, including
interventional cardiologists, over the last 30 years have pro­
duced only anecdotal reports with no confirmed evidence of
increased cancer mortality in these populations.7,107–111 Nev­
evertheless, interventional staff members are clearly exposed to
radiation in the course of their duties, and the LNT model
predicts a small increased risk.

Staff stochastic risk can be estimated using effective
dose actually received by a staff member. This should be an
appropriately calculated value and not the raw reading from a
film badge worn outside the lead apron.7,112 The most highly
irradiated operators in a properly functioning interventional
laboratory probably receive an effective dose of a few mSv/
year. Most laboratory staff receive < 1 mSv/year. By way of
comparison, the natural background radiation level in Den­
ver exceeds that in New York City by about 1 mSv/year.

**Basic Principles of Reducing Staff Radiation Exposure**

Operators can use several methods to reduce their exposure
to radiation.1,7,9,113 One important factor under the oper­
or’s control is reducing patient dose—the ultimate source of
exposure of the operator and staff. Reducing fluoro and cine
time is an obvious dose reduction measure. This and other
patient dose reduction methods have already been discussed.

Increasing distance from the x-ray beam is the sec­
ond major radiation-reduction tool. When hand injection
is required, the operator must be close to the patient. This
may not be as necessary when using a power injector. Lean­
ing over the patient to get a better view of the monitor dur­
ing cine brings the operator very close to the beam. Standing
upright, or when possible taking a step back will significantly
reduce operator dose. Staff has greater freedom of movement
than operators. They should be as far from the table as prac­
ticable while the beam is on unless their immediate duties
require them to be closer.

The use of appropriate radiation shielding is the third key
factor. This includes structural shielding, tableside shielding,
and personal protective clothing. Cath-lab walls, doors, and
windows are well shielded in compliance with regulatory
requirements. Simply not being unnecessarily in the proce­
dure room is a major dose reduction measure.

Tableside protective drapes, pull-down eye shields, and
roll-around shields provide substantial radiation protection
without placing a physical burden on the worker. All of these
should be used to the greatest practicable extent.

A large variety of radioprotective garments are available.
These come in a wide variety of styles. Wraparound one-piece
or two-piece styles are preferred in the cath lab so that the
wearer is still protected when facing away from the table. The
attenuator is lead and/or other high atomic number materi­
als. Attenuation is usually stated in terms of lead equivalence
with 0.5 mm being typical in the United States. High lead­
equivalent garments are heavy and often impose hazardous
class skeletal loads.101,102 The wearer needs to balance
radiogenic against orthopedic risks when selecting appropriate
gear. Safely reducing radiation protection weight requires data
from long-term personal monitoring and a consultation with
the qualified physicist responsible for the laboratory.

Finally, the increasing concern regarding radiogenic cata­
ract is reflected by the ICRP’s proposal to reduce the annual
dose limit to the eyes from 150 to 20 mSv. Busy intervention­
alis will exceed this level without proper eye protection.5
Ideally, this is a combination of pull-down shields and radioprotective eyewear. Monitoring of one’s eye dose is essential.

Situational awareness is an often unstated fourth component of radiation protection. Two examples: (1) Staff need to know when radiation is being produced. Fluoroscopes with last-image-hold and looped-replay give few clues in this regard. A “beam-on” light is integrated into many fluoroscopes. Auxiliary warning lights should be installed if these are absent. (2) Oftentimes, the nurse is asked to attend to the patient’s needs during a procedure. These duties can occur in a potentially high radiation zone, and the operator should refrain from irradiating when staff is close to the patient. The nurse is also expected to tell the operator when it is safe to resume x-ray.

Beam angulation influences the scatter field near the operator.\textsuperscript{114} This is particularly important during shots such as the left lateral or left anterior oblique cranial projections, which place the operator in close proximity to the beam entry point. As shown in Figure 2.14, in the lateral position, there is an order of magnitude more scatter on the x-ray tube side of the patient relative to the image receptor side.

**Staff Radiation Monitoring**

At present, interventional cardiology cannot be practiced without operator irradiation. Readings above or below an individual’s expected value should be investigated.\textsuperscript{7} The investigation of unusual monitoring data often suggests simple corrective actions that reduce risk. Experience has shown that it is highly unlikely that any individual working in the cath lab and taking standard radiation precautions will approach a dose level of regulatory concern.

Radiation monitors are individually assigned and are to be worn whenever that individual is in a radiation environment. Wearing monitors when you are a patient or in other nonoccupational situations can give incorrect results. Practices such as leaving a lead apron in the laboratory with its laboratory always monitor his or her own exposure using “radiation badges”.\textsuperscript{1,7} In addition to this being a legal requirement, routine monitoring is an indispensable tool for managing and minimizing operators’ risk.

**INTRAVASCULAR CONTRAST AGENTS**

Shortly after publication of the classic papers by Roentgen in the 1890s, the search began for effective and nontoxic contrast agents to define vascular anatomy. Early experimentation involved a number of heavy metals (bismuth, barium, thorium), which unfortunately proved to be extremely toxic. The development of iodinated contrast agents has led to the major advancements in x-ray–based imaging that have characterized the past century.

**Iodinated Contrast Agents**

Modern contrast agents are based on iodine, which by virtue of its high atomic number and chemical versatility has proved to be an excellent agent for intravascular opacification. Inorganic iodine (sodium iodide), however, causes marked toxic reactions. Experiments in 1929 thus explored an organic iodide preparation (Selectan) that contained one iodine atom per benzoic acid ring. In the 1950s, a series of substituted triiodobenzoic acid derivatives were developed, which contain three iodine atoms per ring. These agents differ from each other in terms of the specific side chains used in positions 1, 3, and 5 (Figure 2.19), influencing both solubility and toxicity.

Ratio-1.5 ionic compounds are substituted ionic triiodobenzoic acid derivatives that contain three atoms of iodine for every two ions (that is, the substituted benzoic acid ring and the accompanying cation). Included in this family of high-osmolar contrast agents are agents such as Renografin (Bracco), Hypaque (Nycomed), and Angiovisit (Berlex), which are mixtures of the meglumine and sodium salts of diatrizoic acid. Functionally similar agents are based on iothalamic acid (Conray [Mallinckrodt]) or metrizoic acid (Isoopaque). These agents have a sodium concentration roughly equal to blood, pH titrated between 6.0 and 7.0, and a low concentration (0.1 to 0.2 mg/mL) of calcium disodium EDTA. Higher or lower sodium concentrations may contribute to ventricular arrhythmias during coronary injection, and calcium binding by sodium citrate may cause greater myocardial depression. To have an iodine concentration of 320 to 370 mg I/mL, as
Figure 2.19

Sample structures and properties of current available contrast agents. The traditional high-osmolar ionic contrast media (OCM or ratio 1.5) are Na+/meglumine salts of substituted triiodobenzoic acid, which have three iodine atoms per anion/cation pair, with six times the osmolality of blood. Two types of low-osmolality contrast media (LOCM or ratio 3) are also shown: the true nonionic agents and the Na+/meglumine salt of an ionic dimer, which have three iodine atoms per nonionic molecule or six iodine atoms per anion/cation pair, with an osmolality two to three times that of blood. The newest class of isoosmolar contrast medium (IOCM or ratio 6) is a nonionic dimer with six iodine atoms per molecule and an osmolality equal to that of blood. Also included are the iodine contents (in mg I/mL), the osmolality (Osm, in mOsm/kg-H_2O), and the viscosity at 37°C. *Mixed sodium and meglumine salt; see text for details.

is required for LV and coronary contrast injection, solutions of these agents are markedly hypertonic (with an osmolality >1,500 mOsm/kg, roughly six times that of blood).

In the mid-1980s, the first ratio-3 lower-osmolality contrast materials (LOCM) were introduced. Although it is still ionic (as a mixture of meglumine and sodium salts), ioxaglate (Hexabrix [Mallinckrodt]) is a ratio-3 agent by virtue of its unique dimeric structure that includes six molecules of iodine on the dimeric ring (three atoms of iodine for every one ion). To achieve an iodine concentration of 320 mg I/mL, ioxaglate has an osmolality roughly twice that of blood and contributes to a lower incidence of undesirable side effects related to hypertonicity.115

A more significant modification in the late 1980s, however, was the introduction of true nonionic ratio-3 contrast agents. These low-osmolality contrast agents are water-soluble in a noncharged form, without an associated cation. Examples include iopamidol (Isovue [Bracco]), iohexol (Omnipaque [Nycomed]), metrizamide (Amipaque, [Winthrop]), ioversol (Optiray [Mallinckrodt]), and ioxilan (Oxilan [Cook]), each containing three atoms of iodine for every molecule.116 With calcium disodium EDTA as a stabilizer and tromethamine (1.2 to 3.6 mg/mL) as a buffer, an iodine content of 320 to 370 mg I/mL can be achieved with an osmolality of 600 to 700 mOsm/kg, between two and three times that of blood. Their viscosity (which influences ease of injection through small-lumen catheters) is roughly 6 to 10 times that of water.

In the late 1990s, a ratio-6 nonionic dimeric compound (iodixanol, Visipaque [Nycomed]) was released as an isoosmolar contrast agent. This agent requires the addition of sodium and calcium chloride to bring its osmolality up to that of blood (290 mOsm/kg).117

In summary, available contrast media can be classified as high osmolar (1,500–2,000 mOsm/kg), low osmolar (600–1,000 mOsm/kg), and isoosmolar (290 mOsm/kg). There is extensive evidence that low-osmolar and isoosmolar contrast media are better tolerated by patients undergoing coronary and peripheral angiography when compared to high-osmolar
contrast media. They produce fewer episodes of bradycardia and hypotension, precipitate less angina, and cause less nausea and sensation of heat than traditional high-osmolar contrast agents.\textsuperscript{118,119} There is also evidence that the non-ionic ratio-3 and ratio-6 agents produce fewer allergic side effects\textsuperscript{120} and are less nephrotoxic in human studies.\textsuperscript{121,122} For all of these reasons, coronary and vascular angiography is now routinely performed with low-osmolar contrast agents.

Whether isoosmolar contrast media provide an additional advantage when compared to low-osmolar contrast media in the prevention of contrast-induced nephropathy (CIN) remains controversial.\textsuperscript{133,134} Randomized clinical trials and metaanalysis have shown a benefit of the isoosmolar agent iodixanol when compared with iohexol and ioxaglate, but no benefit when compared with iopamidol, ioversol, or iopromide.\textsuperscript{124} It has been suggested that in addition to the osmolality, the viscosity of the contrast agent might play a role in the development of CIN, with a higher viscosity associated with a higher risk. The effect of viscosity might explain some of the differences observed among low-osmolar contrast agents. A detailed description of the prevention and management of adverse reactions to contrast agents is provided in Chapter 4.

### Gadolinium

Gadolinium is a rare earth metal that has paramagnetic properties. These properties allow movement of the metal ions within a magnetic field. In its salt form, gadolinium is very toxic. However, through a process of chelation by which large molecules create a complex surrounding gadolinium ions, less toxic gadolinium compounds have been developed and are currently used for magnetic resonance (MR) imaging.\textsuperscript{125} The use of gadolinium in contrast-enhanced magnetic resonance angiography (MRA) of the aorta and of peripheral arteries is described in Chapter 19.

Due to the risk of CIN with the use of iodinated contrast agents in patients with chronic renal failure, there was initial enthusiasm in the development of gadolinium-enhanced coronary angiography in this patient population.\textsuperscript{126} However, more recent studies have shown that gadolinium does not seem to provide added benefit when compared to iodinated contrast agents in the prevention of CIN in high-risk patients.\textsuperscript{137,138} In addition, there have been several reports on the development of a rare systemic fibrosing disease, nephrogenic systemic fibrosis (NSF), in patients with chronic renal failure receiving gadolinium contrast agents.\textsuperscript{129,130} The relationship between NSF, chronic renal failure, and gadolinium administration appears to be more than just an association, given its relatively high frequency in patients with chronic renal failure who receive gadolinium (as high as 4%).\textsuperscript{129,130} The identification of gadolinium deposits in tissue of patients who develop NSF further corroborates this hypothesis.\textsuperscript{131–134} Therefore, the current recommendation is to avoid the use of gadolinium in patients with advanced renal failure (GFR < 30 ml/min/1.73 m\textsuperscript{2}), in patients on dialysis, and in patients with hepatorenal syndrome.\textsuperscript{135,136}

### Carbon Dioxide

Following the introduction of iodinated media, the search for even less toxic contrast agents has continued incessantly. Carbon dioxide (CO\textsubscript{2}) gas was initially used in the 1950s as a contrast agent for the diagnosis of pericardial effusions. The development of digital subtraction angiography has expanded the use of CO\textsubscript{2} and as of today CO\textsubscript{2} angiography has emerged as an alternative approach that provides the advantage of virtually no risk of allergic reactions or renal toxicity.\textsuperscript{137,138} It is currently used for angiography of several vascular arterial and venous beds and to guide endovascular interventions. The evolution of CO\textsubscript{2} delivery systems has simplified the application of CO\textsubscript{2} to angiography, although familiarity with the technique and preparation of the system is critical to minimize the risk of air contamination, or the accumulation of CO\textsubscript{2} bubbles that can lead to embolism or occlusion of small vessels. Given an association of CO\textsubscript{2} angiography with a risk of cerebral, coronary, and spinal artery embolization, its use has been limited to vascular beds below the diaphragm.

### FUTURE DIRECTIONS

As described in the next chapter (Chapter 3), the cardiac catheterization laboratory is evolving toward the new paradigm of the multimodality imaging suite, which integrates imaging from CT, 2D and 3D echocardiography, MR, and other imaging and mapping systems. Within this evolving paradigm, the use of x-ray imaging, fluoroscopy, and radiographic contrast agents remains a mainstay for diagnostic and therapeutic cardiovascular interventions. Thus, a thorough understanding of appropriate and safe use of x-ray equipment and contrast agents will continue to be part of the basic knowledge required from interventional cardiovascular specialists.

### REFERENCES


Cardiac catheterization is undergoing a major change that involves the emergence of a multitude of new therapeutic interventions.¹ This revolution is the result of the development of two critical technologies and the skills to use them. The first technology includes the therapeutic devices, often accompanied by novel delivery systems, and the second technology is the medical imaging that allows the use of therapeutic devices.² The subject of this chapter is the new cardiac catheterization imaging paradigm, which includes new imaging modalities and their integration into the cardiac catheterization laboratory. The paradigm shift can also be described by a movement to three-dimensional (3D) imaging complementing (and in the future possibly replacing) two-dimensional (2D) imaging formats.

Cardiac catheterization is intensely image guided. It is useful to first consider what this means, how image guidance initially evolved, and how the emergence of new interventions is having a profound impact on image guidance technologies. Unlike surgeons who use their eyes to directly observe cardiac and vascular structures during a traditional open heart operation, proceduralists cannot see or locate their catheters and guide where they are going without the visualization provided by medical imaging. Rather, the proceduralist views a monitor that displays a medical image. The image is an abstraction of the reality that is defined by direct observation and by specific visual skills that allow recognition of the key objects. There are many specific nuances that must be learned by the proceduralist. The early success of cardiac catheterization was made possible by the development of this unique visual skill set, the creation of catheters for diagnostic and therapeutic uses, and the development of high-quality fluoroscopy and cineangiography.

**LIMITATIONS OF TRADITIONAL IMAGING SYSTEMS**

Fluoroscopy is a real-time imaging modality; the proceduralist activates the x-ray system with the foot pedal and is able to immediately see the instantaneous movement of catheters, assuming they are manufactured with materials that are radiopaque. The format of the resultant image is one of the limitations of fluoroscopic imaging; the image is abstract and not inherently a complete anatomic image. This flat 2D projection is analogous to a “shadow image” but with a broader range of gray scales proportional to the variable penetration of x-rays. Years of experience and technology refinements have made fluoroscopy the workhorse modality of the cardiac catheterization laboratory.

In response to the inability to appreciate depth in the x-ray image, the cardiac catheterization imaging system was developed to allow the proceduralist to easily change the imaging perspective by altering the gantry position. Other imaging aids were developed such as road mapping using angiographic images. In addition, diagnostic and therapeutic procedures such as percutaneous coronary intervention (PCI) extensively use a system for catheter advancement called the “over-the-wire” technique. This technique is used as an alternative to the difficulty and potential danger associated with unassisted advancement of catheters in the 3D branching vascular beds both leading to the heart but also within the coronary tree.³ The over-the-wire technique converts this 3D pathway to the target into a 2D-like linear rail needed to complete the intervention using the simplicity, familiarity, and other virtues of only traditional fluoroscopy. Furthermore, relatively small amounts of contrast can be intermittently injected to visualize the small
tubular vascular structures during the final placement of therapeutic devices such as coronary stents.\textsuperscript{4,5}

In prior editions of leading textbooks in cardiac catheterization the imaging material was limited to x-ray imaging and its use for diagnostic and therapeutic catheterization involving coronary and other vascular beds. The development of new interventions often targeting dynamic soft tissue and requiring new imaging modalities for navigation in large cardiac chambers has changed the educational and training needs.\textsuperscript{6} The over-the-wire technique and exclusive use of fluoroscopy, while still used, are limited by the challenges of initial navigation in open 3D space within chambers, particularly when aiming at targets such as a mitral perivalvular leak. In addition, with the evolution of PCI and other cardiac interventions it has become clear that the imaging needs to guide cardiovascular therapies are often different from the imaging needs of diagnostic procedures. It is important to understand these differences when considering and selecting new imaging modalities (Table 3.1).

**EVOLUTION OF CARDIAC IMAGING IN THE CARDIAC CATHETERIZATION SUITE**

The purpose of medical imaging during a therapeutic cardiac catheterization is to enable the efficient, safe, and effective performance of the sequential tasks needed for the specific intervention. The choice of imaging is dictated by the task to be performed. Each imaging modality has unique features and the same modality might have different versions.\textsuperscript{7,8} The performance of tasks as part of an intervention requires real-time imaging, of which there are only two types: fluoroscopy and ultrasound (Figure 3.1). Table 3.2 provides a comparison of these two modalities as an additional overview to understand the emergence of new approaches in the cardiac catheterization laboratory.

The development of interventions for the broad family of structural heart disease (SHDs) has occurred in concert with the emergence and integration of additional imaging modalities and new aspects of x-ray imaging. The nature of these new interventions is covered in other chapters. The new imaging modalities presented in this chapter are relevant to all three domains of interventional techniques, that is, coronary, vascular, and SHD.\textsuperscript{7,9}

As seen with the evolution of intravascular ultrasound or intracoronary imaging, the key to the efficient use of new technology is its integration into the cardiac catheterization laboratory infrastructure.\textsuperscript{10} There are multiple levels of integration including image acquisition, processing, display, and archiving. The commercially available products that incorporate these needs for integration are rapidly evolving. All this adds the new complexity of choosing the cardiac catheterization system that provides multimodality imaging appropriate for the anticipated types of procedures that will be performed in the room.

<table>
<thead>
<tr>
<th>Table 3.1 Major Differences Between Cardiac Imaging for Dedicated Diagnostic Purposes Versus Image Guidance of Therapeutic Procedures</th>
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<td><strong>Dedicated Diagnostic Medical Imaging</strong></td>
</tr>
<tr>
<td>Comprehensive with image sets for visualization and other derived parameters needed to assess structures and function</td>
</tr>
<tr>
<td>Standardized protocols for image acquisition with predetermined list of views with minor ad hoc changes in imaging views</td>
</tr>
<tr>
<td>Image acquisition and interpretation often completed separately</td>
</tr>
<tr>
<td>Outcome: a report with diagnostic value</td>
</tr>
<tr>
<td>Assessment of value of diagnostic imaging modality: evaluation using hierarchical fashion and leading to appropriateness criteria</td>
</tr>
<tr>
<td>Imaging modality use determined by diagnostic and patient considerations</td>
</tr>
<tr>
<td>Physician skill set related to modality and experience in its diagnostic use</td>
</tr>
</tbody>
</table>
**Imaging Workstation and Display Systems**

The imaging workstation, often with table-side controls, is one addition to the cardiac catheterization facility required by multimodality imaging. Image processing of fluoroscopic and angiographic images has become part of the internal workings of modern x-ray systems but imaging processing involving 3D volumetric image formats, segmentation, and multimodality image fusion with registration requires the imaging workstation. Direct digital links to the computed tomography angiography (CTA) and magnetic resonance angiography (MRA) hospital archival system are needed to enable the intraprocedure use of previously acquired images in patients undergoing an intervention.

The emergence of multimodality imaging has changed the requirement standards of display systems. Monitors must
## Table 3.2 Overview of Real-Time Imaging Modalities to Guide the Performance of Diagnostic and Interventional Tasks in The Cardiac Catheterization Laboratory

<table>
<thead>
<tr>
<th>Specific variables</th>
<th>Fluoroscopy</th>
<th>Ultrasound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Field of view (FOV)</td>
<td>Variable and includes large field that can include whole heart and surrounding structures</td>
<td>Variable but upper limit of multiple cardiac chambers</td>
</tr>
<tr>
<td>System for acquisition</td>
<td>Limited to gantry. Either with one or two gantries (i.e., single versus biplane)</td>
<td>Transducer-based diversity of probes including external application to skin, transesophageal, and intracardiac</td>
</tr>
<tr>
<td>Operator</td>
<td>Interventionalist</td>
<td>Sometimes interventionalist but TEE requires echocardiographers (both physician and sonographer)</td>
</tr>
<tr>
<td>Experience with guidance of interventions</td>
<td>Extensive and well established over decades</td>
<td>Growing over last decade</td>
</tr>
<tr>
<td>Integration of technology in cardiac catheterization laboratory</td>
<td>Complete</td>
<td>Incomplete</td>
</tr>
<tr>
<td>Safety</td>
<td>Radiation-related risks</td>
<td>Probe-related risks</td>
</tr>
<tr>
<td>Strengths and weaknesses in visualization:</td>
<td>1) Excellent</td>
<td>1) Limited</td>
</tr>
<tr>
<td>1) Current generation of intravascular equipment and devices</td>
<td>2) Excellent</td>
<td>2) Limited to access point</td>
</tr>
<tr>
<td>2) Navigation in vascular pathway to heart</td>
<td>3) Excellent for simple tasks but fair to good even with contrast injection for complex tasks</td>
<td>3) Excellent</td>
</tr>
<tr>
<td>3) Navigation in cardiac chamber</td>
<td>4) Poor and limited to intermittent contrast visualization</td>
<td>4) Excellent with caveat that high level of expertise required</td>
</tr>
<tr>
<td>4) Navigation and interaction with soft-tissue targets such as native valves and chamber defects</td>
<td>5) Excellent with contrast injection</td>
<td>5) Poor and nonexistent for active guidance</td>
</tr>
<tr>
<td>5) Navigation and interaction with coronary target</td>
<td>6) Excellent with contrast injection</td>
<td>6) Limited</td>
</tr>
<tr>
<td>6) Navigation and interaction with other vascular targets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Real-time 3D visualization and create views of target/anatomy that are independent of location of image acquisition system</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Future adaptability to robotic guidance systems and holographic display</td>
<td>Limited without fusion with 3D images from another modality</td>
<td>Yes</td>
</tr>
</tbody>
</table>

not only be able to show gray scales but also the color used to represent “depth” in 3D ultrasound images. Initially, the monitor bank was expanded with dedicated monitors for different image-based information. More recently the large single screen technology has emerged. This technology provides maximal flexibility in displaying images and other information needed during the procedure. The potential of displaying medical images in a holographic format is a new exciting development that may be initially tested in the cardiac catheterization environment and studied for its impact on the performance of interventions optimally performed with 3D visualization.

### Development of New Skill Sets

The skill sets of the proceduralist as well as the nature of the team performing these new procedures are evolving as rapidly as the technology. Specifically, the interventional cardiologist in the past was proficient predominantly in using fluoroscopy and performing angiography. The interventional cardiologist of today and of the future must be proficient not only in these older techniques, but also in CTA, MRA, ultrasounds, and potentially Optical coherence tomography (OCT) technology, and in their use for preplanning and for the actual performance of interventions. This evolution has also led to an
expansion of the team of physicians and staff. With complex SHD interventions it has become essential that a colleague expert in ultrasound, including 3D transesophageal echocardiography (TEE), be part of the interventional team.

## Value Assessment

The additional cost associated with new modalities should be evaluated against the clinical benefit and their face validity. Often the claims made by the commercial vendor are limited to technology performance rather than clinical value. The development of appropriateness criteria for diagnostic cardiovascular imaging has been based on determining whether the incremental information exceeds the expected negative consequences of performing the study. This methodology does not fit with the decision-making process used to determine if an imaging guidance modality is appropriate. Appropriateness of the procedure is the issue and some form(s) of image guidance is a necessity. Therefore, the value of a new imaging modality is often based on its utility and value relative to an alternative modality or as adjunctive image guidance. In the setting of cardiac catheterization, the comparison is typically with fluoroscopy and in other settings the comparison may be between different forms of ultrasound guidance or ultrasound versus CTA images used for fluoroscopic overlay. Examples of comparisons of different imaging guidance strategies are listed in Table 3.3.

The value of a new imaging modality for the cardiac catheterization laboratory should be determined in a fashion similar to that used for diagnostic imaging, although with a few key differences. The hierarchy of value that has been developed for diagnostic imaging includes technical aspects of imaging performance, impact on diagnostic, prognostic, and therapeutic thinking and strategies, clinical outcomes, cost effectiveness, and patient satisfaction. Table 3.4 summarizes factors that we believe are important in the evaluation of an image guidance modality. Technical performance is routinely evaluated. Single-center studies are sometimes conducted measuring ease of use and intermediate markers of clinical outcomes. Occasional randomized trials are conducted comparing different imaging approaches. Yet, new technologies are difficult to evaluate due to several factors. First, they must be studied on a procedure-specific basis to assess outcomes. Second, the number of patients studied may need to be large in order to show an impact on infrequent events such as major complications. Third, the relative contribution of the imaging modality on clinical outcomes may be difficult to differentiate from the relative contribution of other determinants, that is, the image guidance modality is part of a complex procedure where experience, patient selection, device performance, and other variables are important. Finally, the approval process for new image guidance technology by governmental regulatory agencies is often based on technical performance and general safety issues rather than on improved patient outcomes. Thus, pivotal randomized trials measuring clinical endpoints are generally not performed.

The acquisition of new image guidance technologies for the cardiac catheterization laboratory is associated with the additional need to monitor and improve quality. The measurement of the quality of cardiovascular imaging has been modality specific and frequently has involved laboratory certification from specific professional organizations and more general hospital accreditation by government agencies. The emergence of cardiac catheterization laboratories with multimodality imaging will not only likely lead to more complex accreditation issues, but also has the opportunity to promote the development and consolidation of performance metrics and best practices for different modalities.

### NEW IMAGING MODALITIES

A decade of technical advances has established the feasibility of percutaneous strategies to treat SHD such as atrial septal defect (ASD), patent foramen ovale, as well as regurgitant

### Table 3.3 Examples of Study Designs to Determine Relative Merits of Different Image Guidance Strategies

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Image Guidance Modality Comparison</th>
<th>Outcome Metrics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary angiography</td>
<td>Rotational versus conventional angiography (multiple fixed gantry positions)</td>
<td>Radiation exposure, contrast volume, time to completion, image content</td>
</tr>
<tr>
<td>Transcatheter atrial septal defect and patent foramen ovale closure</td>
<td>Intracardiac echocardiography versus transesophageal echocardiography</td>
<td>Successful closure, complications, fluoroscopy time, procedure time, need for general anesthesia, patient satisfaction</td>
</tr>
</tbody>
</table>
or stenotic cardiac valves\textsuperscript{18-21} utilizing the emergence of supportive image guidance. As more structural interventions are adopted, proceduralists are required to become adept at utilizing imaging technology that not only identifies vascular lumen or gross anatomy, but also images soft-tissue and adjacent structures. Future structural interventions hinge on the integration of imaging to navigate cardiac chambers, target different structures, and deploy a variety of therapeutic devices. Current methods such as x-ray fluoroscopy, 2D echocardiography, 3D echocardiography (3DE), cardiac MR, and cardiac CT have developed independently and merged into important adjuncts that enable the execution of complex structural interventions.\textsuperscript{8,22-25} In general, there are common elements to the process of executing structural interventions; however, individual procedures emphasize particular elements. The common elements include preprocedural planning, targeting, detection/positioning and tracking, mechanical biofeedback/eye-hand coordination, precise repositioning and alignment, navigation, 3D localization, deployment surveillance, and postprocedure inspection (Figure 3.2). These functions are discussed further in subsequent parts of the chapter and in the case-specific tasks.

### Echocardiography

Complex cardiac interventions occur in a dynamic and anatomically intense 3D environment requiring accurate characterization of structure and function. Ultrasound image generation is dependent upon either transmission or reflection of propagated sound waves and the return frequencies characteristically produced by different tissues. The frequencies used in medical imaging are tuned to both the target tissues and the depth needing to be imaged. These ultrasound images provide the anatomic landscape for interventional procedures. However, the interaction of highly reflective devices such as a “J” wire causes reverberation or signal dropout that must be mentally integrated with tissue effects when attempting to understand the anatomic landscape.\textsuperscript{7,24,26} Conversely, some catheters or wires such as a “glidewire” demonstrate very little ultrasound signature, thus making visibility almost impossible. Understanding the ultrasound characteristic of catheters, wires, and devices and their interaction within the anatomic landscape is critical for guidance of complex interventional procedures.

Traditionally, 2D TEE and intracardiac echocardiography (ICE) have assisted such interventions.\textsuperscript{27,28} 2D TEE is capable of measuring structural defects, guiding navigation of catheters, and monitoring the delivery of devices. The safety and effectiveness of 2D TEE are well established in ASD/ventricular septal defect (VSD) device sizing, equipment navigation, device deployment, and assessment of postprocedural complications such as thrombus formation.\textsuperscript{29,30} Complementary use of echocardiography with x-ray imaging results in reduced radiation exposure when ultrasound guidance for navigation is performed in combination with an effort to reduce fluoroscopy. Despite these advantages, 2D TEE still requires mental integration of multiple imaging planes on the fly when tracking objects that are often in and out of plane.\textsuperscript{31,32} This is especially true when catheters, wires, and devices are variably echogenic. In ASDs for example, defect rims are not reliably imaged within one viewing plane possibly resulting in sizing errors and increasing the risk of device embolization if the incorrect device is deployed.\textsuperscript{33} This is equally true when assessing valvular structures, and when evaluating placement of devices near coronary arteries and their relationship to the annulus of the aortic valve and planes of orientation. Imaging of near structures such as inferior vena cava or pulmonary veins may be inadequate to assess safe navigation or structural obstruction. The advantage of enhanced guidance is balanced by the risk of long interventions that require general anesthesia.\textsuperscript{7}

Development of 3DE has been slow but is now universally available with most vendors marketing 3D packages, and in some cases is acquired using a single cardiac beat. Processing is much

### Table 3.4 Assessment of Image Guidance Technology

<table>
<thead>
<tr>
<th>Technological Assessment</th>
<th>Accuracy, image quality, reliability, graphic user interface, integration into cardiac catheterization laboratory, integration into image archiving system.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scope of Use</td>
<td>General or niche applications, specific diagnostic and therapeutic procedures for which technology is appropriate (proven or expected).</td>
</tr>
<tr>
<td>Competency and Training</td>
<td>Relevance to board certification or hospital credentialing, learning curve, additional personnel needed with specific skill sets.</td>
</tr>
<tr>
<td>Impact on Patient Outcomes</td>
<td>Mortality, frequency, and outcomes of complications, successful versus unsuccessful procedures.</td>
</tr>
<tr>
<td>System, Cost, and Reimbursement</td>
<td>Infrastructure and other support availability for new modality, direct costs, capital costs, other infrastructural issues, personnel time.</td>
</tr>
</tbody>
</table>
more user-friendly compared to prior platforms. Real-time 3D transthoracic echocardiography (RT3D TTE) has been clinically implemented to improve endomyocardial biopsy accuracy and off-pump mitral valve (MV) edge-to-edge repair in a pig model. This was expanded to successful percutaneous ASD closure. The development of real-time 3D imaging with both transthoracic (3D TTE) and transesophageal echocardiography (3D TEE) integrates moving structures with definition of depth in wide field of views providing superior structure resolution. This allows definition of cardiac defects, chambers, and valves while directly and simultaneously monitoring movements of interventional devices.

Real-time 3DE obtained from the TEE probe has improved resolution of the atria, vena cava, and valves. The first available RT3D TEE probe was released utilizing a matrix phase-array transducer (X7-2t, Philips, Andover, MA) that instantaneously acquires a 3D pyramidal dataset. Four different types of datasets may be acquired using this probe: complete volume gated dataset, real-time operator-focused 3D dataset, real-time zoomed 3D dataset, and simultaneous biplane adjustable 2D dataset (Figure 3.3). Volume rendering and perspective are accomplished through color shading of the volume, thereby creating a sense of depth, but precise distances are not well validated within real-time 3D acquisitions.

Complete volume data gated acquisition takes advantage of the RT3D TEE’s wide field of view (FOV) by scanning and integrating a volumetric echosector, thereby displaying...
moving cardiac structures. This is a summation of four adjacent wedge-shaped volumetric datasets acquired sequentially over four cardiac cycles, with subsequent fusion into a single large echosector (Figure 3.3C). The dataset may be viewed offline in operator-defined cropped planes in any axis and orientation, offering several visual vantage points ideal for preprocedural planning.

Real-time 3D images may be acquired via two modes: (1) larger field of view (FOV) with focused thickness (Figure 3.3B) volume that segments heart valves, complex defects, masses, and might allow visualization of the right ventricle (RV); (2) a high magnification mode, which acquires images using an obtuse view angle and a limited sector region of interest with less depth (Figure 3.3A). The wider FOV and greater perspective are ideal for navigating catheters and interventional devices, while the thin sector 3D is better for determining edges of ASDs or leaflet insertion in valve clip procedure. Both volumetric datasets may be rotated or tilted to define desired structures and can be viewed in cropped planes of any axis and orientation. However, a systematic approach to movement of the volume is critical to avoid anatomic confusion. Thus, one could first tilt the image to gain a top view from which rotation like a clock can occur and then move toward key structures like the aortic valve positioned at 12 o’clock to provide standard perspectives such as the “surgeon’s view” of the left atrium (LA). These methods provide the advantage of online manipulation of the dataset, performed from different viewing angles or perspectives without probe repositioning or causing associated workflow interruptions.

While not a volumetric imaging mode, “X-plane” displays adjustable biplane images simultaneously. This unique feature allows operator’s definition of orthogonal specific views without movement of the probe or transducer (Figure 3.3D). The 2D orthogonal view method provides improved fine spatial and temporal resolution, acquired at a higher frame rate than those typically obtained employing 3D imaging. Biplane imaging also has the capability of color flow Doppler imaging that provides more precise 3D localization jets than standard 2D imaging for ASDs or regurgitant valvular lesions.

Volumetric rendered imaging enables visualization of cardiac structures and their relationship with catheters and devices simultaneously, providing eye-hand coordination for steering tasks required in SHD interventions.

**Intracardiac Echocardiography**

ICE provides superior image quality due to its close proximity to the structures from the right atrial position. It obviates the need for general anesthesia and is capable of guiding navigation of catheters and devices, visualizing adjacent structures and sizing defects. Currently, the evidence supports ICE as the modality of choice in percutaneous ASD closure. However, ICE has fewer imaging planes than 2D TEE and may interfere with guiding procedures performed from the right side of the heart. A potential issue with ICE includes cost and associated risks of venous access. To date ICE also does not have 3D imaging available for guidance of complex procedures.
Rotational Angiography

X-ray fluoroscopy is the cornerstone imaging modality in interventional laboratories. Primarily used for angiography, X-ray is also used to navigate catheters and deploy devices. The planar nature of x-ray imaging visualizes insufficiently soft tissue and requires operators to mentally reconstruct cardiac structures. The development of flat panel detectors has blurred the difference between true x-ray imaging and tomographic technologies. Full 3D data such as coronary vascular trees are extracted from the entire volume to evaluate angulation, foreshortening, and motion from a single coronary tree acquisition. A modality called C-arm CT uses rotation with segmented or continuous acquisition and simulates CT imaging. Using advanced gated 180° circular flat panel rotation in combination with contrast injection, whole heart CT-like image can be obtained. This provides large anatomic structure and muscle volume rendering adequate for execution of complex structural interventions. The future holds promise for definition of soft tissue structures and their relationship to adjacent structures.

Computed Tomography Angiography

New interventional devices require manipulation in confined spaces and simultaneous resolution of fine cardiac structures. Fine resolution of cardiac structures requires two key factors: (1) absolute resolution of the imaging system and (2) the ability to effectively stop cardiac motion. Computed tomography (CT) is a 360° map of x-ray attenuation. This map is then converted into intensity values ranging from −300 air to −100 fat, 0 fluid, and +300 calcium. Injection of contrast materials high in iodine content (in combination with CT) allows visualization of chambers and vessels. The advent of faster gantry rotation speeds and increased numbers of detectors and dual sources have improved both spatial and temporal resolution thereby allowing application of multislice CT scanners in SHD.

Implementation of both multiphase contrast injectors and high-concentration contrast agents (Iovue 370 mg/mL) has dramatically improved the image quality, a necessary requirement for delineation of fine structures (i.e., atrial baffles, perivalvular leaks, and origin of the great vessels). Imaging of delicate structure for SHD interventions requires at a minimum 64-row detector systems. Cardiac structure visualization may be enhanced with new 256 or 320 row CT systems that allow data acquisition within 1 to 4 heart beats. Standard 64-row detector or greater CT scanners usually have gantry rotation times of less than 420 ms and operate at multiple tube voltages of 80, 100, and 120 kVp and tube current upward of 800 mAs. CTA image resolution is still based on lowering heart rate (approximately 60 BPM) to obtain the greatest image quality and simultaneously allow the lowest radiation exposure. Dual detector (2 head/tube) systems expand the heart rate range while maintaining high-quality images. Cardiac motion is least prominent during end systole and mid to late diastole making electrocardiographic gating a requirement of any cardiac CT exam. The use of oral or intravenous beta blockers slows the heart rate, thereby limiting cardiac motion and subsequently improving image quality.

High flow rate and multiphase contrast injections allow high-quality images by minimizing contrast artifacts and providing high-contrast differential chamber delineations. Delivery of a dense-contrast bolus that opacifies the cardiac chambers while at the same time prevents beam-hardening artifact in the venous system requires power injection of contrast with adequate washout by saline chaser injection. Creating a contrast concentration gradient between structures or chambers is important for the accurate evaluation of anatomic targets whether this is an ASD or a perivalvular leak. In a typical cardiac exam using a 64-slice scanner, approximately 75 mL of iodinated contrast (Iopamidol—Isovue—370 mg/mL) is injected in the right antecubital vein at 5 mL/second followed by a 30 to 50 mL saline chase also delivered at 3 to 4 mL/second. These methods provide differential chamber contrast concentration necessary for identification of the shunts (Figure 3.4), as well as delineation of fine structures and 3D special relationships often required for preprocedural planning in SHD.

Information regarding the potential right to left direction of ASD shunting can be determined by performing a dynamic contrast-enhanced cardiac exam. Funabashi et al., were able to demonstrate shunt directionality in VSD, ASD, and PDA by comparing the density of right and left chambers. Furthermore, the orientation of a contrast jet on dynamic contrasted cardiac CT can be helpful in the differentiation of secundum ASD from patent foramen, and in shunt visualization of ischemic VSDs, perivalvular leak, or other complex congenital heart disease (CHD) (Figure 3.5).

Optimal acquisition protocols are critical for SHD evaluations. Reducing radiation exposure with the CT component is critical especially when planning complex interventional procedures which have their own dose costs. ECG phase dose modulation or prospectively gated “Step and Shoot” sequential axial imaging technologies provide standard dose reduction strategies. Yet the dynamic nature of cardiac structures often requires assessment throughout the cardiac cycle. Consideration of patient size is also required to properly tailor tube current and voltage to deliver to the patient the minimum radiation dose needed for image acquisition. This is particularly important in young individuals who, because of their disease, have often been subjected to multiple procedures using ionizing radiation.

Successful percutaneous correction of SHD requires a thorough clinical evaluation and comprehensive preprocedure imaging, detailing the structural abnormality. Initial evaluation in most cases is performed by TTE and TEE. However, in the case of large ASDs, for example, the presence or more importantly the absence of an inferior rim may not be completely assessed by TEE. High-resolution multiplanar CTA provides orthogonal thin plane views necessary to identify this problematic anatomy throughout the cardiac
Chapter 3 Integrated Imaging Modalities in the Cardiac Catheterization Laboratory

A large secundum ASD is shown employing CT angiography. Orthogonal views (A, B, C) define the size of the ASD with volumetric 3D display in the lower right image (D). Note the lack of inferior rim, a finding that defines a likely unsuccessful percutaneous closure of the ASD.

Postprocessing of the CTA dataset is important to select those images that will yield the least cardiac motion. Typically, axial datasets are reconstructed retrospectively from 0% to 90% of the R-R interval at between 0.8 to 1.0 mm slice thickness with 50% slice overlap (0.8/0.4, 1.0/0.5 or for noisier data 2/1 mm). Depending upon the presence of metal and the attenuation artifacts from metal the smoothing image data kernel may be set at a smooth or sharp characteristic. Often the sharpest kernel (for CTA images) is required for assessment of perivalvular leaks where adjacent prosthetic valve with sewing ring creates significant artifacts that if not addressed can obscure the target perivalvular leak. The need for nonstandard planes is especially true for pathologic states such as aortic pseudoaneurysm or perivalvular leaks. However, understanding the true adjacency of structures requires 3D volumetric reconstructions. While not as quantitative, they provide the SHD interventionalist with a visual model of the size and orientation of the abnormality (Figure 3.6). This type of view rotation and eye-hand visualization can be extended in a technique called rapid prototyping or 3D modeling using a 3D graphic printer to construct a physical model of key anatomy. To attain this level of image representation and reconstruction, proper initial processing of CTA basic data is required with the addition of image segmentation fine tuning by a clinically knowledgeable individual. The concept of targeting and interventional path planning can be visualized even using actual catheters or devices and can provide crucial information for successful interventions such as transcatheter aortic valve replacement (TAVR).

The characteristics of interventions for SHD are determined by the anatomic variations and technologic limitations
Figure 3.5 CTA images of an infaroseptal ventricular septal defect (arrows) are shown. Note the contrast gradient between the right and left ventricles shown in short-axis (panel A) and horizontal long axis (panel B) projection.

Figure 3.6 Preprocedural planning for aortic valve disease is shown. The top panels are a 3D rapid prototype model characterizing the effect of balloon dilation on aortic valve leaflets. These models are constructed from CT angiograms with CT on the left and aortic valve model at end systole shown on the right. The images are almost identical.
of the proposed procedure. As shown in Figure 3.7, advanced cardiac imaging provides a valuable resource of heart and vessel-specific information to evaluate exclusion characteristics, preprocedure sizing of devices, procedural risk assessment, and possible subsequent complications. This requires a cooperative effort between the imaging specialist who understands the major issues of a specific procedure and the interventionalist who can visualize the procedure and then evaluate the image data. It is the responsibility of the imaging specialist to display the data in a meaningful method to allow the interventionalist to assess the anatomy and characteristic of the intervention.47 Additionally, CTA data may be imported into the catheterization fluoroscopic display system, providing confirmatory soft tissue anatomic structure in similar projections to those obtained by the fluoroscopic x-ray system. The use of these preprocedural imaging methods can improve the safety and possibly shorten the time of interventions for SHD.21,52

**Magnetic Resonance Imaging and Angiography**

Cardiac MR (CMR) imaging is a valuable technique employed to evaluate patients with SHD. The key characteristic of CMR is the stimulation of tissue protons which in turn provides radiofrequency energy specific to different tissue types, thus creating independent tissue signatures that do not require contrast administration. Using these characteristics, cardiac structure, tissue signature, and flow can be determined by

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**Figure 3.7** Diagrammatic processing of an ASD is shown. The CTA preplanning is shown with centerline defining a potential pathway from the inferior vena cava through the defect into the left atrium. 3D images are shown in the center with a rapid prototype model testing different ASD closure delivery catheters on the right.
this technique. CMR routinely includes four major pulse sequence types used in the routine assessment of cardiovascular patients.\textsuperscript{46,47} They can be categorized as bright-blood cine sequence; dark-blood T2-weighted sequence; phase-contrast sequence; and MRA. Cardiac gating is generally necessary to stop cardiac motion and reduce image blurring that normally results from cardiac motion. Usually CMR acquisition employs breath holding to also remove respiratory motion. Adults usually hold their breath voluntarily, but this is more difficult in adolescents and children.

Cardiac function and quantification of volumes and ejection fraction are performed using a bright-blood cine steady-state free precession (SSFP) sequence that produces a series of images, which are played as a composite movie loop averaged over multiple cardiac cycles (cinematic display). Cine images are acquired in standard cardiac axes allowing determination of structural anatomy and physiologic motion.

Dark-blood sequence on the other hand produces images only at a single cardiac phase with bright soft-tissue structures (myocardium and vessel walls), but dark-blood signals inside ventricles and vessel lumen again employing a breath holding technique. Dark-blood images are used to evaluate morphology, tissue characteristic, and connections of the cardiovascular structures. Adding a third inversion pulse provides enhanced proton signal that helps distinguish fluid or edema from fat or tissue.

Phase-contrast sequences generate quantitative velocity mapping similar to Doppler echocardiography. This method is useful for quantifying regurgitant volumes and \( \text{Qp/Qs} \) calculations for perivalvular leaks and shunt pathologies. Phase-contrast sequences for CHD are used to quantify flow and pressure gradient estimated from velocity by the Bernoulli equation. Total flow is calculated by summing velocity across the aortic valve (MV) orifice. Thus with each change of perspective, the segment is selected MR vendors often have preset image render the 2D image into a 3D format. Since CMR has less signal to noise ratio than CTA, these presets are often too stringent for these images and require individual manipulation. Despite this minor limitation of MRA images, similar image quality is provided to those of CTA once adjusted correctly.

**COMPARATIVE ANALYSIS OF ANATOMIC STRUCTURE AND FUNCTION**

**Fluoroscopy/Angiography Versus Echocardiography**

Successful structural interventions begin with preprocedural evaluation of the operating environment, the interventional objective, and its surrounding structures. Comprehensive assessment by 3DE is achieved by analysis of specific cropped planes derived from the complete volume dataset. An example of preprocedural planning and guidance is defined in percutaneous MV repair for valvular regurgitation. Appropriate patient selection is defined by criterion that deployment of a clip is able to reach below A2-P2 segments of the MV. Fluoroscopic evaluation of the valve is not possible with current technology, especially in real time. This procedure also begins with identifying a targeted site for the interatrial transseptal puncture that ensures the delivery guidewire sheath exits with sufficient distance to direct the clip delivery system toward the MV, and extend below the valve.\textsuperscript{49} Placement of a standard Brockenbrough needle and Mullins sheath requires coordination of fluoroscopic positioning and tactile feel as the needle is dragged across internal structures. Unfortunately, abnormal physiology results in rotation and distortion of these structures, secondary atrial enlargement, and displacement of the fossa ovalis often occurs in MV disease.\textsuperscript{37} Pathological states may create unpredictable anatomic variation at the least, and inappropriate placement of the crucial septal puncture may render clipping impossible. Therefore accurate anatomic characterization by RT3D TEE can improve case selection, navigational planning, device selection, and the ability to anticipate complications.\textsuperscript{48} Spatially orienting and localizing targets for interventions is enhanced with RT3D TEE. With 2D modalities, targets could only be visualized in a single plane and centering a target required multiple imaging planes. Targeted volumetric imaging can center target structures and simultaneously monitor catheters and guidewires. Orientation of catheters in 3D space is unpredictable and constantly changes during repositioning and change of echo views. Thus with each change of perspective,
mechanical biofeedback correlation must be performed to assess the catheter or device response to operator manipulation. Visual feedback enables the operator to be reoriented to the external inputs corresponding to moving the delivery system anterior-superior and medial-lateral relative to the MV with a single view rather than using multiple 2D interrogations.

The main advantage of RT3D TEE is safe navigation by monitoring the spatial relationships between catheters and devices, the interventional objective (e.g., A2-P2 segment), and adjacent vital structures (e.g., chordae) simultaneously. The navigation path and targeted volume imaging can ensure clearance of nearby structures. Precise 3D localization is essential to the proper deployment of the mitral clip.57

**Fluoroscopy/Angiography Versus Volumetric Computed Tomography or Magnetic Resonance Imaging**

High-resolution multiplanar CTA or MRA may be required to help identify problematic anatomy.48 Obviously, spatial resolution is key, as also definition of the structure throughout the cardiac cycle in addition to display at the correct orientation to identify the correct structure. The 3D nature of both CMR angiography and CTA allows reorientation and specific cut planes to display 3D structures with the volumetric reconstruction. Definition of the perspective often in off-axis views allows resolution of detailed anatomy not usually visualized in standard cardiac orientations. This is especially true for pathologic states such as ASDs best viewed from the posterior LA or an aortic pseudoaneurysm viewed from the right lateral oblique position. Use of 3D display methods is less standardized and often requires imager interface to display the structure in a meaningful way.4,6,58 Intensity inversion threshold methods are often required to view structures within the chambers. This method codes the contrast dark allowing tissue (gray structures) to stand out from the contrast in the chambers.

**Figure 3.8** An MRA of an ascending aortic pseudoaneurysm (arrows) is shown before (left) and after (right) percutaneous closure with an Amplatzer device. The extent of the pseudoaneurysm is noted with complete closure after device deployment.
Section I General Principles

(MDCT) and MRI of anatomic structures changes the paradigm. The volumetric 3D nature of these images potentially can be used for both planning and execution of invasive procedures that typically involve a therapeutic intervention (Figure 3.9). Such volumetric datasets are imported into the angiographic suite and displayed either adjacent to the fluoroscopic images or as a true image overlay coregistered with the x-ray image. Before the tracking process is initiated, the 3D multimodality-based dataset needs to be registered with the patient's location and orientation on the table during the intervention. Navigation systems linked to interventions must have accurate, perfectly registered datasets that compensate for cardiac and respiratory motion to correlate with the patient's physical condition. The 3D CT or MR volumetric overlay provides tissue characterization of major structures coupled with catheter or guidewire manipulation and guidance that track C-arm rotation and movement. As part of the preprocedural planning centerlines can be imported as well-defining pathways for successful completion of the SHD intervention (Figure 3.10). With only a single cardiac phase depiction, the model sheds light about the size, orientation, and adjacencies around the target point. Addition of cinematic motion of these images often allows significantly improved visualization of such abnormal structures, but currently this is technically challenging. Use of these preprocedural imaging methods hopefully improves the safety and possibly shortens the time of SHD interventions.

Display of images for SHD is one of the most crucial factors in successful completion of a procedure in a safe and timely manner. Factors such as size, perspective, smoothing, color scheme, shading, and brightness play key roles. 2D images are best visualized in a linear gray scale that defines

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**Figure 3.9** Diagrammatic characterization of the process for a perivalvular leak closure is shown. Similar steps are performed with corresponding CTA images used for planning shown in the cutouts. This process defines the pathway for intervention and best views for visualization.
Preprocedural planning is shown for a perivalvular leak. The centerline is drawn planning the pathway from the IVC through the interatrial septum to the lateral mitral perivalvular leak. Note the overlay of the centerline into the fluoroscopic image with aortic calcification shown in red. The guidewire through the orifice is shown by fluoroscopy and follows the previously planned route and trajectory.

Critical structures and is able to track interventional devices. Generally, most commercially available packages generate high-quality images. However, display of 3D TEE images is exponentially more difficult. Currently, three major factors need to be addressed for optimal guidance: (1) focus on the anatomic structure of interest; (2) adjustment of the volume with depth necessary to accomplish the goal; and (3) definition of the best perspective to guide device placement and target visualization.\textsuperscript{39-61}

RT3D TEE imaging is the technical leader in advance guidance of complex interventional procedures. Target structures are usually centered within biplane orthogonal image before proceeding to the zoom mode. The perception of depth is created by portraying light surface color and deep structure as dark colors. Crisp 2D TEE images are required to start with minimum gain necessary to define a homogeneous target structure. Next, appropriate standardized display of common structures allows orientation of the operator. Perspective is a key element that requires identification of the target and a view that provides clear visualization of motion. This guidance view should also show critical structures that should be avoided or maneuvered around. The advantage of RT3D TEE is 3D imaging during cardiac contraction and structural motion. The direct visualization of catheter or device movement that is coupled to manipulation of these devices allows enhanced eye-hand coordination to guide tasks. The learning curve is shortened when clear visualization of movement is linked to physical target motion within the image.\textsuperscript{7,28,61}

3D volumetric imaging is also useful for procedural guidance. Despite these data being only one cardiac phase, the enhanced soft tissue visualization helps define target pathway of structural orientation in comparison to the x-ray image.
Prediction of best projections to identify the target or position catheters is a clear advantage of this technology. This coupled with real-time guidance allows closure of potentially difficult structural defect not previously attainable.99

Physical display of these complex data is often not routine and requires matching of multiple key parameters including absolute resolution, update rate, scan line rate (Hz), output algorithm, and color or gray scale density 32 versus 64 bit.

Even connector types and angiographic system output can be problematic when attempting to display images on standard display monitors. Matching and switching interface boxes are often required to match data signal outputs to the display inputs. Large flat screen high-resolution monitors allow display of multiple inputs simultaneously providing the interventionalist with hemodynamic, RT3D-TEE, fluoroscopic, and potentially CT or MR data, all in interpretable large enough size to identify key factors simultaneously.10,12

**MODALITY SELECTION**

The knowledge and comfort level of proceduralists need to grow when viewing methods that provide target identification, integration of multiple data sources, and image modalities necessary for specific tasks. Assimilation of these tasks into a comprehensive preplanning process and actual procedure is a key part of safe completion of SHD interventions. How proceduralists select the best technology to assist in the interventional procedure is the question.

Advanced cardiac imaging techniques are usually performed after a screening echocardiogram. Selection of the appropriate imaging modality is not only probably related most to the type of SHD problem to be addressed, but may also be determined by availability and local expertise. The decision for selection of the optimal imaging modality should be based on consideration of the absolute spatial resolution, temporal resolution, field of view, and characterization of different tissue types. Either CT or CMR provide extended FOV compared to echocardiography.9 This characteristic is important for pathway planning in the preprocedural evaluation process. CTA possesses inherently greater absolute resolution between 0.4 to 0.6 mm, but is at a cost of lower temporal resolution even when large doses of beta blockers are used to lower the heart rate and improve nonmotion imaging. CMR in general can be performed at most physiologic heart rates without heart rate lowering medications28,37 and provides similar angiographic imaging but without ionizing radiation dose. These are usually only one cardiac phase and acquired at separate times, thus limiting the real-time use for active procedural guidance. 3D TEE clearly provides the best real-time imaging methodology for SHD guidance. Given its excellent spatial and temporal resolution, it is currently the most useful technique to navigate delivery of interventional devices. Development of technology in this field is rapid and dynamic but currently ultrasound provides the most versatile guidance method. Careful consideration to all factors is required to determine both the short-term benefits (i.e., procedural success) and long-term risks (i.e., future cancer) associated with each technology CTA, fluoroscopy, CMR, or RT3D TEE prior to inclusion.

**REAL-TIME THREE-DIMENSIONAL VISUALIZATION: TWO DIMENSIONAL TO THREE DIMENSIONAL**

**Three-Dimensional Fluoroscopy and Coregistration of Computed Tomography Imaging**

Advanced cardiovascular imaging modalities supplement the information that is obtained from either echocardiography or invasive coronary angiography. Cardiovascular CT imaging in the preprocedural planning of complex SHDI has the potential to streamline the intervention, reducing extensive diagnostic angiography and its concomitant radiation and contrast risks. Combined CT coregister data and fluoroscopy can be used to directly guide SHD interventions for pulmonary vascular complex problems. Cardiac phases that most clearly depicted the pulmonary artery (PA) are used to segment cardiac chambers and cardiac vessels. Centerline segmentation algorithms are used to project and identify the expected trajectory through the interventional target in the pulmonary artery. Three-dimensional centerline simulated trajectories can be imported into the catheterization lab and coregistered to fluoroscopic images from a single cardiac phase CT image dataset. CT image data are projected into similar fluoroscopic views to define optimal viewing projections. The same viewing plane as in the catheterization laboratory C-arm and overlaid onto live fluoroscopy can be used to identify positions of initiation and procedure guidance. Target recanalization or dilation followed by device deployment can be determined on the fly when superimposed onto contrast angiographic images (Figure 3.11). Importantly, planning of orientation and best angiographic views are performed well in advance of the interventional procedure. This provides trajectory lines on which a 3D workstation may be imported into the catheterization suite and provide tissue characterization without contrast. Such preprocedure planning may have the potential to reduce total intravenous contrast load, as well as procedure time. SHD interventions can thereby be facilitated by such novel guidance.8,45

**Real-Time Three-Dimensional Echocardiography**

Spatially orienting and localizing targets for interventions is enhanced with RT3D TEE. With 2D modalities, targets can only be visualized in a single plane and centering a target
requires multiple imaging planes. Targeted volumetric imaging can center defects and simultaneously monitor catheters and guidewires. Catheters and devices have complex interactions with their environment and external manipulation due to the strain of physically interacting with a tortuous course from vasculature to the heart and the mechanical properties of the catheter. Orientation of these catheters in 3D space is difficult to predict and constantly changes during repositioning when using 2D echocardiographic views. RT3D TEE, however, allows changing perspective on the fly providing visual bio-feedback correlation that must be performed for mechanical eye-hand coordination to assess catheter or device response to operator manipulation. Visual feedback enables the operator to be reoriented to the external inputs corresponding to moving the delivery system. However, the echocardiographer defines the views and perspective rather than the interventionalist necessary for guiding percutaneous procedures. RT3D TEE views also do not directly correspond to those obtained by x-ray image. This requires cognitive interpolation of the two datasets. New imaging technologies are being developed to synchronize the x-ray and RT3D TEE images and to allow the interventionalist autonomy to define the perspective best suited for the SHD intervention. A prototype of an integrated echocardiographic and fluoroscopic imaging system for interventional use has been developed that registers images of the TEE probe with the x-ray C-arm integrated 3D TEE and fluoroscopic images (Figure 3.12). The technology provides images in multiple 3D views simultaneously with table-side control by the interventionalist. Mental reconstruction errors and incorrect assumptions in catheter repositioning under separate displays may delay guidance or cause incorrect positioning. Such new 3D volumetric guidance technologies may overcome obstacles with standard 3D imaging by improving direct visual feedback. The specific impact of novel features such as x-ray-echo registration, multiple 3D perspectives, and the proceduralist’s control of TEE-derived images is evolving. The impact on the safety and successful performance of simple to complex tasks in different types of SHD interventions is yet to be comprehensively tested.

In the following section we describe case studies that illustrate the integration and clinical applications of the technologies and concepts described above.
Simultaneous fusion of RT3DTEE data (A and B) with C-arm fluoroscopic imaging is shown for an ASD closure procedure (C). Identifying target markers can be placed for orientation and tracking. The center image shows the echosector viewed with the C-arm positioning (C).

CASE 3.1 Coronary Artery Disease—Use of Preprocedure CTA for Challenging Coronary Graft Anatomy

A 76-year-old man status post coronary artery bypass graft surgery (CABG), details unknown, and with atypical chest pain and an indeterminate stress test was referred for coronary angiography and possible PCI. He had several prior catheterizations performed with an inability to find the presumed bypass graft to his LAD. In order to plan and execute a successful procedure a CTA was performed prior to the catheterization. The CTA showed that the origin of the SVG to LAD was atypical and very superior due to the unsuspected presence of an ascending aortic graft. The mid-graft lesion was of unclear severity. The CTA images were transferred to the cardiac catheterization laboratory and registered with fluoroscopy using the sternal wires and the vertebral column as common elements from both imaging modalities. With this overlay the gantry was rotated to a view facilitating placement of a catheter in the ostium of the graft (Figure 3.13 and Video 3.1) thus allowing acquisition of selective graft injections in several views that minimized overlap and foreshortening of the suspected culprit lesion (Figure 3.14 and Video 3.2). It was decided that PCI was not needed. Had PCI been performed, the use of the CTA for intraprocedure image guidance would have allowed effective and efficient guide catheter placement and optimization of lesion views.
CASE 3.2 Congenital Heart Disease: Pulmonary Stenosis—Use of C-Arm CTA to Optimize Placement of Valvuloplasty Balloon and Detect Unsuspected ASD Plus Use of ICE

A 24-year-old woman was referred for treatment of symptomatic congenital pulmonic stenosis. As part of a research protocol a rotational angiography was performed with an inferior vena cava injection and a 10 seconds rotation of the flat detector over a 180° arc. The resultant 3D reconstruction (Figure 3.15, Video 3.3) showed intact pulmonary veins, a possible ASD, and the location of the plane of the stenotic pulmonic valve. The image was segmented to show the outline of the pulmonary arteries and plane of the pulmonic valve. This segmented image was overlaid on live fluoroscopy and used to position the valvuloplasty balloon (Figure 3.16, Video 3.4). ICE confirmed effective tearing of the valve to eliminate the stenosis (Figure 3.17, arrows) and then was used to confirm and close the ASD (Figure 3.18).
**CASE 3.3** Congenital Heart Disease: Secundum Atrial Septal Defect—CTA Preprocedural Planning with Transcatheter Closure Image Guidance Using Real-Time 3D TEE

A 38-year-old male presented with a history of CHD characterized by a secundum ASD. At age 6 he had surgical closure of the ASD. Three months prior to current evaluation he noted sudden onset of difficulty with speech and right-sided weakness. Subsequent evaluation by MRI demonstrated a left-sided cerebral vascular accident thought to be from an embolic source with two other old infarcts. An echocardiogram demonstrated a residual left-to-right shunt by color flow Doppler (Figure 3.19, Video 3.5) posterior in the interatrial septum (blue jet). He was referred for CTA to further assess the extent of prior repair and location of the residual leak. Figure 3.20 shows orthogonal views of the IVC to very posterior left atrial connection in panels A and B. Panel C is the volumetric 3D image visualized from the posterior interatrial septum into the LA. Preprocedural evaluation of the residual ASD demonstrates the inferior and very posterior location (arrow). This results in a clear direct course from the IVC to LA suggesting a mechanism for embolization. Also shown is the centerline course necessary to close the defect (blue and red lines). The location is in an area difficult to characterize by TEE. Given the recent stroke it was decided to close the residual ASD percutaneously. Simultaneous visualization of TEE and CTA data in conjunction with fluoroscopy are shown from a large single flat panel display system (Figure 3.21). Balloon sizing of the ASD is shown with fluoroscopy (panel A); CTA with coronary vessel for perspective (panel B); dual 2D and color flow Doppler images of balloon sizing to verify occlusion of flow (panel C). Figure 3.22 and Video 3.6 show the left atrial disk deployment with a Gore device ready to pull inferiorly into the defect shown by RT3D TEE using a zoom focused 3D TEE from the left atrial perspective. The defect was successfully closed using the percutaneous technique.

![Figure 3.19](image-url)
CASE 3.4 Valvular Heart Disease—Mitral Stenosis Procedural Guidance Using Real-Time 3D TEE

A 42-year-old woman presented with a history rheumatic fever as a child, which resulted in rheumatic heart disease characterized by MV stenosis. She presented with progressive dyspnea on exertion, one prior episode of atrial fibrillation and progressive right heart dysfunction with associated pulmonary arterial hypertension. The clinical deterioration and progressive increase of the mitral valve gradient resulted in referral for mitral balloon valvuloplasty. Following initial evaluation for left atrial appendage thrombus, the second important task defined by TEE guidance is visualizing the interatrial septum in preparation for transseptal puncture. Shown in Figure 3.23 (Video 3.7) is the tenting of the septum by the transseptal needle obtained using the biplane (x-plane) 3D mode. Once the balloon catheter is placed into the LA, the stylet is adjusted usually with counterclockwise rotation of the catheter to guide the balloon into the MV. This method uses direct eye-hand coordination to steer the balloon directly into the target. Once in the target, verification of free motion is performed using RT3D TEE (Figure 3.24, staged movement in the LA of the balloon). Balloon inflation and the evaluation of valve tissue are shown in Video 3.8 compared to fluoroscopic viewing of inflation in Video 3.9. Successful mitral valvuloplasty is judged in 3D by splitting of the commissures. Figure 3.25 is the comparison of the left ventricular view before and after balloon inflation. Note that the anterolateral commissure is split following valvuloplasty. Direct visualization of balloon entrapment provides operator confidence to a safer procedure. This with commissure splitting assessed by 3D TEE characterizes the value of advanced image guidance. The images show splitting of the anterolateral commissure more than the posterolateral commissure.
CASE 3.5  Valvular Heart Disease: Aortic Stenosis—CTA Preplanning and 3D Model Generation Prior to TAVR

The patient is an 82-year-old woman with worsening aortic valve stenosis 10 years post CABG with a vein graft to the LAD and circumflex artery. She had a prior inferior wall MI. She had been hospitalized for frequent episodes of fluid overload and pulmonary edema with atrial fibrillation. She experienced progressive weakness and presented with symptoms of low cardiac output and fluid overload. Her initial TEE of the LV outflow tract is shown in Video 3.10. She was subsequently referred for percutaneous TAVR. Figure 3.26 shows the screening TTE and TEE images on top and the initial CT angiogram with restricted aortic valve leaflet motion secondary to severe stenosis and limited calcification of the valve structure. A simulated aortic angiogram defining the best view for valve implantation is shown in Video 3.11 (Figure 3.27). The best view of the aortic annulus with level coronary cusp tips appears to be at 27° LAO and 5° cranial angulation with the RCA highlighted and the left coronary shown for orientation. A 3D model was constructed to evaluate the preimplantation characteristic of the valve, coronary arteries, and the aortoventricular complex. Initial balloon valvuloplasty appears to place greater stress on the more superior leaflet probably related to aortic arch angulation (Figure 3.28). This type of modeling provided additional information prior to the procedure.

Figure 3.29 shows the CTA placement of the Sapien (Edwards Life Sciences) valve in place and well seated in the region of the annulus. The postprocedural CTA shows the 50:50 placement of the valve stent between LVOT and cusp regions. The postprocedural images document a successful percutaneous implantation of the aortic valve.
CASE 3.6 Valvular Heart Disease—Preplanning and Image Guidance of Perivalvular Leak Closure

This 55-year-old male presented with history of dysplastic aortic valve with previous mechanical bi-leaflet AVR 4 years prior to the current evaluation. Immediately postoperatively he was noted to have a perivalvular leak. He recovered post procedure, but never regained his prior functional status. He noted progressive dyspnea on exertion (DOE) and developed lower extremity edema requiring diuretics. His functional status was limited by major fatigue, even with light activities such as taking a shower. Evaluation for hemolysis revealed a low serum haptoglobin and an elevated LDH of 552 IU/L, both felt secondary to hemolysis from the perivalvular leak.

His initial evaluation included a transesophageal echocardiogram that showed a moderate perivalvular leak (Figure 3.30, Video 3.12). The movie shows the LVOT perivalvular leak where the separation between the sewing ring and aortic valve annulus is noted in systole with orthogonal views. A CT angiogram (Figure 3.31) was performed to clarify the size of the tract and plan trajectory and best orientation to perform a percutaneous closure. Panels A and C show the centerline through the leak (arrow) in medial LVOT sewing ring region which measures 5 mm in diameter. The volumetric 3D image shows the red line tract (panel B), which is through the leak and the best cardiac orientation view, the LAO projection.

Images from the percutaneous closure during the procedure are shown (Figure 3.32, Video 3.13) with catheter positioned through the leak into the LV. Once across the leak a Vascular Plug II™ was placed with the first disk in the LV, the larger central disk in the tract, and the last smaller disk in the LA (Figure 3.33, Video 3.14). Note that valve function is not hampered by the plug. The last movie verifies the position of the plug by RT3D TEE (Figure 3.34, Video 3.15).

The perivalvular leak was significantly reduced by color flow Doppler post procedure. One month later the evidence of hemolysis had normalized. Importantly, the patient could take a shower without needing to rest suggesting significant clinical improvement.
Figure 3.31

Figure 3.32
The classic roles of proceduralists and imaging specialists will continue to blur leading to the necessity for each subspecialty to learn and understand the requirements of the other. The display and guidance image datasets in 3D, currently moving toward 4D and thus using the time component, may provide safer and faster complex interventions. The key will be a seamless integration of imaging technologies into hybrid interventional spaces not solely equipped with fluoroscopic equipment.

It is expected that eventually separate modalities will merge as this is currently being tested in interventional MR systems. The prototype is intervention-based navigation, using emitter units located at the tip of a catheter. Tracking location of the catheter tip can be matched and displayed within the patient’s anatomy based on the registered 3D multimodality dataset. Progressive improvements in display of these datasets could include multilayer displays that have volumetric formats and generate images actually occupying a region in space. A typical volumetric display may provide images of more than 100 million voxels projecting patterned light onto seven or eight rotating, reciprocating surfaces undergoing periodic motion. Holographic multiview displays project views to observers situated in one or more locations providing perspective and adjacencies critical to understand complex interventions. Once representative target structures are displayed, simulated pathways can be constructed to lead to actual procedural guidance.

This advanced compilation of patient-specific datasets identifying cardiac function and pathology supplies the basis for physician-extending technologies such as robotic assistance. The basic robot-assisted system for coronary or intracardiac intervention will involve a robotic manipulator with a controllable catheter (or active catheter) under the direction and guidance of an interventionalist. The tip of the active catheter or device delivery system will be tracked in real time using a navigation system employing a true 3D rendering display providing the location and orientation of the catheter. Robotically assisted systems may improve visualization and precision and allow autonomy from the point of entry of the catheter physically, thus separating the proceduralist from the radiation field and reducing exposure to harmful radiation.12

This merger of image-guided procedures is already occurring with the development of hybrid, procedural/surgical suites equipped with multiple display options, “on table” prewired inputs and data outputs for advanced imaging technologies. Coregistered data are currently a reality and display of key images is available for complex valvular interventions. In the near future, RT3D TEE data will be inserted into the fluoroscopic suite providing real-time imaging for guidance.

The future paradigm shift will be the high-resolution acquisition and characterization of cardiovascular tissues with the structural abnormalities within which the interventionalist navigates to achieve the target objective. This is in contradistinction to current approaches that use vascular structure to navigate into the vicinity of an SHD abnormality and supplemental data to gather a better glimpse of the target. The entire field will be revolutionized with this technical and theoretical change in image guidance.

REFERENCES


The risk of complications is inherent to any medical treatment, irrespective of its invasive nature. In particular, given that cardiac catheterization involves inserting foreign objects (i.e., cardiac catheters) into the circulatory system and the use of catheters and devices to diagnose and treat vascular and structural abnormalities, it is not surprising that cardiac catheterization can be associated with a variety of complications. These complications range from minor problems with no long-term sequelae (e.g., transient bradycardia during coronary contrast injection) to major problems (e.g., cardiac perforation, abrupt closure of a coronary artery during percutaneous coronary intervention [PCI]) that may require immediate surgical attention, to major and irreversible damage (e.g., stroke, myocardial infarction, renal failure, or death). Fortunately, the risk of producing a major complication during most procedure types is generally below 1%, a level at which the risk-benefit ratio still favors the performance of cardiac catheterization to investigate or treat cardiac disorders that are themselves life threatening or symptom limiting. In this chapter, we outline general complications that are common to most procedures. For additional information on less common complications, and on corresponding prevention and bailout techniques, our readers are referred to individual chapters in this textbook and to other textbooks that have been written on this topic.

OVERVIEW

The determinants of the risk for sustaining a complication during an invasive procedure include the clinical characteristics of the patient, equipment limitations, and operator experience. The risk thus varies widely depending on demographics (age, gender), the cardiac anatomy (left main coronary artery disease, severe aortic stenosis, diminished left ventricular function), and the clinical situation (unstable angina, acute myocardial infarction, cardiogenic shock). Other variations in risk are based on the type of procedure being performed (diagnostic catheterization, coronary intervention, and so on) and to some extent on the experience and familiarity of the operator with that particular procedure.

By considering all these factors, the physicians and support staff can arrive at a fairly accurate estimate of the level of risk entailed in any given procedure. Familiarity with those risks can be of immeasurable value in the following: (a) anticipating increased risks of complications; (b) taking extra precautions to avoid them (e.g., placing a prophylactic pacemaker in a patient prior to rotational atherectomy of a right coronary artery lesion); (c) promptly recognizing complications when they occur (e.g., perforation of the right atrium during a transseptal puncture); and (d) taking corrective and potentially lifesaving action (e.g., pericardiocentesis for perforation-induced tamponade).

Before proceeding with any procedure, the details of the planned procedure and its anticipated risks must be discussed candidly with the patient and family. This discussion should include which specific procedures are planned, what benefits are hoped for, the attendant risks and their probabilities, and how the risks and benefits of the planned procedure compare with those of any possible alternatives (e.g., coronary artery bypass graft surgery instead of percutaneous coronary intervention). By covering these cornerstones of informed consent clearly and candidly, the patient and family will be realistically prepared should a complication occur. Such a discussion should be documented in the patient’s chart, and that documentation should specify the type of procedure that is planned, the potential major complications, and their estimated risk of occurrence (see also Chapter 1). If a significant major complication does occur, the patient and family should be informed of the same as soon as the procedure has been completed (or when a delayed complication occurs, as soon as it is recognized). This discussion should describe the nature of the complication (without placing blame on anyone), indicate whether any long-term consequences are expected, and
outline what corrective actions have been and will continue to be pursued. The catheterizing physician should also continue daily inpatient follow-up visits to any patient who has sustained a significant complication, because a patient's feeling of abandonment by an uncaring physician tends to foster a desire for retribution (i.e., a malpractice suit).

Therefore, all individuals performing cardiac catheterization should thoroughly know the potential complications of the procedures they perform, as detailed in this and other chapters. In addition, the catheterization laboratory director should collect information about the frequency of these complications on at least a yearly basis and should review those data with the physician staff to identify where the laboratory as a whole (or an individual operator) is performing below expected standards. The types of complications that are routinely tracked in this process are shown in Table 4.1. This type of data collection, analysis (including breakdown by procedure type and by individual operator), reporting, and subsequent adjustment in laboratory policy and procedures is one of the most important jobs of any catheterization laboratory director and has now become a reporting requirement in several states.

Table 4.1

| Performance Measures and Quality Metrics Currently Reported in the Cath PCI Registry Executive Summary, American College of Cardiology Foundation National Cardiovascular Data Registry. All Hospitals ending 2010Q2.(https://www.ncdr.com/webncdr/cathpci/home/sample-reports). (Access Date 05/31/2013). |
|---|---|
| Section I: PCI Performance Measures | Section II: Quality Metrics |
| PCI Performance Measures | PCI in-hospital risk adjusted mortality (all patients) |
| PCI Process Metrics | Positive stress or imaging study prior to elective PCI |
| | Median time to immediate PCI for STEMI patients (in minutes) |
| | Proportion of STEMI patients receiving immediate PCI w/ in 90" |
| | Median time from ED arrival at STEMI transferring facility to ED arrival at STEMI receiving facility among transferred patients. |
| | Median time from ED arrival at STEMI transferring facility to immediate PCI at STEMI receiving facility among transferred patients (in minutes) |
| | Median fluoro time (in minutes) |
| | Aspirin prescribed at discharge |
| | Thienopyridine prescribed at discharge (patients with stents) |
| | Lipid-lowering agent prescribed at discharge (patients with dyslipidemia) |
| PCI Outcome Metrics | Vascular access site injury requiring treatment or major bleeding |
| | Emergency CABG |
| | Postprocedure MI (among hospitals routinely collecting post-PCI biomarkers) |
| | Postprocedure MI (among hospitals who do not routinely collect post-PCI biomarkers) |
| | Acute kidney injury |
| | Postprocedure stroke |
| | Composite: death, emergency CABG, stroke or repeat target vessel revascularization |
| | PCI in-hospital risk adjusted mortality (patients with STEMI) |
| | PCI in-hospital risk adjusted mortality (STEMI patients excluded) |
| Diagnostic Cath Process Metrics | Incidence of nonobstructive CAD (elective patients only) |
| Diagnostic Cath Outcomes Metrics | Vascular access site injury requiring treatment or major bleeding |
| Utilization Metrics | Median postprocedure length of stay (in days) for PCI patients with STEMI |
| | Median postprocedure length of stay (in days) for PCI patients with no STEMI |
| Data Quality Metrics | Creatinine assessed pre- and post-PCI procedure |
| Test Metrics | Test Metric: Transfusion of whole blood or RBCs |
| | Test Data Quality Metric: Biomarkers assessed post-PCI for elective inpatients |
**DEATH**

**Death as a Complication of Diagnostic Catheterization**

Death as a complication of diagnostic catheterization has declined progressively over the last 30 years. Whereas a 1% mortality was seen with diagnostic catheterization in the 1960s, the first Society for Cardiac Angiography registry of 53,581 diagnostic catheterizations performed in 1979–1981 showed a 0.14% procedure-related mortality. By the second registry of 222,553 patients catheterized in 1984–1987, procedure-related mortality for diagnostic catheterization had fallen further, to 0.1% (i.e., 1 in 1,000). This small reduction in mortality, however, belies the fact that the second registry included many more patients who fell into a high-risk subgroup for the procedure. Based on variables identified from the 218 deaths in the second registry (age older than 60 years, New York Heart Association (NYHA) functional class IV, left ventricular ejection fraction <30%, or left main disease), the mortality for such patients fell by half between the first and second registry. A third registry of 58,332 patients studied in 1990 showed an even lower overall mortality of 0.08%, with a 1.5% incidence of any major complication. A number of baseline variables (including NYHA class, multi-vessel disease, congestive heart failure, and renal insufficiency) were identified in this registry, whose presence predicted an up to eightfold increase in major complication rates (from 0.3% in patients with none of these factors to 2.5%). Several of the major factors are discussed below.

**Left Main Disease**

Although there has been a progressive reduction in the overall mortality of diagnostic cardiac catheterization over the last 25 years, patients with severe left main coronary disease remain at increased risk. Their mortality was 6% in the 1976 report by Bourassa, and 2.8% in the study by Boehr and others performed between 1978 and 1992 (compared with a mortality of 0.13% in patients without such disease). Although the mortality of such patients had fallen to 0.86% in the first Society for Cardiac Angiography registry, this was still more than 20 times higher than the 0.03% mortality seen in patients with single-vessel disease.

Because roughly 7% of patients undergoing coronary angiography have significant left main disease, the protocol used for coronary angiography (see Chapter 15) should always begin with careful catheter entry into the left coronary ostium to facilitate early recognition of ostial left main disease through catheter pressure damping or performance of a test “puff” immediately after engagement. Even without these early warnings of left main disease, we routinely perform the first left coronary injection in the right anterior oblique (RAO) projection with caudal angulation to screen for mid and distal left main disease and get the maximal anatomic information on the first injection. If ostial left main stenosis is suspected, a straight anterior (AP) injection may be performed. If severe left main disease is present, the only other left coronary injection needed is an RAO projection with cranial angulation (to see the left anterior descending and its diagonal branches). If angiography shows a borderline lesion (30% to 50%), additional diagnostics including intravascular ultrasound (IVUS; Chapter 25) or pressure wire (Chapter 24) can be performed after completing diagnostic coronary angiography to inform the subsequent management decision. However, performing a large number of superfluous contrast injections in a patient with a critical left main disease offers little more in the way of important anatomical information and increases the risk of triggering the vicious cycle of ischemia/hypotension/more ischemia that may lead to irreversible collapse.

Careful attention to all other aspects of technique is essential, since even an otherwise minor complication (e.g., a vaso-vagal reaction or arrhythmia) may have fatal consequences in this situation. If a patient with severe left main disease exhibits any significant instability during the procedure, we usually opt to place an intraaortic balloon pump (see Chapter 27) and arrange for prompt coronary artery bypass graft surgery. When the hemodynamics are markedly compromised and the patient is a poor surgical candidate, emergency coronary stenting can be performed if a trained operator and the necessary equipment are available (see Chapters 27 and 28). A similar consideration regarding the use of hemodynamic support applies to any patient with an unstable ischemic syndrome or acute myocardial infarction who behaves in a brittle fashion under the stresses of catheter placement and contrast injection.

**Left Ventricular Dysfunction**

Patients with cardiogenic shock in the setting of acute myocardial infarction or severe chronic left ventricular dysfunction (ejection fraction <30%) also have a several-fold increased risk of procedural morbidity and mortality, particularly when reduction in ejection fraction is associated with a baseline pulmonary capillary wedge pressure >25 mmHg and a systolic arterial pressure <100 mmHg. An effort should be made to bring such congestive heart failure under control before cardiac catheterization is attempted.

Although right heart catheterization is no longer routine (see Chapter 6), it should be performed before angiography in a patient with poor ejection fraction, because it provides valuable data about baseline hemodynamic status and allows ongoing monitoring of pulmonary artery pressure as an early warning about hemodynamic decompensation before frank pulmonary edema ensues. If the baseline pulmonary capillary wedge pressure is >30 mmHg, every effort should be made to improve hemodynamic status before angiography is attempted. This may entail administration of a potent intravenous diuretic (furosemide), supplemental oxygen, a vasodilator (intravenous nitroglycerin or sodium nitroprusside) when the mean arterial pressure is >65 mmHg, or a positive inotrope (dobutamine, milrinone) when the mean...
arterial pressure is <65 mmHg, or when severe congestive heart failure hemodynamics persist despite vasodilator treatment (see below). When frank cardiogenic shock is present or develops during a cardiac catheterization, prompt placement of an intraaortic balloon pump or of alternative percutaneous left ventricular assist devices in the contralateral groin may be required to get the patient safely through the procedure (see Chapter 27). Low-osmolar contrast agents produce less myocardial depression than traditional high-osmolar agents. They have replaced high-osmolar contrast agents for the performance of coronary and vascular angiography and they have greatly enhanced our ability to perform necessary angiography without precipitating hemodynamic decompensation in such unstable patients (see Chapter 2).

Valvular Heart Disease

Despite the preponderance of coronary artery disease as the indication for diagnostic cardiac catheterization patients with severe valvular heart disease are also at increased risk for dying during cardiac catheterization. The VA Cooperative Study on Valvular Heart Disease showed a 0.2% mortality among 1,559 preoperative catheterizations performed in patients with valvular heart disease, with one death in a patient with mitral regurgitation and two deaths in patients with aortic stenosis. With current noninvasive methods for assessing the severity of valvular lesions, there has been debate about whether it is necessary to cross severely stenotic valves in the course of preoperative cardiac catheterization. According to the most recent ACC/AHA update to the 2006 Guidelines for the Management of Patients with Valvular Heart Disease, cardiac catheterization is not recommended for the assessment of severity of aortic stenosis before aortic valve replacement "when noninvasive tests are adequate and concordant with clinical findings (Level of Evidence: C)."

Prior Coronary Artery Bypass Graft Surgery

Patients who have previously undergone coronary bypass surgery make up a growing subgroup of diagnostic and interventional catheterizations. They are typically 5 years older, have more diffuse coronary and generalized atherosclerosis, worse left ventricular function, and require a lengthier and more complex procedure to image both native coronary arteries and all grafts. Despite these adverse risk factors, the Post CABG Trial looked at 2,635 diagnostic angiograms performed in stable patients and found 0% mortality, with major complications in 0.7% (myocardial infarction 0.08%, stroke 0.19%, vascular trauma requiring transfusion or surgery 0.4%).

Pediatric Patients

Pediatric patients may be at higher risk (see Chapter 9). One review of 4,952 patients (median age 2.9 years) studied at the Hospital for Sick Children in Toronto found a mortality of 1.2% confined to patients younger than age 5 years (half in critically ill neonates <30 days of age). Although the risk was lower for diagnostic than for electrophysiologic or interventional procedures, there were three deaths (0.1%) among the 3,149 diagnostic procedures.

Death in the Course of an Interventional Procedure

Because they involve the use of more aggressive catheters, superselective cannulation of diseased coronary arteries, and brief interruption of coronary or even systemic flow (see Chapter 28), interventional procedures tend to carry higher mortality than purely diagnostic catheterizations. In the first 1,500-patient coronary angioplasty registry sponsored by the National Heart, Lung, and Blood Institute (NHLBI) from 1979 to 1982, the mortality of elective angioplasty was 1.1%. This was relatively unchanged at 1.0% in the second NHLBI registry of 1,802 patients treated at 15 centers between 1984 and 1987, mainly because the second registry included more patients with adverse features (advanced age, poor ventricular function, multivessel disease, prior bypass surgery, and so on). In fact, the mortality for single-vessel procedures fell from 1.3% to 0.2% between the first and second registry.

With the introduction of newer devices (e.g., stents, atherectomy, laser) to treat high-risk lesions preemptively or reverse abrupt closure following attempted conventional balloon angioplasty, the overall mortality for elective coronary intervention has fallen further (Chapter 28), but the extension of intervention to other high-risk subsets, including patients with acute myocardial infarction undergoing primary angioplasty, has kept overall mortality close to 1%—roughly 10-fold higher than purely diagnostic catheterization (i.e., 1% vs. 0.1%). Several multivariable models that predict procedural mortality have been developed based on age, ejection fraction, treatment for acute myocardial infarction/shock, urgent/emergent priority, and so on (see also Chapter 28 and 30). In general, there is a wide variation in risk of death in the course of coronary intervention—based on patient comorbidities, clinical indication, and procedure type. While an "average" risk can be quoted to "average" patients, patients with one or more adverse risk factors should be told candidly during the informed consent process that their expected risks are higher than these averages (Figures 4.1 and 4.2). A similar approach can be used when discussing prognosis following PCI for acute myocardial infarction or cardiogenic shock.

MYOCARDIAL INFARCTION

Although transient myocardial ischemia is relatively common during diagnostic catheterization and occurs routinely during coronary intervention, myocardial infarction...
Figure 4.1 Example of a risk prediction rule for percutaneous coronary intervention (PCI) mortality. For the estimation of risk, the total score can be calculated by adding individual scores if the comorbidity is present. For # of diseased vessels, a score of 0.5 should be added for each major epicardial vessel that has >70% stenosis. The total score can then be transferred to the horizontal axis of the plot, and the corresponding probability of death can be estimated on the vertical axis. Scores ≤2.5 are associated with a risk of death <0.8%, while scores >7 are associated with a risk of death >40%. (Reproduced with permission from: Moscucci M, Kline-Rogers E, Share D, et al. Simple bedside additive tool for prediction of in-hospital mortality after percutaneous coronary interventions. *Circulation* 2001;104(3):263–268.)

Figure 4.2 Mayo clinic risk score for major cardiovascular complications of percutaneous coronary intervention (PCI) (in-hospital death, Q-wave myocardial infarction, urgent or emergent coronary artery bypass surgery, and stroke) after coronary intervention assigns integer coefficients for each named clinical variable and reads the estimated mortality risk that corresponds to the total of the integer coefficients from the curve and the valve on the Y-axis (Reproduced with permission from: Singh M et al. Correlates of procedural complications and a simple integer risk score for percutaneous coronary intervention. *J Am College Cardiol* 2002;40(3):387–393.)
is an uncommon but important complication of diagnostic cardiac catheterization. In the late 1970s, data from the Coronary Artery Surgery Study showed a myocardial infarction rate of 0.25% for coronary angiography. In the first, second, and third registries conducted by the Society for Cardiac Angiography and Interventions, the risk of myocardial infarction fell progressively, from 0.07%, to 0.06%, to 0.05%. However, the risk of precipitating myocardial infarction during diagnostic catheterization is clearly influenced by patient-related factors that include the extent of coronary disease (0.06% for single-vessel disease, 0.08% for triple-vessel disease, and 0.17% for left main disease), the clinical indication (e.g., unstable angina or recent subendocardial infarction), and the presence of insulin-dependent diabetes. The progressive reduction in overall risk of myocardial infarction since the 1970s likely reflects greater attention to procedure technique including catheter flushing, pressure damping, and management of the arterial sheath during catheters exchange—all nuances that are now considered integral parts of coronary angiography (see Chapter 15). However, it should also be pointed out that this decrease might also reflect better patient preparation with beta blockade, use of preprocedure aspirin and preprocedure statins, as well as ready availability of ad hoc PCI for unstable patients with anatomically suitable disease.

Interventional Procedures

Coronary interventions may produce myocardial infarction by a variety of mechanisms that include dissection, abrupt vessel closure, “snowplow” occlusion of side branches, spasm of the epicardial or arteriolar vessels (no reflow), thrombosis, or distal embolization (see Chapters 28 and 29). Q-wave myocardial infarction was reported in 4.8% of patients in the first NHLBI registry and 3.6% in the second NHLBI registry. This includes roughly half of the 6% of percutaneous transluminal coronary angioplasty (PTCA) patients who were sent for emergency bypass surgery owing to abrupt vessel closure. Over the last decade, experience with coronary stenting has led to marked reduction in the need for emergency bypass surgery (to roughly 0.2%; see Chapters 28 and 31), and accordingly the incidence of Q-wave infarction has fallen to <1%.

Largely as a spin-off of trials conducted with the platelet glycoprotein IIb/IIIa receptor blockers in the mid-1990s, however, the official definition of periprocedural myocardial infarction has now been broadened to include non-Q-wave infarctions (more properly called non-ST-elevation myocardial infarctions) detected by elevation of cardiac biomarkers above the 99th percentile of upper limit of normal. According to the updated universal definition of myocardial infarction, PCI-related myocardial infarction (type 4a) is defined as a cardiac CK-MB or troponin elevation of >3× the upper reference limit in patients with normal baseline levels (see Chapter 28 for a more extensive discussion). Patients with these low-level enzyme elevations are more likely to have some degree of chest discomfort due to occlusion of small side branches or distal microembolization (Figure 4.3), but this finding is common also in patients without enzyme elevation, where it presumably represents stimulation of adventitial pain receptors by local stretching at the treatment site.

Several studies have evaluated the relationship between elevations of CK-MB and long-term mortality. Although
elevation above five or eight times normal corresponds to a significant amount of myocardial necrosis and carries the same adverse impact on long-term prognosis as a Q-wave infarction (Figure 4.4A). Long-term follow-up of patients from several multicenter trials has shown that patients with even low-level (one to three times normal) elevation of postprocedural CK after PCI have a greater incidence of late adverse outcomes (Figure 4.4B). Similar results have been shown by analysis evaluating the relationship between troponin elevations and long-term mortality. Whether any such relationship is cause and effect, or simply an association of both periprocedural cardiac biomarker elevation and late events with a common confounding variable (such as the diffuse underlying atherosclerosis) remains to be determined. However, it has also been suggested that due to the higher sensitivity of troponin, a larger percentage of patients will meet the definition of a myocardial infarction when troponin is used when compared to the same patients when CK-MB is used. Some of these patients will not have any evidence of myocardial necrosis even when a very sensitive imaging modality such as contrast-enhanced CMR is used.

Cerebrovascular complications

Cerebrovascular accidents (strokes) are uncommon but potentially devastating complications of diagnostic cardiac catheterization. Early experience showed an incidence as high as 0.23% in the 1973 study of Adams and others, compared with the 0.07% incidence for the more recent diagnostic catheterizations included in the Society for Cardiac Angiography registries. Every invasive cardiologist should be familiar with potential etiologies, preventive strategies, and treatments for catheterization-related stroke, and should develop the routine habit of speaking with the patient directly at the end of the procedure. If the patient is less alert, has slurred speech, and either visual, sensory, or motor symptoms during or after a left heart procedure, there should be a low threshold for performing a screening neurologic exam or obtaining an urgent stroke neurology consultation. For major hemispheric events, an urgent carotid angiogram and neurovascular rescue should be considered (usually with a prior computed tomography [CT] or magnetic resonance [MR] scan to exclude hemorrhage), in the hope that neurovascular rescue will minimize the risk of major long-term neurologic deficit or death (if a qualified neurointerventionalist is available).

The risk of stroke is somewhat higher with coronary intervention, as expected based on the use of guiding catheters, multiple equipment exchanges in the aortic root, aggressive anticoagulation, and longer procedure times. A review of 12,407 patients who underwent PCI at the Washington Hospital Center showed a 0.38% risk of per-procedural stroke (roughly half hemorrhagic and half embolic). Risk factors included age older than 80 years, use of an intraprocedural balloon pump, and saphenous vein graft intervention. Patients who sustained a stroke had a 37% in-hospital and 56% 1-year mortality, compared with 1.1% in-hospital and 6.5% 1-year mortality in patients who did not sustain a stroke.

Although cerebral hemorrhage must always be excluded, the main cause of catheterization-related strokes seems to be embolic. There is some evidence that many such emboli are dislodged from unsuspected aortic plaque or diffuse atherosclerosis, given the observation that atherosclerotic debris is liberated from the wall of the aorta in 40% to 60% of cases during advancement of large-lumen guiding catheters over a 0.035-inch guidewire. Sensitive measures such as transcranial Doppler monitoring of the middle-cerebral artery shows common high-intensity transients during contrast injections.
or catheter movements,42 and diffusion-weighted magnetic resonance imaging (MRI) before and after retrograde left heart catheterization shows ≤20% incidence of scan defects (but only a 3% neurologic event rate) when aortic stenotic valves are crossed.43 Most neuroophthalmologic complications (i.e., retinal artery embolism)44 and the syndrome of diffuse cholesterol embolization45 also appear to be caused by emboli released by disruption of unrecognized plaques on the walls of the aorta, liberating cholesterol crystals, calcified material, or platelet-fibrin thrombus into the aortic root.

So, we routinely advance our end-hole (i.e., coronary angiographic or, particularly, guiding) catheters around the arch to the ascending aorta over the guidewire, and we pay careful attention to flushing and injection technique, and to minimizing dwell time of guidewires in the aortic root of patients who are not fully anticoagulated (see Chapter 6). There can be no excuse, however, for contributory technical malfeasance such as sloppy catheter flushing, introduction of air bubbles during contrast injection, inadvertent placement of wires and catheters into the arch vessels, prolonged (>3 minutes) wire dwell times during attempts to cross a stenotic aortic valve, or failure to carefully wipe and immerse guidewires in heparinized saline before their reintroduction during left-sided heart catheterization.

In addition to aortic root sources, embolic material may also originate in the cardiac chambers, thrombotic coronary arteries, or the surface of cardiac valves. One should thus avoid placing the pigtail catheter fully out to the left ventricular apex in patients with suspected aneurysm or recent myocardial infarction, since either condition may be associated with potentially dislodgable mural thrombus. A clot contained in an occluded native coronary artery or vein graft can also be inadvertently withdrawn or propelled out of that vessel and into the aortic root during attempted coronary intervention or forceful injection of contrast through a distal superselective catheter. Care must also be taken to avoid transseptal catheterization or mitral valvuloplasty in patients with left atrial thrombus, which may increase the incidence of clinical stroke. Even avoiding such patients, there is an unexpectedly high incidence of new hyperintense brain lesions by MRI after percutaneous balloon mitral valvuloplasty46 suggesting that small subclinical emboli may occur more commonly than previously suspected. In patients with right-to-left shunting (including atrial septal defects with Eisenmenger physiology and patients with right ventricular infarction and a patent foramen ovale), paradoxical embolization may also lead to stroke. In such patients, the same level of care regarding flushing catheters and sheaths that is routine during left heart procedures should also be extended to right heart procedures.

The question of embolic risk also invariably comes up when it is necessary to perform catheterization on patients with endocarditis of left-sided (aortic and mitral) heart valves. Although these vegetations look friable and can embolize spontaneously, they have already withstood repeated trauma from opening and closing of the affected valves without dislodgment. In a series of 35 patients with active endocarditis who underwent left-sided cardiac catheterization (five of whom had prior spontaneous systemic emboli), none had a catheterization-induced embolic event.47 With current noninvasive techniques for assessing the left ventricle and mitral valve, it is not necessary to enter the left ventricle in a patient with left-sided endocarditis.

Beyond cerebrovascular emboli from intracardiac, arterial, or catheter sources, patients receiving aggressive anticoagulation, antiplatelet, or thrombolytic therapy are also prone to spontaneous intracerebral bleeding as a potential cause for postprocedure neurologic complications. If any doubt exists, and particularly if thrombolytic therapy or intensive anticoagulation is being considered as treatment for a presumptive cerebrovascular embolus, neurologic consultation and CT or MRI scanning are advisable. The distinction is critical, because there have been reported cases of resolution of embolic strokes that occurred during cardiac catheterization after selective infusion of a thrombolytic into the occluded cerebral vessel,48 as well as successful treatment of patients with posterior fossa bleeds as the result of prompt recognition and neurosurgical evacuation.

Local complications at the catheter introduction site are among the most common problems seen after cardiac catheterization procedures, and probably are the single greatest source of procedure-related morbidity. Specific problems include vessel thrombosis, distal embolization, dissection, poorly controlled bleeding at the puncture site, the development of pseudoaneurysm, arteriovenous fistula, retroperitoneal hematoma, and the development of femoral neuropathy. Ongoing bleeding may be owing to a poorly placed puncture, vessel laceration, excessive anticoagulation, or poor technique in either suture closure, mechanical groin compression, or use of a puncture-sealing device (see Chapters 6, 7, and 8).

With the femoral approach, poorly controlled bleeding may present as free hemorrhage, femoral or retroperitoneal hematoma, pseudoaneurysm, or arteriovenous fistula. Although frank hemorrhage and hematoma are generally evident within 12 hours of the procedure, the diagnosis of pseudoaneurysm may not be evident for days or even weeks after the procedure. Given the common and troublesome nature of postprocedural vascular complications, all cardiac catheterization operators must understand vascular access and closure techniques completely to recognize and treat each type of complication. Early experience with the femoral approach by Judkins and others reported a 3.6% local complication rate,48 but the Society for Cardiac Angiography registries reported a 0.5% to 0.6% incidence of vascular complication for diagnostic catheterization, which was similar for the brachial and femoral approaches.7 Brachial complications tend to be thrombotic whereas femoral complications tend to
be hemorrhagic, but exceptions to this general rule can and do occur. Complications of radial artery access are described in Chapter 7.

Femoral Artery Thrombosis

Femoral artery thrombosis can occur in patients with a small common femoral artery lumen (peripheral vascular disease, diabetes, female gender), in whom a large-diameter catheter or sheath (e.g., an intraaortic balloon pump) has been placed, particularly when the catheter dwell time is long or when prolonged postprocedure compression is applied. Such patients have a white painful leg with impaired distal sensory and motor function, as well as absent distal pulses. If this develops during the catheterization procedure and is not corrected promptly by sheath removal, a flow-obstructing dissection or thrombus at the femoral artery puncture site or a distal arterial embolus should be suspected. This requires urgent attention via vascular surgery consultation (for exploration and correction of any local dissection or plaque avulsion and Fogarty embolectomy of the distal vessel as needed to restore distal pulses). Alternatively, operators skilled in peripheral intervention may be able to puncture the contralateral femoral artery, cross over the aortic bifurcation, and address a common femoral occlusion percutaneously49 (Figure 4.5). Either way, failure to restore limb flow within 2 to 6 hours may result in extension of thrombosis into smaller distal branches, with muscle necrosis requiring fasciotomy or even amputation, and predispose to the development of renal failure.

Femoral Vein Thrombosis

Femoral venous thrombosis and pulmonary embolism are rare complications of diagnostic femoral catheterization (Figure 4.6). A small number of clinical cases have been reported, however, particularly in the setting of venous compression by a large arterial hematoma, sustained mechanical compression (see Chapter 6), or prolonged procedures with multiple venous lines (e.g., electrophysiologic studies).50 However, the actual incidence of thrombotic and pulmonary embolic complications may be substantially under-reported, since most are not evident clinically. Asymptomatic lung scan abnormalities have thus been described in up to 10% of patients after diagnostic catheterization.31

Hemorrhagic Complications

Although thrombotic complications do occur, poorly controlled bleeding from the arterial puncture site is a more common problem after cardiac catheterization by the femoral approach.32 Uncontrollable free bleeding around the sheath suggests laceration of the femoral artery. If such free bleeding does not respond to replacement with the next larger diameter sheath, the bleeding should be controlled by manual compression around the sheath until the procedure is completed. Anticoagulation may be reversed, and an attempt made to remove the sheath and control bleeding with prolonged (30- to 60-minute) compression or to place a femoral closure device (see Chapter 6). The vascular surgeons should be consulted regarding operative repair should the bleeding continue.

Figure 4.5

Femoral artery thrombosis. The morning after AngioSeal closure of the right femoral artery, this patient experienced sharp pain and swelling at the site, managed by 30 minutes of compression. After that, he reported severe pain and loss of sensation in a white limb. Upper left. Crossover from the contralateral side showed occlusion of the common femoral with reconstitution (arrow). Upper center. After balloon dilation, there was a prominent filling defect consistent with thrombus. Upper right. After AngioJet thrombectomy, the filling defect has decreased in size. Lower left. Distal injection, however, showed thrombotic occlusion of both the anterior tibial (AT) and the tibioperoneal (TP) trunk. Lower center. After catheter suction, patency of these vessels was restored. Lower right. Distal angiogram shows filling of both the dorsalis pedis and posterior tibial vessels. (Case courtesy of Dr. Andrew Eisenhauer, Brigham and Women’s Hospital.)
Formation of a hematoma—a collection of blood within the soft tissues of the upper thigh—is more common than free bleeding. It tends to cause a tender mass the size of a baseball or softball. If ongoing bleeding stops with manual compression, the hematoma will usually resolve over 1 to 2 weeks as the blood gradually spreads and is reabsorbed from the soft tissues. Larger hematomas may require transfusion, but surgical repair of a hematoma (as opposed to a false aneurysm, see later section) is generally not required. Given the discomfort caused by large hematomas, and the potential of such hematomas to evolve into false aneurysms, accurate puncture and puncture site compression or closure technique to minimize hematoma formation are essential parts of good catheterization technique.

The level of anticoagulation and antiplatelet therapy as well as increased sheath size, female gender, and advanced age all increase the risk of hemorrhagic complications. During the era (1990–1996) when uninterrupted transition from intravenous heparin to oral warfarin was used for stenting, vascular complications were as high as 10%. Even before the switch to less aggressive anticoagulant protocols (aspirin and ticlopidine or clopidogrel), second-generation stents that permit use of smaller 6F sheaths, and the widespread use of puncture-closure devices, the incidence of hemorrhagic access site complications after stenting remains at 1% to 2% (see Chapter 6). The tendency of platelet glycoprotein IIb/IIIa blockers to increase local hemorrhagic complications, however, has been tempered by lower levels of heparinization and the growing use of bivalirudin as an alternative antithrombotic agent associated with a lower risk of bleeding. Various approaches for collagen plugging or percutaneous suture-mediated closure of the femoral arterial puncture site have been introduced in the last several years (see Chapter 6). Although these devices avoid the discomfort of prolonged manual or mechanical compression and allow earlier or even immediate ambulation, clinical trials have failed to demonstrate significant reduction of major vascular complications compared with those caused by compression. It is possible that this class of devices will
improve sufficiently to make closure of the femoral artery puncture site so reliable as to eliminate the 1% to 2% incidence of complication. Until that time, operators must be prepared to recognize and repair them when they occur or to work from other access sites such as the radial artery (where hemorrhagic complications are unheard of, and thrombosis with a negative Allen test) is usually inconsequential (see Chapter 7), in patients at high risk for a femoral complication.

Retroperitoneal Bleeding

Retroperitoneal bleeding or hematoma is a relatively rare complication that is associated with high morbidity and mortality. In an analysis of 112,340 consecutive patients undergoing PCI in a large, multicenter registry, retroperitoneal hematoma (RPH) occurred in 482 patients (0.4%). In that study, female sex, body surface area < 1.8 m², emergency procedure, history of chronic obstructive pulmonary disease, cardiogenic shock, use of preprocedural IV heparin, use of preprocedural glycoprotein IIb/IIIa inhibitors, adoption of sheath size ≥8F, and use of vascular closure devices emerged as independent predictors of RPH, whereas the use of bivalirudin was associated with a lower risk. When compared with patients who did not develop RPH, the development of RPH was associated with a higher frequency of postprocedure myocardial infarction (5.81% vs. 1.67%, \( P < 0.0001 \)), infection and/or sepsis (17.43% vs. 3.00%, \( P < 0.0001 \)), and heart failure (8.00% vs. 1.63%, \( P < 0.0001 \)). The overall mortality rate in patients who developed RPH was 6.6%. RPH may occur if the front or back wall of the femoral artery is punctured above the inguinal ligament, allowing the resulting hematoma to extend into the retroperitoneal space. Trauma or perforation of the inferior epigastric artery and in rare instances bleeding from a common femoral artery entry site can also lead to the development of RPH. Such bleeding is not evident from the surface, but should be considered whenever a patient develops unexplained hypotension (particularly, if it responds only briefly to aggressive volume loading), fall in hematocrit, or ipsilateral flank pain following a femoral catheterization procedure. The diagnosis may be confirmed by CT scanning or abdominal ultrasound (Figure 4.7). The best prevention for retroperitoneal bleeding is careful identification of the puncture site to avoid entry of the common femoral artery near or above the inguinal ligament, and meticulous attention to advancement of guidewires. The treatment is usually expectant (volume replacement with intravenous normal saline, transfusion, bed rest) rather than surgical. More recently, effective catheter-based interventions have emerged. They include an ipsilateral (or contralateral if the problem is low in the iliac) approach for localization and tamponade of the retroperitoneal bleeding site, using a peripheral angioplasty balloon followed by placement of a covered stent, as possible alternatives. This is particularly relevant when the cause is a sheath-induced laceration of a tortuous iliac artery, bleeding from which can be fatal within a matter of minutes without such catheter-based control (Figure 4.8). Figure 4.9 illustrates a proposed algorithm for the management of patients with suspected RPH.

Femoral Neuropathy

Femoral neuropathy is another rare complication of femoral artery access. It can occur from direct trauma to the femoral nerve, from compression by a hematoma, or from direct prolonged compression during achievement of hemostasis. Two different clinical syndromes have been recognized.
The first (and most concerning) syndrome is associated with large RPHs resulting in a lumbar plexopathy involving the femoral, obturator, or lateral femoral cutaneous nerves. In these patients, a sensory neuropathy and motor deficit might persist. In the second syndrome, a groin hematoma or false aneurysm can result in paresthesias involving the medial and intermediate cutaneous branches of the femoral nerve.

**Pseudoaneurysm and Arteriovenous Fistula**

A pseudoaneurysm may develop if a hematoma remains in continuity with the arterial lumen (i.e., following dissolution of the clot plugging the arterial puncture site; Figure 4.10). Blood flowing in and out of the arterial puncture expands the hematoma cavity during systole and allows it to decompress back into the arterial lumen in diastole. Since the hematoma cavity contains no normal arterial wall structures (i.e., media or adventitia), this condition is referred to as false or pseudoaneurysm. It can often be distinguished from a simple hematoma on physical examination by the presence of pulsation and an audible bruit over the site, but Duplex ultrasound scanning is confirmatory. Since all but the smallest (<2-cm diameter) false aneurysms tend to enlarge and ultimately rupture, we usually have the vascular surgeons repair them (generally under local anesthesia) when they are detected. Less invasive alternatives to vascular surgical repair include ultrasound-guided compression of the narrow neck through which blood exits the femoral artery for 30 to 60 minutes, which may permanently close the track and eliminate the need for surgery, or injection of the false aneurysm cavity with procoagulant solutions or embolization coils during ultrasound, or contralaterally inserted balloon occlusion of the aneurysm neck (Figure 4.11). False aneurysms smaller than 2 cm in diameter may be followed expectantly, since up to half close, before a 2-week follow-up ultrasound.

The keys to avoiding pseudoaneurysm formation are accurate puncture of the common femoral artery and effective initial control of bleeding after sheath removal (see Chapter 6). Punctures of the superficial femoral or profunda artery (i.e., puncture below the bifurcation of the common femoral) are significantly more likely to lead to false aneurysm formation because of the smaller caliber of the artery and the lack of a bony structure against which to compress after sheath removal. Fluoroscopic localization of the skin nick to overlie the inferior border of the femoral head effectively avoids this error (see Chapter 6). Effective initial control is also essential, because allowing a hematoma to form makes effective control more difficult and initiates natural thrombolytic activity in the hematoma that may dissolve the early fibrin plug at the puncture site.

An arteriovenous fistula results from ongoing bleeding from the femoral arterial puncture site that decompresses into an adjacent venous puncture site (Figure 4.10). This can be recognized by a to-and-fro continuous bruit over the puncture site, and may not be clinically evident until days after a femoral catheterization procedure. These fistulae may enlarge with time, but at least one-third close spontaneously within 1 year, after which surgical repair should be entertained. The most common findings at surgery are a low
puncture (i.e., of the superficial femoral or profunda, transecting a small venous branch), emphasizing the importance of careful puncture technique in avoiding this femoral vascular complication.

**ARRHYTHMIAS OR CONDUCTION DISTURBANCE**

Various cardiac arrhythmias (tachycardia or bradycardia) or conduction disturbance may occur during the course of diagnostic or therapeutic cardiac catheterization. Most, like ventricular premature beats (VPBs) during catheter entry into the right or left ventricle, are devoid of clinical consequence. Others, like asystole or ventricular fibrillation, pose immediate risk. Finally, some rhythm disturbances (like atrial fibrillation) are well tolerated in most patients, but may trigger profound hemodynamic decompensation in patients with severe coronary disease, aortic stenosis, or hypertrophic cardiomyopathy by excessively increasing heart rate or eliminating the atrial “kick” needed to maintain diastolic filling of a stiff left ventricle.

An important part of safe cardiac catheterization is thus for the operator and the nurses/technicians to monitor the surface electrocardiogram (ECG) on the same physiologic monitor used to display the pressure tracings. The monitoring equipment typically also generates an audible beep with each QRS complex to serve as another information modality while the operator is intent on watching the fluoroscopic image. The technicians should be trained to call out any disturbance in rhythm such as VPBs that may otherwise escape the operator’s attention. The tools to treat these rhythm disorders—including a defibrillator capable of synchronized or asynchronous countershock, temporary transvenous pacing leads and pacemaker generator, and the full array of antiarrhythmic drugs—must be immediately accessible in any cardiac catheterization laboratory. The ability to promptly recognize and reverse major rhythm disturbances (e.g., by promptly countershocking ventricular fibrillation, sometimes even before the patient fully loses consciousness) can avoid progression to full cardiopulmonary arrest that would require the institution of cardiopulmonary resuscitation (CPR). Still, all operators and cardiac catheterization support staff should be current in their basic and advanced cardiac life support (ACLS) certification, including the newest guidelines published in 2010 and prepared to institute ventilatory and circulatory support without delay, when necessary. Duplication of ACLS protocols here would be beyond the scope of

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**Figure 4.9** Suggested algorithm for the management of patients with suspected retroperitoneal hematoma. (Reproduced with permission from: Chetcuti SJ, Cohen GC, Mosucci M. Local arterial and venous vascular access site complication. In: Mosucci M, ed. Complications of Cardiovascular Procedures: Incidence, Risk Factors and Bailout Techniques. Philadelphia, PA: Lippincott Williams & Wilkins, 2011.)

CT, computed tomography.
Common significant femoral vascular complications. **Upper left.** Angiographic appearance of a false aneurysm of right femoral artery (arrow) that developed 4 to 5 days following percutaneous retrograde femoral arterial catheterization complicated by a significant local hematoma after groin compression. Note that the arterial puncture had been made in the superficial (rather than common) femoral artery. **Upper right.** Schematic diagram showing the surgical approach to the false aneurysm cavity and the underlying puncture. **Lower left.** Angiographic appearance of an arteriovenous fistula with simultaneous filling of the femoral artery (left) and vein (right). **Lower right.** Diagram showing the potential anatomic situations (overlying arterial and venous branches) that may underlie fistula formation after femoral puncture. (From Fukumoto Y, Tsutsui H, Tsuchihashi M, Masumoto A, Takeshita A. The incidence and risk factors of cholesterol embolization syndrome, a complication of cardiac catheterization: a prospective study. *J Am College Cardiol* 2003;42(2):211–216, with permission.)
Ventricular Fibrillation

Ventricular ectopy or even brief (three- to five-beat) runs of ventricular tachycardia are not uncommon during passage of catheters into the right or left ventricle. Even balloon-flotation right heart catheterization may cause such brief runs of ventricular tachycardia in up to 30% of patients, with sustained ventricular tachycardia in 3% and ventricular fibrillation in 0.7% of cases. This emphasizes the importance of controlling the catheter position in the right ventricle and smooth passage through the right ventricular outflow tract; similar issues relate to careful positioning of the pigtail catheter free in the midportion of the left ventricle (see Chapter 17). If a sudden increase in ectopic activity is noted, or if a run of ventricular tachycardia is initiated, the offending catheter must be repositioned immediately so that baseline cardiac rhythm is restored. The same holds true for ventricular ectopy precipitated when the tip of a guidewire is placed into a small intramyocardial branch (usually a septal branch of the left anterior descending) during coronary intervention. The guidewire should be withdrawn slightly and repositioned in the main vessel. Other than these mechanical stimuli, ventricular fibrillation can also be induced by catheter transmission of “leakage” electrical currents into the heart. This problem has been effectively eliminated, however, by the adoption of standards for grounding systems in the cardiac catheterization laboratory that ensure a maximum leakage current of 20 μA between any two exposed conductive surfaces.

Although ventricular tachycardia and ventricular fibrillation may result from catheter manipulation, the most common is intracoronary injection (particularly using an ionic [high-osmolar] contrast agent) into the right coronary artery. Although this is less common with the current low-osmolar agents (see Chapter 2), it can still occur if the contrast injection is prolonged or performed with a partially damped catheter pressure (see Chapter 15). But changes in injection technique and the formulation of contrast agents used for coronary angiography have progressively reduced the incidence of this complication from 1.28% in the 1973 publication of Adams, to 0.77% in the 1970–1974 series from the Montreal Heart Institute, to less than 0.4% in the Society for Cardiac Angiography registry, and now to 0.1% with the routine use of nonionic low-osmolar agents. The incidence of ventricular fibrillation may be somewhat higher, however, in patients with baseline prolongation of the QT interval.

Some of the most refractory ventricular ectopy is seen in the setting of profound transmural ischemia or early myocardial infarction. Ventricular fibrillation or unstable ventricular tachycardia should be treated with prompt countershock, whereas lower-grade ventricular ectopy may respond to loading with intravenous amiodarone (150 mg over 10 minutes, with additional boluses of 150 mg over 10 minutes for breakthrough ectopy, followed by an infusion of 1 mg/min for 6 hours, and then 0.5 mg/min), or procainamide (20 to 50 mg/min watching for fall in blood pressure or broadening of QT or prolongation of QRS intervals by 50%, or total...
cumulative dose of 17 mg/kg). Although amiodarone is very effective for ischemic ventricular ectopy, its administration is associated with hypotension felt to be secondary to a solvent in the solution (Tween 80) that may cause arterial hypotension. A formulation without this solvent is now available in the United States. Magnesium sulfate (1 to 2 gm intravenously over 2 minutes) may be given for suspected hypomagnesemia or torsades de pointes. However, it is rare for witnessed and promptly treated ventricular fibrillation as occurs in the catheterization laboratory to result in a prolonged arrest. In that case, however, the full ACLS protocol should be initiated. Of course, precordial compression and bag/mask ventilation should be begun as arrangements for endotracheal intubation are made, in the case of ventricular fibrillation that does not respond immediately to countershock.

Atrial Arrhythmias

Atrial extrasystoles are common during catheter advancement from the right atrium to the superior vena cava, or during looping of the catheter in the right atrium to facilitate passage in a patient with enlargement of the right-sided heart chambers. These extrasystoles usually subside once the catheter is repositioned, although they may progress to atrial flutter or fibrillation in sensitive patients. Both rhythms tend to revert spontaneously over a period of minutes to hours, but may require additional therapy if they produce ischemia or hemodynamic instability. Atrial flutter can be treated by a brief (15-second) but rapid (300 to 400 beats per minute) burst of right atrial pacing, following which reversion to sinus rhythm or onset of atrial fibrillation (with a more controlled ventricular response) can be expected. Care must be taken, however, to ensure a stable atrial pacing location, since catheter migration into the ventricle during burst pacing may trigger ventricular fibrillation.

Atrial flutter or atrial fibrillation are generally benign during catheterization, but may cause clinical sequelae if the ventricular response is rapid (>100) or if the loss of the atrial kick causes hypotension in a patient with mitral stenosis, hypertrophic cardiomyopathy, or diastolic left ventricular dysfunction. If tolerated poorly in such individuals, atrial fibrillation or flutter may require synchronized DC cardioversion. If no significant hemodynamic dysfunction occurs, intravenous beta-blockers (metoprolol 5 mg, or esmolol at a loading dose of 500 µg/kg/min for 30 seconds, followed by an infusion of 50 µg/kg/min, with a maximum maintenance dose of 300 µg/kg/min) or a calcium channel blocker (diltiazem or verapamil) may be given and up-titrated until adequate control of the ventricular response is achieved. Once the ventricular response is controlled, chemical conversion to normal sinus rhythm can usually be accomplished by administration of intravenous procainamide or ibutilide. Because the latter agent can cause QT prolongation and torsade, it should not be given to patients who are on other QT-prolonging drugs, have reduced potassium or magnesium concentrations, bradycardia, or baseline QTc intervals >440 milliseconds. If there is significant hemodynamic instability from either atrial flutter or atrial fibrillation, however, the most rapid and reliable therapy is synchronized cardioversion (starting at 35 to 50 watt-seconds, after appropriate intravenous sedation).

Other narrow complex tachycardia such as paroxysmal supraventricular tachycardia can be treated with vagal maneuvers (carotid sinus massage), intravenous adenosine, or verapamil. Synchronized DC cardioversion should be reserved for prolonged episodes with hemodynamic compromise. In the setting of Wolf-Parkinson-White syndrome, however, these agents should be avoided in preference to amiodarone.

Bradyarrhythmias

Transient slowing of the heart rate used to occur commonly during coronary angiography, particularly at the end of a right coronary artery injection performed using a high-osmolar ionic contrast agent. Since forceful coughing helps to clear contrast from the coronary arteries, support aortic pressure and cerebral perfusion during asystole, and restore normal cardiac rhythm, patients should be warned at the beginning of the procedure that they may be asked to cough forcefully and that they must do so without hesitation when asked. This problem is far less common now with the widespread use of low-osmolar agents (see Chapter 2).

Vasovagal reactions, in which bradycardia is associated with hypotension, nausea, yawning, and sweating, should be suspected when bradycardia is more prolonged. This is one of the more common complications (with a roughly 3% incidence) seen in the cardiac catheterization laboratory, triggered by pain and anxiety, particularly in the setting of hypovolemia. Some elderly patients may exhibit the hypotensive findings of a vasovagal reaction without the hallmark finding of bradycardia. In the study by Landau et al., more than 80% of such reactions occurred as vascular access was being obtained, with 16% occurring during sheath removal. This highlights the importance of adequate preprocedure sedation and adequate administration of local anesthetic before catheter insertion is attempted. The treatment of vasovagal reaction consists of the following: (a) cessation of the painful stimulus; (b) rapid volume administration (elevation of the legs on a linen pack and hand pumping of saline through the sidewall of the venous sheath or peripheral intravenous line); and (c) atropine (0.6 to 1.0 mg intravenously). If hypotension persists, additional pressor support (norepinephrine or Neo-Synephrine) may be needed. Although the vasovagal episode itself tends to be benign, patients with critical valvular heart disease may develop severe and even irreversible decompression if they are allowed to remain hypotensive from an indolently treated vasovagal reaction. When the vasovagal constellation occurs during catheter manipulation, (instead of sheath insertion or removal), it should still be treated as outlined above, but the operator should be aware that vagal stimulation is one of the earliest findings in cardiac perforation (see below) as the pericardium is irritated by blood.
Conduction disturbances (bundle branch block or complete AV block) are an uncommon but potentially serious cause of bradycardia during cardiac catheterization. They may be precipitated when the catheter impacts the area of the right bundle during right-sided heart catheterization. This may cause a transient change in complex on the monitor ECG, but requires no treatment except in the patient with preexisting left bundle branch block. With right bundle branch block superimposed on preexisting left bundle branch block, asystole and cardiovascular collapse may ensue unless an adequate escape rhythm (i.e., a junctional escape) takes over. The same scenario may be seen when left bundle branch block is produced as the aortic valve is crossed in a patient with preexisting right bundle branch block. When complete heart block develops, atropine is rarely helpful in the setting of inadequate junctional escape and hemodynamic deterioration, but should be given anyway, since it has few adverse effects. Coughing may help support the circulation and maintain consciousness as a temporary pacing catheter is inserted. Isuprel can be helpful, but is rarely indicated in the cardiac catheterization laboratory where temporary pacing can be rapidly initiated. At one time, temporary pacing catheters were placed prophylactically in patients with bundle branch block or planned right coronary intervention, but this has been abandoned because frank asystole is rare and there is generally adequate time for insertion of a pacing catheter. The only procedures for which we currently place prophylactic right-sided heart catheters are rotational atherectomy or rheolytic thrombectomy (particularly in the right and circumflex coronary arteries).

PERFORATION OF THE HEART OR GREAT VESSELS

Perforation of the cardiac chambers, coronary arteries, or the intrathoracic great vessels is fortunately a rare event in diagnostic catheterization. In the cooperative study from 1968, 100 patients (0.8%) had perforation during diagnostic catheterization. Most involved the cardiac chambers, particularly the right atrium (33 cases), right ventricle (21 cases), left atrium (10 cases), and the left ventricle (10 cases). Most (30 of 33) right atrial perforations involved transeptal catheterization. The right ventricle was the most common site for perforation in the remaining (non-transseptal) diagnostic procedures, related to the use of stiff catheters (woven Dacron right heart catheters [i.e., Courmand], endomyocardial biopsy, or temporary pacing catheters). Elderly women (age older than 65 years) seem particularly susceptible, because the walls of the right-sided heart chambers tend to be thinner.

When cardiac perforation does occur, it is usually heralded by bradycardia and hypotension owing to vagal stimulation (see vasovagal reaction, above). As blood accumulates in the pericardium, the cardiac silhouette may enlarge and the normal pulsation of the heart borders on fluoroscopy will become blunted. Hemodynamic findings of tamponade may develop in the form of pulsus paradox and elevation of the right atrial pressure with loss of the “y” descent (see Chapter 23). If the patient is hemodynamically stable, a portable transthoracic ECG may help document the presence of blood in the pericardial space, but if hemodynamic compromise is severe or progressive, immediate pericardiocentesis should be performed via the subxiphoid approach (see Chapter 38). We use a disposable kit containing an 18-gauge needle, a J-tip guidewire, and a tapered catheter with multiple side holes, which is immediately available in the catheterization laboratory. Once pericardiocentesis has stabilized the situation, the operator must decide whether or not emergency surgery will be needed to close the site of perforation. Most perforations, in fact, will seal so that surgery is unnecessary, as illustrated in an 18-year review from the Mayo Clinic. During this period, 92 patients (0.08% of invasive procedures) developed tamponade, including 1.9% of valvuloplasties, 0.23% of electrophysiology studies, 0.08% of coronary angioplasties, and 0.006% of diagnostic catheterizations. Most (57%) patients were in frank hemodynamic collapse (systolic pressure <60 mmHg) at the time of pericardiocentesis. Echo-guided pericardiocentesis was successful in 91 cases, as was the only therapy required in 82% of cases (the remaining 18% also required surgical intervention). There were no procedural deaths in this series, but there were three major complications (pneumothorax, intercostal artery injury, and right ventricular laceration), and seven patients (8%) died within 30 days of the procedure.

In the modern interventional laboratory, however, the most common cause of tamponade is perforation or rupture of a coronary artery. This was unheard of in the era of diagnostic catheterization and was a reportable rare complication with conventional balloon coronary angioplasty. With the use of hydrophilic-coated guidewire, platelet IIb/IIa receptor blockers, and more aggressive atherectomy technologies, the incidence of coronary perforation may be as high as 1%. A classification of coronary artery perforation is listed in Table 4.2. Some perforations, particularly those limited to deep injury to the vessel wall with localized perivasculary contrast staining, can simply be observed (Type I perforation). However, such patients are at risk for delayed tamponade during the several hours following the procedure and must be monitored expectantly. In contrast, free perforations (Type III) may lead to the development of frank tamponade within seconds to minutes (Figure 4.12), particularly when the patient is well anticoagulated or has received a IIb/IIa blocker. The first countermeasure is to seal the site of leakage by inflation of a balloon catheter that spans the perforated segment. Once this is done, anticoagulation should generally be reversed (i.e., giving protamine 1 mL equals 1 mg for each 1,000 units of heparin) if possible. Percardiocentesis may also be necessary if hemodynamic embarrassment is present. Although many localized coronary perforations will seal with just prolonged balloon inflation and reversal of anticoagulation, ongoing bleeding is the rule for free perforations. Non-surgical options then include coil embolization if the bleeding...
site is in a small distal branch, or placement of a covered stent (see Chapter 31) to seal the perforation site in a larger proximal vessel. A free perforation with ongoing leakage, however, is a strong indication for emergent surgical repair.93,94

Perforation of the great vessels (aorta or pulmonary artery) is extremely rare. The aorta is sufficiently elastic to resist perforation, except in the case of weakening by ascending aortic dissection or aneurysm. Aortic puncture may occur, however, during attempted transseptal puncture with too anterior a needle orientation (see Chapter 6). Ascending aortic dissection can also result from vigorous use of a guiding catheter or extension from a proximal coronary dissection.92 If the dissection remains localized angiographically and is confined to the first few centimeters of the aortic root, it can usually be managed medically and will resolve within weeks (Figure 4.13).

Rupture of the pulmonary artery is also rare, but care must be taken not to use stiff-tip guidewires in these thinner-walled vessels. Perforation of the branch pulmonary arteries has been reported when balloon flotation catheters are inflated while positioned in a distal branch (rather than in the left or right main pulmonary artery).95 Patients typically develop massive hemoptysis of bright red blood and respiratory distress. This requires tamponade of the proximal pulmonary artery, embolization of the bleeding branch, and placement of a double-lumen endotracheal tube to protect the uninjured lung (or even emergency lobectomy or pneumonectomy). Placement of the patient with the lacerated pulmonary artery down may help maintain aeration of the uninjured lung until the double-lumen tube is placed. To avoid this serious complication, a balloon-tip catheter should never be inflated in a distal position under fluoroscopy or at the bedside without a clear pulmonary artery trace, and then only in a slow gradual fashion just until the waveform changes shape (i.e., from pulmonary artery to pulmonary capillary wedge).

### Table 4.2

<table>
<thead>
<tr>
<th>Ellis Classification of Coronary Artery Perforation93</th>
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</thead>
<tbody>
<tr>
<td><strong>Morphology</strong></td>
</tr>
<tr>
<td>Type I</td>
</tr>
<tr>
<td>Extrapulmonary crater without extravasation</td>
</tr>
<tr>
<td>Type II</td>
</tr>
<tr>
<td>Pericardial or myocardial blush without contrast jet extravasation and without a ≥1-mm exit hole</td>
</tr>
<tr>
<td>Type III</td>
</tr>
<tr>
<td>Extravasation through a frank perforation with a ≥1-mm exit hole.</td>
</tr>
<tr>
<td>Type III—Cavity Spilling</td>
</tr>
<tr>
<td>Perforation into an anatomic chamber, such as coronary sinus, atria, or ventricles.</td>
</tr>
</tbody>
</table>

### INFECTIONS AND PYROGEN REACTIONS

Because cardiac catheterization is an inherently sterile procedure, infection is extremely unusual. Recommended technique includes shaving and cleaning the catheter introduction site with chlorhexidine gluconate, use of a nonporous drape, and adequate operator clothing (including a scrub suit, gown, and sterile gloves).96,97 Endocarditis prophylaxis is not recommended when cardiac catheterization is performed with standard sterile precautions, but bacteremia has been reported after long or complex PCI interventions.98 Administration of a single dose of a cephalosporin 30 to 60 minutes prior to the procedure should thus be considered when a delayed intervention is performed by exchanging sheaths placed in an earlier diagnostic procedure, in a patient at high risk (prosthetic valve) undergoing a complex procedure, or when any break in sterile technique is suspected. When performing a repeat procedure within 2 weeks of an initial diagnostic procedure, the contralateral groin should be used since an increased infection rate has been reported with early reuse of the same groin site.99 Special care should also be taken when performing catheterization through a femoral graft since such grafts appear more prone to infection with potentially disastrous consequences,100 and when implanting a foreign body (e.g., a femoral closure device, see Chapter 6).

The AHA/ACC task force does not insist that the operator performs a surgical scrub or wears a surgical cap and mask during femoral procedures.2 These precautions are, however, recommended for catheterization by the brachial approach, where the risk of infection is 10 times higher than that for the femoral approach (0.62% vs. 0.06%). Full sterile precautions (hand scrub, cap, and mask including a splash shield) are also strongly recommended for the femoral approach when the procedure is prolonged, when the sheath will remain in
Figure 4.12  

Coronary perforation and management. **Upper left.** Immediately after 18 atm postdilation of a mid left anterior descending coronary artery (LAD) stent through a 6F catheter, coronary perforation with free extravasation of contrast was noted (arrow). **Upper right.** The patient became hypotensive within minutes, and the angioplasty balloon was reinflated within the area of perforation to seal the leak as pericardiocentesis was performed via the subxiphoid route. **Lower left.** Via the contralateral groin, an 8F guiding catheter was engaged in the left coronary ostium, and a wire and Jomed covered stent were advanced to the point of perforation. **Lower right.** After this stent was deployed, there was no further extravasation, and the heparin was not reversed as the platelet glycoprotein IIb/IIIa receptor blocker was continued to protect the patency of the stents that had been placed in the right and proximal left anterior descending coronary arteries.

The most common allergic reactions (≤1% of procedures) are triggered by iodinated contrast agents. In contrast to true anaphylactic reactions (which are mediated by IgE),
reactions to contrast appear to involve degranulation of circulating basophils and tissue mast cells by direct complement activation (i.e., an anaphylactoid reaction).\cite{105} Release of histamine and other agents causes the clinical manifestations (sneezing, urticaria, angioedema of lips and eyelids, bronchospasm, or in extreme cases, shock with warm extremities owing to profound systemic vasodilation), which can be classified as mild, moderate, or severe (Table 4.3). Risk of such reactions is increased in patients on beta blockers, and in patients with other atopic disorders, allergy to penicillin, or allergy to food products and may be as high as 15% to 35% in patients who have had a prior reaction to contrast. Premedication is recommended for patients with a strong history of atopic reactions and with prior history of reactions to contrast administration. It should be noted that there are currently no data linking allergies to shellfish and allergic reactions to contrast media. Thus, premedication is currently not recommended for patients allergic to shellfish or seafood.\cite{2,106} A widely used premedication protocol includes (a) Prednisone 50 mg by mouth 13 hours, 7 hours, and 1 hour before contrast administration; (b) diphenhydramine (Benadryl) 50 mg intravenously, intramuscularly, or by mouth 1 hour before contrast injection;

Table 4.3

<table>
<thead>
<tr>
<th>Classification #1\cite{106}</th>
<th>Classification #2\cite{107}</th>
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<tbody>
<tr>
<td><strong>Mild</strong></td>
<td></td>
</tr>
<tr>
<td>Single episode of emesis, nausea, sneezing, or vertigo</td>
<td>Cough, erythema, hives, nasal congestion, pruritus, scratchy throat, sneezing</td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td></td>
</tr>
<tr>
<td>Hives, erythema, emesis more than once, or fever or chills (or both)</td>
<td>Bradycardia, bronchospasm, chest pain, dyspnea, facial edema, hypertension, transient hypotension, mild hypoxemia, tachycardia, diffuse urticaria</td>
</tr>
<tr>
<td><strong>Severe</strong></td>
<td></td>
</tr>
<tr>
<td>Shock, bronchospasm, laryngospasm or laryngeal edema, loss of consciousness, convulsions, fall or rise in blood pressure, cardiac arrhythmia, angina, angioedema, or pulmonary edema</td>
<td>Cardiopulmonary arrest, refractory hypotension, moderate or severe hypoxemia, laryngeal edema</td>
</tr>
</tbody>
</table>

and (c) H2 blockers. The addition of antihistamines can reduce the incidence of adverse reactions and particularly of cutaneous reactions. In addition, it is currently recommended to hold beta blockers in patients with prior history of adverse reactions. The availability of newer low- and iso-osmolar non-ionic contrast agents (see Chapter 2) adds a further margin of safety, since the rate of severe cross-reactions in patients with prior reaction to an ionic contrast agent is also <1%. For this indication, the true nonionic agents are preferable to ionic low-osmolar agents, to which cross-reactions may still occur. In patients with a severe prior allergic reaction to contrast, use of a nonionic contrast agent can be combined with steroid and antihistamine premedication, although even then breakthrough allergic reactions may occur.

When a patient with a well-documented prior severe contrast reaction needs to undergo repeat catheterization, aortic pressure should be recorded before the catheter is cleared with contrast, since even this small amount of contrast can cause significant histamine release. The “money shots” of the coronaries should be obtained first, since a severe contrast reaction to the left ventriculogram may preclude further angiography. If a severe reaction occurs, it can be reversed with an intravenous injection of dilute epinephrine: 1 mL of 1:10,000 epinephrine (i.e., 0.1 mg of epinephrine/mL) is drawn up from the syringe on the crash cart, diluted further to a total volume of 10 mL (10 μg/mL), and labeled so that it is not mistaken for flush. The epinephrine is administered into the right-sided heart catheter in boluses of 1 mL (or 10 μg) every minute, until arterial pressure is restored. It is rare to have to give more than 10 mL (100 μg) in total, and excessive doses should be avoided, since they may precipitate life-threatening hypertension, tachycardia, or even ventricular fibrillation.

Although reactions to contrast are the most common allergic reaction in the cardiac catheterization laboratory, reactions to protamine sulfate, a biologic product derived from salmon eggs, can also occur. These reactions seem to be more common in insulin-dependent diabetics who have received NPH insulin (that contains protamine). In current practice, with no heparin given for most diagnostic catheterizations and widespread use of puncture-closure devices, it is rare to administer protamine in the catheterization laboratory. Table 4.4 summarizes guidelines for the management of individual reactions.

Another allergic reaction that should be considered—even though it is rarely seen in the cardiac catheterization laboratory itself—is heparin-induced thrombocytopenia (HIT) (see also below). Up to 10% of patients will have a fall in platelet count to <50,000 after 4 days of heparin exposure owing to a direct nonimmune mechanism (so called HIT-1). But a much smaller number (<1%) will exhibit a more profound fall in platelets combined with arterial and venous thrombosis owing to an antibody that binds to the complex of heparin with platelet factor 4 and causes platelet activation (HIT-2 or HITT, heparin induced thrombocytopenia and thrombosis). This usually does not develop until day 5, unless there has been prior sensitization to heparin, and can be diagnosed by blood testing, which should be done in any postprocedure patient who develops thrombocytopenia. If positive, an alternative nonheparin (i.e., neither unfractionated nor low-molecular weight heparin) anticoagulant agent should be used (see below). If thrombocytopenia develops after a coronary interventional procedure, the assay for heparin antibodies is particularly important to distinguish it from the thrombocytopenia that develops in 1% to 3% of patients treated with a 1lb/IIIa receptor blocker (see below).

**ONTRAST-INDUCED NEPHROPATHY/ACUTE KIDNEY INJURY**

Temporary or permanent renal dysfunction is a serious potential complication of cardiac angiography. The potential mechanisms of contrast-induced nephropathy (CIN) include vasomotor instability, increased glomerular permeability to protein, direct tubular injury, or tubular obstruction. At least 5% of patients experience a transient rise in serum creatinine (>0.5 mg/dL or a relative increase of 25%) following cardiac angiography, making CIN the third most common cause of hospital-acquired renal failure. It may occur in 15% of the general catheterized population, or ≤50% of patients who have risk factors including diabetes, preexisting renal dysfunction, multiple myeloma, volume depletion, or other drug therapy (e.g., gentamicin, angiotensin-converting enzyme inhibitors, nonsteroidal antiinflammatory drugs [NSAIDs]). Most such creatinine elevations are nonoliguric, peak within 1 to 2 days, and then return to baseline by 7 days, but may rarely go on to require chronic dialysis. The occurrence of CIN increases the length of hospital stay and is associated with a fivefold increase in in-hospital mortality. If dialysis is required, there is a further increase in mortality (from 1.1% to 7.1% with CIN to 35.7% with CIN plus dialysis).

The main defense against CIN is limitation of total contrast volume to 3 mL/kg (or 5 mL/kg divided by serum creatinine, in patients with elevated baseline creatinine), In the 1990 Society for Cardiac Angiography and Intervention (SCAI) registry, the mean volume of contrast administered during diagnostic cardiac catheterization was 130 mL for diagnostic procedures and 191 mL for angioplasty procedures, indicating that staying within 3 mL/kg limit for patients with normal renal function should usually be possible. In patients with reduced renal function and especially with diabetes, extra attention must be paid to limiting unnecessary angiographic views and multiple contrast puffs during interventional wire and device placement, which may drive up the total contrast volume. As described in Chapter 2, available contrast agents can be classified as high osmolar, low osmolar, and isoosmolar. There is now evidence that low-osmolar contrast agents are associated with a lower incidence of CIN in patients with renal insufficiency when compared to high-osmolar contrast agents. The role of isoosmolar,
Table 4.4  Recommended Management of Adverse Reactions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urticaria and skin itching</td>
<td>1) No treatment. 2) Diphenhydramine 25–50 mg IV. 3) Epinephrine 0.3 cc of 1:1,000 solution sub-Q q 15 min up to 1 cc. 4) Cimetidine 300 mg or ranitidine 50 mg in 20 cc NS IV over 15 min.</td>
</tr>
</tbody>
</table>
| Bronchospasm                    | a) \( \text{O}_2 \) by mask (b) Oximetry.  
Mild: Albuterol inhaler 2 puffs.  
Moderate: Epinephrine 0.3 cc of 1:1,000 solution sub-Q q 15 min up to 1 cc.  
Severe: 1) Epinephrine IV as a bolus(es) of 10 pg/min and then an infusion of 1–4 pg/min; observe for desired effect with BP and EKG monitoring. 2) Diphenhydramine 50 mg IV. 3) Hydrocortisone 200–400 mg IV. 4) Optional: H2 blocker as outlined.  
Preparation of epinephrine IV: Bolus dose: 0.1 cc of 1:1,000 solution or 1 cc of 1:10,000 diluted to 10 cc (10 pg/cc). Infusion dose: 1 cc of 1:1,000 or 10 cc of 1:10,000 in 250 cc NS (4 pg/cc). |
| Facial edema and Laryngeal edema | Call anesthesia.  
Assess airway.  
(a) \( \text{O}_2 \) by mask. (b) Intubation. (c) Tracheostomy tray.  
Mild: Epinephrine 0.3 cc of 1:1,000 solution sub-Q q 15 min up to 1 cc.  
Moderate/Severe: 1) Epinephrine IV as outlined. 2) Diphenhydramine 50 mg IV. 3) Oximetry/ABG. 4) Optional: H2 blocker as outlined. |
| Hypotension/Shock                | Call anesthesia.  
Assess airway.  
(a) \( \text{O}_2 \) by mask. (b) Oximetry/ABG. (c) Intubation. (d) Tracheostomy tray.  
1) Simultaneous administration:  
(a) Epinephrine IV—Bolus(es) 10 pg/min IV until desired BP response obtained, then infuse 1–4 pg/min to maintain desired BP. Preparation of solution as outlined above.  
(b) Large volumes of 0.9% NS (1–3 liters in first hour).  
2) Diphenhydramine 50–100 mg IV. 3) Hydrocortisone 400 mg IV. 4) CVP/Swan-Ganz.6  
Unresponsive: 5) H2 blocker as outlined. 6) Dopamine 2–15 pg/kg/min IV. 7) ACLS support. |


Nonionic contrast media (iodixanol) in further reducing the incidence of CIN when compared to low-osmolar contrast media is controversial. Several studies and metaanalyses have suggested that iodixanol is associated with a lower incidence of CIN when compared to iohexol and ioxaglate, but not when compared with iopamidol, ioversol, or iopamidate.\(^{122-126}\) Adequate prehydration is also critically important in any patient with impaired baseline renal function. In one classic
study, 26% of patients with a mean baseline serum creatinine of 2.1 mL/dL had a rise in serum creatinine by >0.5 mg/dL. Hydration with 1/2 normal saline for 12 hours before and after the contrast procedure provided the best protection against creatinine rise (which then occurred in 11%), but 26% to 28% of patients who received hydration in combination with either furosemide or mannitol had such a rise. Another landmark study has shown that hydration with 0.9% normal saline appears to be superior when compared to 0.45% normal saline. Promising results were also shown with the use of sodium bicarbonate (154 mEq/L). However, in a more recent, larger, randomized clinical trial, sodium bicarbonate was not superior to normal saline in the prevention of CIN. A strategic approach toward the prevention of CIN, including hydration protocols, is summarized in Table 4.5.

Postprocedure hemofiltration in the intensive care unit has also been reported to reduce the incidence of CIN in one study, presumably by direct contrast removal and consequent shortened renal exposure. However, its overall benefit remains unclear and its routine use in high-risk patients is currently not recommended.

The free-radical scavenger n-acetyl cysteine (600 mg orally before and twice a day after contrast exposure) has shown some benefit although other trials have failed to show benefit. Following a more recent negative randomized clinical trial and registry analysis, the use of n-acetyl cysteine is no longer recommended.

There is also some support for afferent arteriolar vasoconstriction as a mechanism for CIN, but renal-range dopamine actually worsens it. The selective DA-1 receptor,

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### Table 4.5 Practical Approach to Prevention of Contrast-Induced Nephropathy

<table>
<thead>
<tr>
<th>Patients at Risk and Procedure Strategy—Minimize Contrast Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients receiving intravenous or intraarterial contrast media should undergo assessment of baseline renal function and clinical assessment for the identification of additional risk factors for the development of CIN.</td>
</tr>
</tbody>
</table>

| Several studies have shown increasing risk of CIN with increasing contrast doses, and the additional importance of a contrast dose threshold, including either <125 mL or a weight- and creatinine-adjusted contrast dose calculated using the formula (5 cc of contrast/serum creatinine in mg/dL) X body weight in kg. |

| Minimize total amount of contrast media by avoiding unnecessary views or unnecessary tests, e.g., left ventriculography when ejection fraction (EF) is already available from noninvasive tests, and by using biplane angiography if available. |

| Use of smaller catheter might be associated with a lower amount of contrast per case. Use of biplane angiography can help in minimizing the amount of contrast used for visualization of coronary artery segments. |

<table>
<thead>
<tr>
<th>Hydration Protocols</th>
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<tbody>
<tr>
<td>Isotonic 0.9% normal saline is superior to 0.45% saline.</td>
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</tbody>
</table>

| 0.9% NS 1 mL/kg/h starting 12 h before the procedure and continued for 12 h after the procedure. |

| A 3 mL/kg bolus infusion of 154 mEq/L of sodium bicarbonate 1 h before contrast administration, followed by an infusion of 1.5 mL/kg/h during the procedure and for 4 h thereafter is an alternative to 0.9% NS, but on the basis of most recent data, it does not appear to provide any advantage. |

| A 3 mL/kg bolus infusion of 154 mEq/L of NaCl (0.9% NS) 1 h before contrast administration, followed by an infusion of 1.5 mL/kg/h during the procedure and for 4 h thereafter. |

<table>
<thead>
<tr>
<th>Role of Contrast Media and of Pharmacological Interventions</th>
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<td>Among the characteristics of contrast media, a higher viscosity and higher osmolarity appear to be associated with an increased risk of CIN. Thus, low-osmolar contrast media should be used.</td>
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| It remains to be determined whether the use of isoosmolar (280–290 mOsm/kg) contrast media is associated with additional benefits. |

| Of the many pharmacological interventions tested in the prevention of CIN, N-acetyl cysteine is no longer recommended. |

| Preprocedure statin use has been found to be associated with a lower incidence of CIN and other complications of PCI, and therefore it is generally recommended. |

fenoldopam, provides more potent afferent arteriolar vasodilation and had positive results in a pilot trial. Unfortunately, in the CONTRAST trial the primary end point of CIN occurred in 33.6% of patients assigned to receive fenoldopam versus 30.1% assigned to receive placebo (relative risk, 1.11; 95% confidence interval, 0.79–1.57; P = 0.61), thus consistent with no benefit of fenoldopam in preventing CIN. A device that allows selective simultaneous infusion of fenoldopam into both renal arteries (BenePhit™ Infusion System, FlowMedica, Fremont, CA) and more profound renal vasodilation with little or no systemic hypotension is under investigation for CIN.

Another cause of renal failure following cardiac catheterization is systemic cholesterol embolization. This clinical syndrome is seen in 0.15% of catheterizations, but cholesterol emboli can be identified pathologically in many more patients. Patients at greatest risk are those with diffuse atherosclerosis or abdominal aortic aneurysm, in whom insertion of a guiding catheter will frequently produce a shower of glistening particles on the table drapes. The hallmarks of cholesterol embolization are evidence of peripheral embolization (including livedo reticularis, abdominal or foot pain, and purple toes). Episodic hypertension or systemic cosinophilia may be apparent well before the other manifestations develop. Renal failure due to cholesterol embolization tends to develop slowly (over weeks to months, rather than over 1 to 2 days as is seen with CIN). Half of the patients with this syndrome progress to frank renal failure. Renal biopsy can confirm the presence of cholesterol clefts, but is seldom necessary for diagnosis. Treatment is purely supportive.

OTHER COMPLICATIONS

Hypotension

Reduction in arterial blood pressure is one of the most common problems seen during catheterization. This reduction represents the final common manifestation of a variety of conditions including the following: (a) hypovolemia, owing to inadequate prehydration, blood loss, or excessive contrast-induced diuresis; (b) reduction in cardiac output, owing to ischemia, tamponade, arrhythmia, or valvular regurgitation; or (c) inappropriate systemic arteriolar vasodilation, owing to vasovagal, excessive nitrates administration, or a vasodilator response to contrast or mixed inotropic-vasodilator drugs such as dopamine or dobutamine. Few places, however, are as well equipped as the cardiac catheterization laboratory to recognize, diagnose, and treat hypotension. If routine right heart catheterization has not been done, evolving hypotension is certainly an adequate reason to insert such a catheter to differentiate among hypovolemia, high output syndrome (including sepsis), and cardiogenic shock.

Low filling pressures mandate rapid volume administration through the peripheral intravenous line and the side arm of the venous sheath (500 to 1,000 mL of normal saline can be given in 5 minutes by this route) and consideration of potential sites of blood loss (expanding thigh hematoma, retroperitoneal bleeding). If low filling pressures are combined with inappropriate bradycardia, atropine should be given for a potential vasovagal reaction. High filling pressures, however, suggest primary cardiac dysfunction and should prompt consideration of ischemia, tamponade, or sudden onset of valvular regurgitation. Such patients should be supported empirically by inotropic agents (dopamine, dobutamine, milrinone), vasopressors (norepinephrine or Neo-Synephrine), or circulatory support devices (see Chapter 27), until a more precise cause is uncovered and treated. The operator also must decide whether the precipitating problem will require surgical intervention or whether a corrective intervention should be performed in the cardiac catheterization laboratory. If bradycardia is present and does not respond to atropine, consideration should be given to atrial (or AV) sequential pacing to preserve the atrial kick in such patients.

One of the most common oversights in managing hypotension is the failure to assess the cardiac output through thermodilution or measurement of pulmonary arterial oxygen saturation. On several occasions, high pulmonary arterial saturation in a hypotensive patient has signaled coexistent sepsis, contrast reaction, or an idiosyncratic vasodilator reaction to dopamine infusion. The essential importance of initial empiric and then definitive correction of hypotension and its causes—before hypotension leads to secondary ischemia and an irreversible spiral of left ventricular dysfunction—cannot be overemphasized in salvaging patients who might otherwise go on to have major complications.

Volume Overload

Patients in the cardiac catheterization laboratory are prone to volume overload owing to the administration of hypertonic contrast agents, myocardial depression or ischemia induced by contrast, poor baseline left ventricular function, as well as their supine position and attempts to volume load patients at risk for contrast-induced renal dysfunction. The best treatments are prevention by optimizing volume status before or early during the procedure and by use of low-osmolar contrast agents. The support measures described above (inotropes, diuretics, vasodilators, balloon pumping) should also be applied in a progressive manner before the patient goes into frank pulmonary edema with the resultant agitation and desaturation. Once pulmonary edema develops, even more aggressive treatment is warranted. Allowing the patient to sit up partially while morphine and nitroprusside are administered to bring filling pressures down may be necessary. If respiratory failure seems imminent, anesthesia support should be requested early enough to allow intubation before a full arrest develops.
Anxiety/Pain

Cardiac catheterization procedures should be well tolerated with oral sedative pretreatment (midazolam [Versed] 1 to 2 mg, and fentanyl 25 to 50 μg) and liberal use of local anesthetic at the catheter insertion site. However, the amount of discomfort, level of anxiety, and tolerance for either vary widely from patient to patient. The first effort should be to understand why the patient is having pain (vascular complication, perforation, coronary occlusion, ischemia) and whether anything can be done to reverse the problem. In the meantime, the catecholamine surge associated with pain and anxiety may worsen the condition of a patient who came to the cardiac catheterization laboratory with unstable angina, aortic stenosis, congestive heart failure, or hypertrophic myopathy. It is thus routine practice also to manage such complaints symptomatically by administering small intravenous doses of fentanyl (25 to 50 μg) and midazolam (Versed 0.5 to 2.0 mg). Care must be taken, however, not to oversedate the patient or to overlook an important and treatable cause for patient complaints. Guidelines for monitoring conscious sedation require monitoring of blood pressure, respiratory rate, and pulse oximetry after such medications are administered. The antagonist drugs—naloxone (Narcan) for opiates and flumazenil (Mazicon) for benzodiazepines—should also be stocked wherever the agonist drugs are used for conscious sedation.

Respiratory Insufficiency

Problems with adequate ventilation or oxygenation are not uncommon in the cardiac catheterization laboratory; they may result from pulmonary edema, baseline lung disease, allergic reaction, obstructive sleep apnea, or oversedation. Patients are monitored throughout the procedure with a finger pulse oximeter to detect progressive desaturation. Data from such monitoring show that low-flow supplemental oxygen (2 L/min via nasal prongs) helps avoid episodes of desaturation (saturation <90%) that otherwise occur with surprising frequency during cardiac catheterization (34%) or coronary angioplasty (56%). If oxygen consumption is to be measured as part of a calculation of cardiac output by the Fick method, supplemental oxygen administration should not be begun until after that measurement (or should be interrupted for at least 10 minutes before the oxygen consumption is measured). In most laboratories, however, the oxygen consumption is assumed at 125 mL/m² rather than measured, under which circumstance there is absolutely no reason to discontinue supplemental oxygen administration during a Fick measurement of cardiac output.

Retained Equipment

Although diagnostic and therapeutic cardiac catheters have a high degree of reliability, failures can and do occur thereby devices knot, become entrapped, or leave fragments in the circulation. Most of these events are precipitated when such devices are stressed beyond their design parameters, for example, when a coronary angioplasty guidewire is rotated multiple times in a single direction while its tip is entrapped in a total occlusion, or when a bare-mounted coronary stent cannot be advanced across a lesion and strips off the delivery balloon during attempted withdrawal. Operators should thus be familiar with device performance limits and avoid placing devices into situations that promote failure. Operators should also be familiar with the use of vascular snares, biopsy, balloons, and other devices and techniques that can be used to recover the errant fragments when devices do fail (Figure 4.14).

 Retrieval of fractured pacemaker lead. When this biventricular pacemaker ceased to pace the atrium, the fractured end of the lead was found free in the right ventricle (upper left, arrow), the loop of this lead was grasped with a deflectable mapping catheter (upper right, arrow), and the free end was pulled down into the inferior vena cava. The free end was grasped with a biopsy (lower left, arrow), and a goose-neck snare was advanced over the lead to allow it to be removed through a 12 F femoral venous sheath (lower right). (Case provided courtesy of Dr. Laurenc E. Epstein, Brigham and Women’s Hospital.)
CONCLUSION

Advances in technology and in adjunctive pharmacotherapy have resulted in a marked increase in the safety of cardiac catheterization and of cardiovascular interventional procedures. However, complications will occur. Therefore, it is critical that operators performing cardiac catheterization are familiar with factors associated with an increased risk of complications, with their recognition, and with bailout techniques.

REFERENCES


Adjunctive Pharmacology for Cardiac Catheterization

KEVIN CROCE and DANIEL I. SIMON

An important part of interventional catheterization involves mastery of a broad range of drugs that includes anticoagulant, antiplatelet, vasoactive, sedative, and antiarrhythmic agents. There is little doubt that refinements in antiplatelet (e.g., ADP receptor antagonists) and anticoagulant (e.g., bivalirudin) adjunctive pharmacology have contributed significantly to the improvements in percutaneous coronary intervention (PCI) success, safety, and durability over the last decade, and this chapter focuses on evidence-based recommendations for antithrombotic therapy during PCI highlighting the guidelines from the American College of Cardiology Foundation/American Heart Association/Society for Cardiac Angiography and Interventions (ACCF/AHA/SCAI).1

ANTIPLATELET AGENTS

The three classes of antiplatelet agents that are approved for use in PCI patients include cyclooxygenase inhibitors (aspirin), platelet P2Y12 ADP receptor antagonists (ticlopidine, clopidogrel, prasugrel, ticagrelor), and glycoprotein (GP) IIb/IIIa inhibitors. These agents are commonly used in combination to reduce pre-, intra-, and post-procedural adverse cardiovascular events in patients undergoing PCI. In addition, current guidelines recommend dual antiplatelet therapy with aspirin and an ADP receptor antagonist for all PCI patients based on reduction of ischemic events and stent thrombosis following coronary intervention.14

Aspirin

Mechanism of Action and Pharmacokinetics

Aspirin (acetylsalicylic acid, aspirin) exerts its antiplatelet effect primarily by interfering with the biosynthesis of cyclic prostanoids (e.g., thromboxane A2, TXA2). Aspirin irreversibly inhibits the cyclooxygenase activity of prostaglandin H synthase 1 (Cox-1) and prostaglandin H synthase 2 (Cox-2) which produce intermediate compounds that are used to generate several prostanoids including arachidonic acid-derived TXA2, which promotes platelet aggregation.6 Aspirin irreversibly acetylates key serine residues on Cox-1 and Cox-2 and prevents conversion of arachidonic acid to prostanoid precursors. The platelet activating prostanoid TXA is mainly produced by Cox-1 while the vasodilator and platelet inhibitor prostacyclin (PGI2) is primarily produced by Cox-2. Higher aspirin doses are required to inhibit Cox-2 compared to Cox-1, which is the reason why aspirin exerts antiplatelet effects at half the dose that is required for analgesia (80 to 100 mg versus 325 mg). Aspirin is rapidly absorbed in the upper gastrointestinal tract (GI) and plasma levels peak <40 minutes after administration.7 Aspirin-mediated platelet inhibition is seen within 40 to 60 minutes of ingestion, and Cox is irreversibly inhibited for the life of the platelet (7 to 10 days).7

Dosing for Percutaneous Coronary Intervention

The optimal aspirin dose for PCI is not firmly established, but randomized trials have shown inhibition of Cox-1 at doses ranging between 50 and 100 mg/day.6 Clinical studies have demonstrated that aspirin doses of 75 to 150 mg are as effective as higher doses for the prevention of cardiovascular events.6 When given in combination with warfarin or the ADP receptor antagonist class of antiplatelet agents, the aspirin dose should probably be lowered to 80 to 100 mg based on a post-hoc analysis of data from the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study in which similar efficacy, but less major bleeding, was seen in the low-dose (<100 mg) aspirin group.10
The CURRENT/OASIS-7 (Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events/Organization to Assess Strategies in Ischemic Syndromes) trial was the first prospective randomized study to compare low-dose versus high-dose aspirin in acute coronary syndrome (ACS) patients undergoing coronary angiography. Patients were randomized in a 2 x 2 factorial manner to open-label low-dose (75 to 100 mg daily) versus high-dose (300 to 325 mg daily) aspirin and to standard dose (300 mg loading dose followed by 75 mg daily thereafter) or high dose (600 mg loading dose followed by 150 mg daily for 7 days and then 75 mg daily thereafter) clopidogrel for 1 month. With regard to aspirin dose, the results of CURRENT/OASIS-7 did not show significant differences in efficacy between low- and high-dose aspirin. Although there was a trend toward increased GI bleeding in the high-dose aspirin group (0.38% versus 0.24%; P = 0.051), there were no differences in major bleeding.

### Evidence for Use in Percutaneous Coronary Intervention Patients

Aspirin is a cornerstone treatment of coronary artery disease (CAD) because four randomized trials have demonstrated that aspirin therapy results in approximately 50% reduction in the risk of death or myocardial infarction (MI) in patients with unstable angina (UA) and non-ST segment elevation myocardial infarction (NSTEMI). The Swedish angina pectoris aspirin trial, in which 2,035 patients were allocated to receive 75 mg aspirin daily or placebo, showed that aspirin therapy led to significant reductions in death and MI in several patient subsets; UA (46% reduction), stable angina (53% reduction), and patients undergoing coronary angioplasty (33% reduction).

The benefits of aspirin in reducing cardiovascular death, MI, and stroke in patients with CAD has led to the near universal use of this medication in PCI patients. PCI with balloon angioplasty or intracoronary stenting results in local vascular trauma, endothelial denudation, and platelet and fibrin deposition, and thus early trials showed a 3.5% to 8.6% risk of abrupt vessel closure or subacute thrombosis. The initial studies examining aspirin in PCI included combined antiplatelet regimens with dipyridamole, which reduced the incidence of periprocedural MI during PCI by 77% compared to placebo when administered 24 hours prior to balloon angioplasty and continued for 4 to 7 months. Dipyridamole, however, was shown to provide no additional benefit beyond that conveyed by aspirin alone during elective angioplasty. Aspirin has been shown to be particularly effective in patients undergoing intracoronary stent placement, especially in combination with platelet P2Y12, ADP receptor antagonists.

### Adverse Reactions

Because of its antiplatelet effects, aspirin increases the risk of bleeding. Metaanalysis studies have demonstrated a 60% increase in the risk of a major extracranial bleed with aspirin therapy, although aspirin does not appear to increase the risk of fatal bleeding. Aspirin sensitivity includes anaphylactoid reactions, respiratory sensitivity, and cutaneous sensitivity (urticaria and/or angioedema). Aspirin allergic patients that require aspirin therapy for PCI and stenting can be desensitized so that they can tolerate dual antiplatelet therapy following stent implantation.

### Guideline Recommendations

The 2011 ACCF/AHA/SCAI Guidelines for Percutaneous Coronary Intervention specifically addresses aspirin in the context of dual antiplatelet therapy following PCI. The recommendations are as follows:

1. Patients already taking daily aspirin therapy should take 81 mg to 325 mg before PCI. (Class 1, level of evidence: B)
2. Patients not on aspirin therapy should be given nonenteric aspirin 325 mg before PCI. (Class 1, level of evidence: B)
3. After PCI, use of aspirin should be continued indefinitely (Class 1, level of evidence: A).

Of note, aspirin dose should be reduced to 81 to 100 mg when used concomitantly with ticagrelor.

### ADP Receptor Antagonists

#### Mechanism of Action and Pharmacokinetics

ADP receptor antagonists attenuate platelet activation by selectively and irreversibly (clopidogrel, prasugrel, ticlopidine) or reversibly (ticagrelor) binding and inhibiting the platelet P2Y12 ADP receptor, which plays a critical role in orchestrating platelet activation and aggregation. P2Y12 receptor activation results in sustained platelet aggregation and stabilization of the platelet aggregate. When given in combination with aspirin, ADP receptor antagonists inhibit platelet aggregation to a greater extent than either agent alone. Currently four ADP receptor antagonists are approved for clinical use in the United States (ticlopidine, clopidogrel, prasugrel, and ticagrelor). An additional intravenous ADP receptor antagonist, cangrelor, is currently under clinical investigation. Cangrelor has rapid onset and offset, and although it does not does not appear to be superior to oral regimens in the PCI setting, it is currently being evaluated in bridging patients to cardiac surgery.

#### Ticlopidine

Ticlopidine is the first-generation ADP receptor antagonist that was approved for use as an antiplatelet agent in 1991. Ticlopidine is a thienopyridine class ADP receptor antagonist, which is an inactive prodrug that requires conversion by hepatic cytochrome P450-3A4 enzymes to produce active metabolites. The inhibition of platelet aggregation by ticlopidine is concentration dependent and ticlopidine metabolites bind irreversibly to the P2Y12 receptor resulting in
inhibition for the life of the platelet. Administration of ticlopidine results in maximal platelet inhibition 2 days after the initiation of therapy. However, due to safety concerns (mainly high rates of neutropenia) and twice daily dosing, ticlopidine has been largely replaced by clopidogrel (a second-generation thienopyridine) due to its better safety profile.46

Clopidogrel
The second-generation thienopyridine clopidogrel differs structurally from ticlopidine by the addition of a carboxymethyl group. Clopidogrel is also a prodrug that requires hepatic cytochrome P450-3A4 conversion to produce active metabolites.33,34 Eighty-five percent of clopidogrel is hydrolyzed by human carboxylesterase-1 into an inactive metabolite, and the remaining 15% of clopidogrel then undergoes a two-step hepatic cytochrome P450 (CYP)-dependent oxidation process. The activation processes involved in clopidogrel metabolism lead to a delay in peak antiplatelet effect that varies from 6 to 9 hours depending on the loading dose. Clopidogrel is six times more potent than ticlopidine and these two drugs do not share common metabolites.37 The inhibition of platelet aggregation by clopidogrel is concentration dependent and irreversible.35 Following cessation of clopidogrel therapy, platelet function recovers in 5 to 7 days due to the synthesis of new platelets.39

It has recently been recognized that there is significant response variability in the degree of platelet inhibition achieved with clopidogrel and the topic of clopidogrel response variability has been reviewed extensively.30-41 The degree of platelet inhibition achieved with clopidogrel is affected by several clinical factors, such as compliance, age, ethnicity, body weight, diabetes, dyslipidemia, renal function, MI presentation, congestive heart failure, and interaction with drugs that alter prodrug conversion.42-47 In addition, specific polymorphisms that reduce the activity of hepatic CYP2C19 enzymes (e.g., CYP2C19*2 and CYP2C19*3) decrease hepatic conversion of clopidogrel, and carriers of these reduced-function CYP2C19 alleles have significantly lower levels of active metabolite, diminished platelet inhibition, and higher rates of adverse cardiovascular events and stent thrombosis following PCI.48 The prevalence of CYP2C19 polymorphisms is significant, and varies from 30% to 60% depending on ethnic background.49-50 Polymorphisms in genes that influence GI absorption, such as ABCB1, also influence platelet inhibition by clopidogrel.51,52 and medications that inhibit CYP activity such as certain proton pump inhibitors appear to decrease clopidogrel efficacy by diminishing clopidogrel conversion to the active metabolite.53 The clinical importance of ABCB1 polymorphisms and clopidogrel drug-drug interactions (e.g., atorvastatin and omeprazole) remain uncertain with regard to their effect on cardiovascular outcomes in PCI patients. In some countries where access to the newer ADP receptor antagonists prasugrel and ticagrelor is limited, the antiplatelet agent cilostazol is added to aspirin and clopidogrel to treat clopidogrel hyporesponders. Cilostazol is a phosphodiesterase-3 inhibitor that increases platelet inhibition in pharmacodynamic studies where poor clopidogrel responders were treated with triple aspirin, clopidogrel, and cilostazol therapy.54,55

Prasugrel
Compared to ticlopidine and clopidogrel, the third-generation irreversible thienopyridine ADP receptor antagonist prasugrel has more rapid onset of action (1 to 2 hours), achieves a greater degree of platelet inhibition, has fewer drug-drug interactions, and less interindividual response variability (Figure 5.1).48,56,57 Prasugrel is also a prodrug; however, compared to clopidogrel, prasugrel conversion occurs via more efficient hepatic oxidation pathways that result in rapid metabolite production and peak platelet inhibition 30 to 60 minutes after loading dose administration.48,56,57 Prasugrel activity is not altered by genetic polymorphisms in hepatic CYP2C19 enzymes.58

 Ticagrelor
The third-generation non-thienopyridine ADP receptor antagonist ticagrelor is a reversibly binding, direct acting, noncompetitive agent. Ticagrelor and prasugrel are similar in the timing of their onset of action (<60 minutes), and both of these newer agents provide a greater degree of platelet inhibition with less interindividual variability compared to clopidogrel.59 Ticagrelor is not a prodrug and thus does not require hepatic conversion to an active metabolite. In addition, because ticagrelor is a reversible inhibitor, platelet function normalizes within 3 to 5 days following the last dose, which is faster compared to irreversible thienopyridine agents.59

Dosing for Percutaneous Coronary Intervention
In the setting of PCI, ticlopidine is administered 250 mg twice daily with antiplatelet doses of aspirin. The recommended loading dose of clopidogrel is 600 mg in the setting of PCI which is followed by 75 mg daily.1 In patients undergoing PCI, the clopidogrel loading dose should be given as early as possible.1 Pretreatment with clopidogrel prior to PCI improves 30-day outcomes compared to no pretreatment60,61 and, owing to the delay in the onset of clopidogrel action, the benefit of pretreatment is greatest when clopidogrel is administered more than 6 hours prior to the start of the PCI.62 Several clinical studies have demonstrated that increased loading (900 mg) and maintenance doses of clopidogrel can increase platelet inhibition in patients who are slow clopidogrel metabolizers or in patients who have high on-treatment platelet reactivity on standard dose clopidogrel.63,64 Higher clopidogrel dosing has been shown to shorten the onset of action, reduce interindividual variability, and improve early outcomes without increasing bleeding.63,65 Despite the ability of high maintenance dose clopidogrel to increase platelet inhibition, high maintenance dosing strategies have
not consistently improved cardiovascular outcomes when patients with poor clopidogrel response are prospectively identified with platelet function testing. In the setting of PCI, prasugrel is administered with a 60 mg loading dose followed by 10 mg daily. Because of the rapid onset of action, prasugrel preloading was not routinely done prior to diagnostic angiography in clinical studies. Ticagrelor dosing for PCI is accomplished with a 180 mg load followed by 90 mg twice daily. When prescribing ticagrelor, aspirin should be used at low 81 to 100 mg doses because ticagrelor had reduced clinical efficacy in clinical trials when coadministered with high-dose aspirin.

Evidence for Use in Percutaneous Coronary Intervention Patients

The early experience with coronary stenting was notable for unacceptably high rates of subacute stent thrombosis that occurred in 3% to 5% of patients and was associated with MI, need for urgent coronary artery bypass grafting (CABG), and/or death. Aggressive anticoagulation regimens (including intravenous heparin and dextran, warfarin, and dipyridamole) to minimize the risk of stent thrombosis led to frequent bleeding complications and prolonged hospitalizations.

When aspirin is used in combination with a thienopyridine, several studies have demonstrated up to 5-fold reductions in acute and subacute stent thrombosis compared with either aspirin alone, warfarin, heparin, or long-term low-molecular-weight heparin (LMWH).

The CURE study randomized 12,562 patients who presented within 24 hours of symptoms to receive clopidogrel 300 mg load, followed by 75 mg daily and aspirin versus aspirin and placebo. There was a significant reduction (9.3% versus 11.4%, RRR 20%, \(P < 0.001\)) in the primary endpoint (death from cardiovascular cause, nonfatal MI, or stroke) in the group receiving clopidogrel. The benefit with clopidogrel was noted early (within 24 hours of treatment), was sustained at 1 year, and was observed in all patients with ACSs regardless of their level of risk. In a prespecified substudy of CURE, patients who underwent PCI and were randomized to clopidogrel had a 31% relative risk reduction in death and MI compared to placebo-treated PCI patients. Furthermore, long-term (9 to 12 months) compared to short-term (4 weeks) clopidogrel therapy post PCI was associated with a 31% lower rate of cardiovascular death, MI, or revascularization (\(P = 0.03\)).

The clopidogrel to reduce events during observation (CREDO) trial demonstrated the benefit of clopidogrel...
pretreatment and long-term therapy in a relatively stable CAD population undergoing stenting. Patients were randomly assigned to receive a 300 mg clopidogrel loading dose or placebo, 3 to 24 hours before PCI, followed by clopidogrel 75 mg daily for 28 days post PCI. Patients loaded with clopidogrel were continued on active drug from day 28 through 12 months and those patients in the control group received placebo. There was a significant 27% (P = 0.02) reduction in death, MI, or stroke in patients receiving clopidogrel, suggesting that clopidogrel therapy in addition to aspirin should be continued for a minimum of 9 months post PCI.

In CURE, there was a significant increase in major bleeding in those receiving clopidogrel compared to placebo (3.7% versus 2.7%, P = 0.001), which was most notable in patients requiring CABG. In contrast, CREDO only showed a trend toward more Thrombolysis in Myocardial Infarction (TIMI) major bleeding with clopidogrel compared to placebo (8.8% versus 6.7%, P = 0.07), and no excess bleeds among patients undergoing CABG. These findings have led to the recommendation to delay elective CABG for 5 days after stopping clopidogrel, and possibly avoiding preloading of clopidogrel in unstable angina (UA)/NSTEMI patients until after the coronary anatomy is identified and the need for CABG excluded. However, it is important to emphasize that the risk-benefit of pretreatment needs to be established for each individual patient, recognizing the consistent and substantial benefit of clopidogrel pretreatment in reducing the risk of death and MI.

Prasugrel was compared head to head with clopidogrel in The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38 trial, which tested the hypothesis that a newer antiplatelet agent with greater potency and less variable response would reduce ischemic events compared to standard-dose clopidogrel. The study randomized 13,608 patients with moderate-to-high-risk ACS (10,074 with UA or non-ST-elevation MI and 3,534 with ST-elevation MI) undergoing PCI to prasugrel (60 mg loading dose, 10 mg QD) or clopidogrel (300 mg loading dose, 75 mg QD) for a duration of 6 to 15 months (median duration 14 months). The primary efficacy endpoint was death from cardiovascular causes, nonfatal MI, or nonfatal stroke and the primary safety endpoint was non-CABG TIMI major bleeding. The primary efficacy endpoint occurred in 9.9% of patients receiving prasugrel and 12.1% of patients receiving clopidogrel (hazard ratio [HR] for prasugrel versus clopidogrel, 0.81; 95% confidence interval [CI], 0.73 to 0.90; P < 0.001). There were significant reductions in the prasugrel group in the rates of MI (prasugrel, 7.4% versus clopidogrel, 9.7%; P < 0.001), urgent target-vessel revascularization (prasugrel, 2.5% versus clopidogrel, 3.7%; P < 0.001), and stent thrombosis (prasugrel, 1.1% versus clopidogrel, 2.4%; P < 0.001). These improvements in cardiovascular outcomes led the FDA to approve prasugrel for use in ACS patients undergoing PCI in 2009.

The reversible ADP receptor antagonist ticagrelor was also compared head to head against clopidogrel in The Study of Platelet Inhibition and Patient Outcomes (PLATO) trial. PLATO randomized 18,624 patients admitted to the hospital with an ACS to ticagrelor (180 mg loading dose, 90 mg twice daily thereafter) versus clopidogrel (300 to 600 mg loading dose, 75 mg daily thereafter) and examined the rate of adverse cardiovascular events up to 12 months. The primary endpoint, a composite of death from vascular causes, MI, or stroke occurred in 9.8% of patients receiving ticagrelor as compared with 11.7% of those receiving clopidogrel (HR, 0.84; 95% CI, 0.77 to 0.92; P < 0.001). In secondary endpoint analyses, ticagrelor reduced the rate of MI (5.8%
in the ticagrelor group versus 6.9% in the clopidogrel group, \( P = 0.005 \) and death from vascular causes (4.0% versus 5.1%, \( P = 0.001 \)). The FDA approved ticagrelor for ACS patients in 2011.

### Adverse Reactions

All of the ADP receptor antagonists increase the risk of bleeding. In CURE, clopidogrel use with aspirin was associated with an increase in bleeding compared to placebo with aspirin (3.7% versus 2.7%; relative risk, 1.38; \( P = 0.001 \))\(^{26} \) and in the Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS) major peripheral or bleeding complication were similar between clopidogrel (1.3%) and ticlopidine (1.2%).\(^{36} \) Compared to clopidogrel, the more potent agents prasugrel and ticagrelor do increase bleeding in patients undergoing PCI.\(^{56,67} \) In TRITON TIMI 38, prasugrel use was associated with increased life-threatening bleeding (prasugrel, 1.4% versus clopidogrel, 0.9%; \( P = 0.01 \)), which included nonfatal bleeding (prasugrel, 1.1% versus clopidogrel, 0.9%; HR, 1.25; \( P = 0.23 \)) and fatal bleeding (prasugrel, 0.4% versus clopidogrel, 0.1%; \( P = 0.002 \)).\(^{67} \) Similarly, in PLATO ticagrelor caused a higher rate of major bleeding not related to CABG (ticagrelor, 4.5% versus clopidogrel, 3.8%, \( P = 0.03 \)), including more instances of fatal intracranial bleeding.\(^{36} \)

The incidence of adverse reaction to ticlopidine is significant; diarrhea, nausea, and vomiting are common with ticlopidine, occurring in 30% to 50% of recipients\(^{72} \) and neutropenia, which is a serious side effect, occurs in 1.3% to 2.1% compared with 0.10% with clopidogrel.\(^{73,74} \) With ticlopidine, most cases of neutropenia develop within the first 3 months of therapy and initially may be clinically silent. Complete blood counts should be performed every 2 weeks during the first 3 months of therapy.\(^{73} \) Bone marrow aplasia and thrombotic thrombocytopenic purpura (TTP) have been reported with ticlopidine.\(^{76-78} \) The estimated incidence of ticlopidine-associated TTP is 1 per 1,600 to 5,000 patients treated\(^{77,78,79} \) while the incidence of TTP with clopidogrel appears to be lower.\(^{77} \) Allergic or hematologic reactions to clopidogrel occur in approximately 1% of patients and limited information on switching thienopyridine in patients with adverse reactions is available.\(^{80} \) Desensitization protocols using escalating doses of oral clopidogrel have been proposed for clopidogrel-allergic patients;\(^{81} \) however, recent availability of the non-thienopyridine ticagrelor may provide an option for switching ADP receptor antagonist class rather than embarking on desensitization.

The incidence of adverse nonhemorrhagic reactions for prasugrel and clopidogrel are similar. Post hoc subgroup analysis of TRITON TIMI 38 identified less clinical efficacy and greater bleeding in patients with prior history of stroke or transient ischemic attack, in elderly patients (age \( \geq 75 \) years), in patients with low body weight (<60 kg), and in patients undergoing urgent CABG. Increased risk of bleeding in these subgroups resulted in an FDA black box warning stating that prasugrel should not be prescribed to patients with any history of stroke or transient ischemic attack or to patients with severe liver dysfunction. In addition, prasugrel is not recommended for elderly patients (age > 75 years) as this subgroup had increased risk of fatal and intracranial bleeding with uncertain benefit except in high-risk subsets (those with history of diabetes or prior MI). Prasugrel should also be avoided with concomitant use of medications that increase bleeding risk (i.e., Coumadin) and should be used with caution in patients with low body weight (<60 kg). The two most common nonhemorrhagic side effects seen with ticagrelor are dyspnea (ticagrelor, 13.8% versus clopidogrel 7.8%) and bradycardia/ventricular pauses (ticagrelor 6.0% versus clopidogrel 3.5%).

### Guideline Recommendations

The 2011 ACCF/AHA/SCAI Guidelines for Percutaneous Coronary Intervention specifically address oral ADP receptor antagonists for patients undergoing PCI. The recommendations are as follows:

1. A loading dose of a P2Y\(_{12} \) receptor inhibitor should be given to patients undergoing PCI with stenting (Level of Evidence: A).

   Options include:
   - a. Clopidogrel 600 mg (ACS and non-ACS patients) (Class I, level of evidence: B)
   - b. Prasugrel 60 mg (ACS patients) (Class I, level of evidence: B)
   - c. Ticagrelor 180 mg (ACS patients) (Class I, level of evidence: B)

2. The duration of P2Y\(_{12} \) inhibitor therapy after stent implantation should generally be as follows:
   - a. In patients receiving a stent (BMS or DES) during PCI for ACS, P2Y\(_{12} \) inhibitor therapy should be given for at least 12 months. Options include clopidogrel 75 mg daily, prasugrel 10 mg daily, and ticagrelor 90 mg twice daily. (Class I, level of evidence: B)
   - b. In patients receiving DES for a non-ACS indication, clopidogrel 75 mg daily should be given for at least 12 months if patients are not at high risk of bleeding. (Class I, level of evidence: B)
   - c. In patients receiving BMS for a non-ACS indication, clopidogrel should be given for a minimum of 1 month and ideally up to 12 months (unless the patient is at increased risk of bleeding; then it should be given for a minimum of 2 weeks). (Class I, level of evidence: B)

### Intravenous Glycoprotein IIb/IIIa Inhibitors

#### Mechanism of Action and Pharmacokinetics

Platelet GP IIb/IIIa receptors mediate the “final common pathway” of platelet aggregation by binding fibrinogen and
other adhesive proteins that bridge adjacent platelets and have thus served as a primary focus of pharmacologic antiplatelet strategies. Three parental GP IIb/IIIa receptor antagonists abciximab (Reopro), eptifibatide (Integrilin), and tirofiban (Aggrastat) are currently approved for clinical use by FDA.

Abciximab

Abciximab is a humanized Fab fragment engineered from the murine monoclonal antibody 7E3 directed against GP IIb/IIIa. Unlike small-molecule agents, abciximab interacts with the GP IIb/IIIa receptor at sites distinct from the ligand-binding RGD sequence site, and exerts its inhibitory effect noncompetitively. The antibody has unique pharmacokinetics, with the majority of the drug cleared from plasma within 26 minutes, but much slower clearance from the body with a functional half-life up to 7 days. Because of the high affinity of abciximab for GP IIb/IIIa receptors, the number of abciximab molecules bound to platelets is considerably higher than the free plasma pool of the drug for the duration of treatment, and platelet-associated abciximab can be detected for more than 14 days after the infusion is stopped. The use of intracoronary GP IIb/IIIa antagonists has been advocated by some interventional cardiologists largely on the basis of smaller angiographic trials. Interestingly, the recent Intracoronary Abciximab and Aspiration Thrombectomy in Patients with Large Anterior Myocardial Infarction (INFUSE-AMI) trial indeed indicates that intracoronary abciximab in the setting of primary PCI for STEMI improved left ventricular function to a greater extent than aspiration thrombectomy.

Eptifibatide

The cyclic heptapeptide eptifibatide is based on barbourin, a 73-amino acid peptide isolated from the venom of the Southeastern pygmy rattlesnake Sistrurus miliarius barbouri. With the recommended bolus (180 µg/kg followed by second 180 µg/kg bolus) and infusion (2 µg/kg/minute) regimen, peak plasma levels are established shortly after the bolus dose, and slightly lower concentration are subsequently maintained throughout the infusion period. Plasma concentrations decrease rapidly after the infusion is discontinued and eptifibatide has an elimination half-life of 2.5 hours, with the majority of the drug eliminated through renal mechanisms.

A lower infusion dose (1 µg/kg/minute) of eptifibatide is recommended in patients with creatinine clearance less than 50 mL/minute. Substantial recovery of platelet aggregation is apparent within 4 hours of discontinuing the infusion.

Tirofiban

Tirofiban is a peptidomimetic inhibitor that occupies the binding pocket on GP IIb/IIIa and thereby competitively inhibits platelet aggregation mediated by fibrinogen or von Willebrand factor. The stoichiometry of both eptifibatide and tirofiban needed to achieve full platelet inhibition is >100 molecules of drug per GP IIb/IIIa receptor. This compares with a stoichiometry of 1.5 molecules of abciximab for each receptor. Like eptifibatide, substantial recovery of platelet aggregation is apparent within 4 hours of stopping the infusion. Pharmacodynamic studies have led to the development of high loading dose tirofiban regimens that appear to be more efficacious than the FDA-approved regimen.

Dosing for Percutaneous Coronary Intervention

Preclinical and clinical pharmacodynamic studies suggest that 80% inhibition of platelet aggregation by light transmission aggregometry should be the target for clinically effective antiplatelet activity. The level of platelet inhibition varies between the three GP IIb/IIIa inhibitors following the recommended bolus and infusions. In general, the bolus and infusion regimen of abciximab and the double bolus and infusion regimen of eptifibatide are associated with rapid and profound inhibition of platelet function. Several studies have documented that the FDA-approved bolus and infusion regimen for tirofiban achieves suboptimal levels of platelet inhibition for up to 4 to 6 hours, and this suboptimal level of inhibition likely accounts for inferior clinical results in the PCI setting.

The clinical relevance of these pharmacodynamic observations was tested in the TARGET (Tirofiban and ReoPro Give Similar Efficacy) trial, which randomized 5,308 patients to tirofiban (10 µg/kg bolus followed by an infusion of 0.15 µg/kg/minute for 18 to 24 hours post PCI) or abciximab before undergoing PCI with the intent to perform stenting. The primary endpoint was a composite of death, nonfatal MI, or urgent target vessel revascularization (TVR) at 30 days. The primary endpoint (6.0% versus 7.6%, P = 0.038) as well as the incidence of MI (5.4% versus 6.9%, P = 0.04) were significantly lower in the abciximab group compared to the tirofiban group, respectively. There was no significant difference in the rate of major bleeding between the two groups. Increasing the tirofiban bolus 2.5-fold (25 mg/kg) appears to enhance platelet inhibition and improve PCI outcomes compared to the FDA-approved dosing regimen. The degree of platelet inhibition appears central to the efficacy of GP IIb/IIIa inhibitors; achieving >95% platelet inhibition 10 minutes after the bolus in patients undergoing PCI was associated with a 55% reduction in MACE compared to those patients with <95% platelet inhibition.

Evidence for Use in Percutaneous Coronary Intervention Patients

The landmark trial demonstrating efficacy of GP IIb/IIIa inhibition in the balloon angioplasty setting is the Evaluation of IIb/IIIa platelet receptor antagonist 7E3 in Preventing Ischemic Complications (EPIC) trial. In this study, high-risk patients undergoing balloon angioplasty were randomized to abciximab bolus and infusion versus abciximab bolus alone versus placebo. The group treated with abciximab bolus and...
infusion had a 35% lower rate of death, MI, or unplanned urgent revascularization at 30 days compared to the placebo group (8.3% versus 12.8%, \( P = 0.008 \)). No significant benefit with abciximab bolus alone was observed, suggesting that shorter duration of platelet inhibition was insufficient to favorably affect clinical outcomes. Major bleeding complications occurred in an unacceptably high proportion of patients treated with abciximab compared to placebo (major bleeding 14% versus 7%, transfusion 15% versus 7%, respectively). Procedural modifications, including performing front-wall arterial access only, reducing arterial sheath size from 8F to 6F; reducing heparin dosing to target activated clotting time (ACT) 200 to 250 seconds rather than >300 seconds, removing sheaths as soon as possible (ACT < 180 seconds) rather than overnight, and abandoning the use of routine venous sheaths, successfully reduced major bleeding complications to less than 1.0% to 1.5% in subsequent trials.

The benefit of GP IIb/IIIa inhibition patients undergoing elective stent placement has been shown in two large, randomized controlled trials.101,102 The Evaluation of IIb/IIIa inhibitor for Stenting (EPISTENT) trial randomized 2,399 patients to stent plus placebo, stent plus abciximab, or balloon angioplasty plus abciximab.103 The primary 30-day endpoint, a combination of death, MI, or urgent revascularization, occurred in 10.8% of patients in the stent plus placebo group, 5.3% of those in the stent plus abciximab group (HR 0.48; \( P < 0.001 \)), and 6.9% in the group undergoing balloon angioplasty plus abciximab (HR 0.63; \( P = 0.007 \)). These benefits were maintained at 6 months104 and 1 year,105 with a significant reduction in 1-year mortality in patients treated with stent plus abciximab compared with stent without the IIb/IIIa inhibitor (2.4% versus 1.0%, \( P = 0.037 \)). No significant differences in bleeding complications were noted among the various groups.

The Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy (ESPRIT) trial randomized 2,064 patients undergoing stenting to epifibatide (180 \( \mu \)g/kg bolus followed by a 20 \( \mu \)g/kg/hour infusion, with a second bolus of 180 \( \mu \)g/kg given 10 minutes after the first bolus) or placebo.102 In this trial, patients were administered a loading dose of clopidogrel or ticlopidine on the day of the procedure. The trial was terminated early for efficacy. The primary endpoint—a composite of death, MI, urgent revascularization, or thrombotic bailout at 48 hours—was reduced by 37% with epifibatide (10.5% versus 6.6%, \( P = 0.0017 \)). Death or MI at 48 hours was significantly reduced with epifibatide compared to placebo (5.5% versus 9.2%, RRR = 40%, \( P = 0.0013 \)). These benefits were maintained at 6 months106 and 1 year.107 Major bleeding was rare, but occurred more frequently in patients receiving epifibatide compared to placebo (1.3% versus 0.4%, respectively; \( P = 0.027 \)).

Three large, randomized clinical trials have evaluated each of the three GP IIb/IIIa inhibitors in UA/NSTEMI patients undergoing PCI. In the c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) trial, patients (\( n = 1,265 \)) with refractory angina undergoing PCI were randomly assigned to receive abciximab 18 to 24 hours prior to PCI and for 1 hour after completion of the procedure or placebo.108 MACE was reduced in the abciximab group compared to placebo (15.9% versus 11.3%, \( P = 0.012 \), respectively). There was a significant increase in major bleeding (1.9% versus 3.8%, \( P = 0.043 \)) and the need for transfusion (3.4% versus 7.1%, \( P = 0.005 \)) in the abciximab group compared to placebo. The Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Sign and Symptoms (PRISM-PLUS) trial randomized 1,915 patients with UA/NSTEMI to tirofiban alone, tirofiban plus heparin, or placebo infusion plus heparin.109 The combination of tirofiban and heparin led to a 32% risk reduction in the rate of death, MI, or recurrent refractory ischemia at 7 days compared with heparin alone (12.9% versus 17.9%, respectively, \( P = 0.004 \)). Tirofiban was also beneficial in the subgroup of patients undergoing PCI (RRR of death or MI at 30 days = 0.44).

In the Platelet Glycoprotein IIb/IIIa in UA: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial, 10,948 patients with UA/NSTEMI were randomized to epifibatide or placebo.109 The primary endpoint of 30-day death or MI was reduced in those patients receiving epifibatide versus placebo (14.2% versus 15.7%, \( P = 0.042 \), respectively). This treatment benefit was more pronounced among patients undergoing PCI within 72 hours of presentation (11.6% versus 16.7%, \( P = 0.01 \), respectively). Moderate or severe hemorrhage was more common in the epifibatide group (12.8% versus 9.9%, \( P < 0.001 \), respectively).

Four trials support the use of abciximab in primary PCI for STEMI, reducing MACE at 30 days by 35% to 54%.110-113 In the Abciximab before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-Term Follow-up (ADMIRAL) trial, 300 patients with acute MI were randomized to abciximab plus stenting or stenting alone prior to angiography.111 At 30 days, the primary endpoint—a composite of death, reinfarction, or urgent TVR—occurred in 6% of the patients in the abciximab group, as compared with 14.6% of those in the placebo group (\( P = 0.01 \)). This beneficial effect was sustained at 6 months (7.4% versus 15.9%, \( P = 0.02 \)) in ADMIRAL, but not in the two other trials.110-113

Upstream administration of GP IIb/IIIa inhibitors prior to PCI in patients presenting with STEMI has been studied in six trials. In a metaanalysis of these trials, TIMI grade 3 flow (20.3% [84/413] versus 12.2% [51/418]) was significantly more common in the early (prior to transfer to the cardiac catheterization laboratory) group compared with the late (catheterization laboratory) group (odds ratio [OR], 1.69; 95% CI, 1.28 to 2.22; \( P < 0.001 \); and OR, 1.85; 95% CI, 1.26 to 2.71; \( P < 0.001 \), respectively). The early administration of GP IIb/IIIa inhibitors was associated with a 28% reduction of mortality from 4.7% to 3.4%, which was not significant but consistent with similar trends for reinfarction and the composite ischemic endpoint. Thus, early administration of GP IIb/IIIa inhibitors in STEMI appeared to improve coronary patency with favorable trends for clinical outcomes. However,
the prospective, randomized EARLY-ACS trial showed no significant benefit of upstream initiation compared to cardiac catheterization laboratory initiation of eptifibatide.114

GP IIb/IIIa inhibitors have been shown to reduce major adverse cardiac events (death, MI, and urgent revascularization) by 35% to 50% in patients undergoing PCI115 (Table 5.1). Although no single study demonstrated a significant reduction in mortality alone with GP IIb/IIIa inhibitors, a metaanalysis suggests that these agents as a class reduce death by 20% to 30%.119 (Figure 5.3). The mechanism by which GP IIb/IIIa inhibitors reduce long-term mortality is unclear, and cannot be explained solely by their ability to reduce periprocedural death or MI. Investigators have postulated that this therapy may also be associated with significant anti-inflammatory properties that may favorably influence the course of atherosclerotic disease.116,117 a contention that remains unproven at this time.

Although GP IIb/IIIa inhibitors have demonstrated ability to reduce adverse cardiovascular events, in the modern era of thienopyridine use and stenting, the clinical benefit of routine GP IIb/IIIa inhibitors has been inconsistent. The CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) trial demonstrated that STEMI patients treated with stenting did not benefit as much as patients treated with balloon angioplasty.113 In low-risk elective PCI patients that were preloaded with 600 mg of clopidogrel, abciximab increased bleeding and did not improve ischemic outcomes.116,119 Although there is no benefit to routine GP IIb/IIIa inhibitor use in thienopyridine-treated low-risk elective PCI cohorts, data do justify targeted GP IIb/IIIa inhibitor use in high-risk patients. In the Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment-2 (ISAR-REACT-2) study abciximab reduced ischemic endpoints without increasing bleeding in high-risk ACS patients.120

Although older studies demonstrated reduction in ischemia when GP IIb/IIIa inhibitors were used upstream before PCI,121,122 a recent study performed in the thienopyridine and stenting era showed that in ACS patients undergoing invasive management, upstream GP IIb/IIIa inhibitor use increased bleeding to the same degree that it reduced ischemic events compared to a strategy of provisional GP IIb/IIIa inhibitor use at the time of PCI.114 Similarly, the Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events (FINESSE) trial demonstrated that in ST-segment elevation MI patients, early abciximab use increased bleeding without clinical benefit when compared to provisional use during PCI. Table 5.2 summarizes data from trials examining GP IIb/IIIa inhibitor use in the modern era of thienopyridine preloading and stenting.

**Adverse Reactions**

As outlined above, when GP IIb/IIIa inhibitors are utilized with dose-adjusted heparin and early sheath removal, studies demonstrate a 0 to 1% absolute increase in major bleeding that occurs primarily at femoral access sites.109,121-126 In a metaanalysis of eight clinical trials, abciximab increased the incidence of mild thrombocytopenia (≥50,000 < 100,000) compared to placebo group (4.2% versus 2.0%, P = 0.001; (Table 5.1)

### Table 5.1 Outcomes of Patients Receiving Glycoprotein IIb/IIIa Inhibitors

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of Studies (n)</th>
<th>Active Treatment</th>
<th>Control Arm</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI (30 d)</td>
<td>20 (20,137)</td>
<td>537/11,676 (4.6)</td>
<td>585/8,461 (6.9)</td>
<td>0.63 (0.56-0.70)</td>
</tr>
<tr>
<td>MI (6 mo)</td>
<td>13 (15,250)</td>
<td>481/8,485 (5.7)</td>
<td>550/6,765 (8.1)</td>
<td>0.67 (0.60-0.76)</td>
</tr>
<tr>
<td>Composite (30 d)</td>
<td>20 (20,137)</td>
<td>926/11,676 (7.9)</td>
<td>978/8,461 (11.6)</td>
<td>0.65 (0.59-0.72)</td>
</tr>
<tr>
<td>Composite (6 mo)</td>
<td>13 (15,250)</td>
<td>1,817/8,485 (21.4)</td>
<td>1,624/6,765 (24.0)</td>
<td>0.85 (0.80-0.90)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>20 (20,137)</td>
<td>531/11,676 (4.6)</td>
<td>273/8,461 (3.2)</td>
<td>1.26 (1.09-1.46)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>18 (19,612)</td>
<td>14/11,373 (0.1)</td>
<td>10/8,239 (0.1)</td>
<td>0.89 (0.46-1.72)</td>
</tr>
</tbody>
</table>

*The composite outcome includes death, MI, or revascularization. For the last component, we used any target vessel revascularization, except for studies where this was not a trial outcome, in which case, urgent or all revascularizations were counted.

*The ADMIRAL and ERASER trials provided no data on hemorrhagic stroke. There was no statistically significant heterogeneity, and random effects estimates were very similar (data not shown), except for the composite outcome at 30 days (P = 0.04 for heterogeneity, and random effects RR 0.66 [95% CI, 0.57-0.75]) and major bleeding (P = 0.08 for heterogeneity, random effects RR 1.19 [95% CI, 0.96-1.48]).

Metaanalysis of 20 trials involving 20,137 patients shows >35% reduction in periprocedural myocardial infarction (MI) (using a CK-MB greater than three times normal definition), with a parallel reduction in the composite outcome including death, MI, or revascularization (Note: MI was the most prevalent component and therefore drove the reduction in the composite endpoint).

Modified from Karvouni E, et al. Intravenous glycoprotein IIb/IIIa receptor antagonists reduce mortality after percutaneous coronary interventions.
Figure 5.3 Metanalysis of GP IIb/IIIa inhibitors and mortality reduction. Mortality at 30-day (A) and at 6-month (B) follow-up. Risk ratios and 95% confidence intervals are shown for each study and for the random effects summary. P, PTCA; S, stenting. (From Karvouni E, et al. Intravenous glycoprotein IIb/IIIa receptor antagonists reduce mortality after percutaneous coronary interventions. J Am Coll Cardiol 2003;41:30.)

OR 2.13). Eptifibatide or tirofiban with heparin did not increase mild thrombocytopenia compared with placebo with heparin (OR 0.99). Patients receiving abciximab with heparin had more than twice the incidence of severe thrombocytopenia (defined as >20,000 and <50,000) than those receiving placebo with heparin (1.0% versus 0.4%, P = 0.01; OR 2.48). Eptifibatide or tirofiban with heparin did not cause a significant excess of severe thrombocytopenia compared with placebo with heparin (0.3% versus 0.2%, P = 0.16). ACS trials tended to report higher incidence of thrombocytopenia compared to
is associated with more ischemic events, bleeding complications from GP IIb/IIIa receptor inhibitors are infrequent and are producing heparin-induced thrombocytopenia (HIT). 127

The 2011 ACCF/AHA/SCAI Guidelines for Percutaneous Coronary Intervention specifically address intravenous GP IIb/IIIa inhibitor use in patients undergoing PCI. The recommendations are as follows:

**Guideline Recommendations**

The 2011 ACCF/AHA/SCAI Guidelines for Percutaneous Coronary Intervention specifically address intravenous GP IIb/IIIa inhibitor use in patients undergoing PCI. The recommendations are as follows:

**STEMI**

1. In patients undergoing primary PCI treated with unfractionated heparin (UFH), it is reasonable to administer a GP IIb/IIIa inhibitor (abciximab, double-bolus eptifibatide, or high-bolus dose tirofiban), whether or not patients were pretreated with clopidogrel. (For GP IIb/IIIa inhibitor administration in patients not pretreated with clopidogrel, Class 2, level of evidence: A; for GP IIb/IIIa inhibitor administration in patients pretreated with clopidogrel, Class 2, level of evidence: C.)

2. In patients undergoing primary PCI with abciximab, it may be reasonable to administer intracoronary abciximab. (Class 2, level of evidence: B)

3. Routine precatheterization laboratory (e.g., ambulance or emergency department) administration of GP IIb/IIIa inhibitors as part of an upstream strategy for patients with STEMI undergoing PCI is not beneficial. (Class 3, level of evidence: B)

**UA/NSTEMI**

1. In UA/NSTEMI patients with high-risk features (e.g., elevated troponin level) not treated with bivalirudin and not adequately pretreated with clopidogrel, it is useful at the time of PCI to administer a GP IIb/IIIa inhibitor (abciximab, double-bolus eptifibatide, or high-bolus dose tirofiban) in patients treated with UFH. (Class 1, level of evidence: A)

2. In UA/NSTEMI patients with high-risk features (e.g., elevated troponin level) treated with UFH and adequately pretreated with clopidogrel, it is reasonable at the time of PCI to administer a GP IIb/IIIa inhibitor (abciximab, double-bolus eptifibatide, or high-bolus dose tirofiban). (Class 2, level of evidence: B)

PCI trials, perhaps because of longer heparin infusions producing heparin-induced thrombocytopenia (HIT). 127

While uncommon, severe and profound (<20,000) thrombocytopenia requires immediate cessation of GP IIb/IIIa therapy. An algorithm for the evaluation and management of these patients has been proposed (Figure 5.4). 128 Pseudothrombocytopenia secondary to platelet clumping as well as HIT needs to be ruled out. The platelet count usually returns to normal within 48 to 72 hours in most cases. Severe and profound thrombocytopenia from GP IIb/IIIa receptor inhibitors are infrequent and are more commonly associated with abciximab use. Regardless of its etiology, thrombocytopenia in patients undergoing PCI is associated with more ischemic events, bleeding complications, and transfusions. 129 The mechanism(s) of thrombocytopenia is unknown. The platelet count falls within hours of GP IIb/IIIa administration. Readministration of abciximab, but not the small molecule inhibitors (eptifibatide and tirofiban), is associated with a small increased risk of thrombocytopenia. 130

### Table 5.2 Randomized Trials of Glycoprotein IIb/IIIa Inhibitor Therapy During PCI in the Context of Routine Stenting and Adequate Thienopyridine Pre-loading

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>n</th>
<th>Study Population</th>
<th>% Complex (Type B/C) Coronary Lesions</th>
<th>% Diabetes</th>
<th>GPI vs. Placebo</th>
<th>% Patients Requiring Transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISAR-REACT (2004)</td>
<td>2,159</td>
<td>Stable CAD</td>
<td>65</td>
<td>21</td>
<td>4% vs. 4%, P = NS</td>
<td>2% vs. 2%, P = NS</td>
</tr>
<tr>
<td>ISAR-SWEET (2004)</td>
<td>701</td>
<td>Stable CAD diabetes</td>
<td>68</td>
<td>100</td>
<td>5.7% vs. 4.3%, P = 0.39</td>
<td>3.4% vs. 1.4%, P = 0.09</td>
</tr>
<tr>
<td>BRAVE-3 (2009)</td>
<td>800</td>
<td>STEMI</td>
<td>—</td>
<td>19</td>
<td>4.7% vs. 3.5%, P = NS</td>
<td>3.7% vs. 1.8%, P = 0.06</td>
</tr>
<tr>
<td>ISAR-REACT 2 (2006)</td>
<td>2,022</td>
<td>ACS ↑ troponin in 51%</td>
<td>80</td>
<td>25</td>
<td>8.9% vs. 11.9%, P = 0.03</td>
<td>4.2% vs. 3.3%, P = NS</td>
</tr>
</tbody>
</table>

*In the BRAVE-3 trial, abciximab was not associated with a reduction in infarct size (the primary end point). Patients were pre-loaded with 600 mg of clopidogrel in the emergency department. In patients with elevated troponin values, event rates with GPI versus placebo: 13.1% vs. 18.3%, P = 0.02. In patients without troponin elevation, event rates with GPI versus placebo: 4.6% vs. 4.6%, P = 0.99.

ACS, indicates acute coronary syndrome(s); GPI, glycoprotein IIb/IIIa inhibitor; N/A, not available; NS, nonsignificant; PCI, percutaneous coronary intervention; TIMI, Thrombolysis In Myocardial Infarction; UFH, unfractionated heparin; MI, myocardial infarction; CAD, coronary artery disease; STEMI, ST-segment elevation myocardial infarction. Adapted from Hanna EB, et al. J Am Coll Cardiol Interv 2010;3:1209–1219.
Stable Ischemic Heart Disease

1. In patients undergoing elective PCI treated with UFH and not pretreated with clopidogrel, it is reasonable to administer a GP IIb/IIIa inhibitor (abciximab, double-bolus eptifibatide, or high-bolus dose tirofiban). (Class 2, level of evidence: B)

2. In patients undergoing elective PCI with stent implantation treated with UFH and adequately pretreated with clopidogrel, it might be reasonable to administer a GP IIb/IIIa inhibitor (abciximab, double-bolus eptifibatide, or high-bolus dose tirofiban). (Class 2, level of evidence: B)
Adjunctive antithrombotic agents for PCI function by inhibiting protease activity of blood coagulation enzymes (Figure 5.5) resulting in decreased thrombin production or activity and decreased fibrin formation. The main antithrombotic agents used during PCI include UFH, LMWHs (enoxaparin and dalteparin), factor Xa agents (fondaparinux), and direct thrombin inhibitors (bivalirudin and argatroban).

Unfractionated Heparin

UFH is a commonly used anticoagulant during PCI. UFH is a heterogeneous mixture of polysaccharide molecules that range from 2,000 to 30,000 Daltons. The anticoagulant mechanism of action of UFH is related to factor Xa inhibition by a specific pentasaccharide moiety and to thrombin inhibition by long-chain saccharide units. The long pentasaccharides chains (>18 units) bind to antithrombin resulting in a 1,000-fold increase in antithrombin inhibitory activity. The UFH:antithrombin complex inactivates multiple proteases including factors Xa, IXa, Xla, XIla, and thrombin. The inhibitory activity of UFH is a ratio of 1 to 1 for factor Xa and thrombin. By inhibiting thrombin activation, UFH prevents fibrin formation and inhibits thrombin-induced platelet activation. Immediate anticoagulant effect can be achieved following IV bolus injection followed by continuous IV infusion, making IV administration the preferred route for ACSs. UFH binds to a number of plasma proteins and cell surface proteins that attenuate its activity. This nonspecific protein binding results in variable anticoagulant activity and thus requires monitoring of the therapeutic effect. At standard doses, UFH elimination occurs through a nonlinear depolymerization process that occurs when UFH binds to endothelial cells and macrophages. The half-life of UFH is approximately 30 minutes following administration of an IV bolus of 25 U/kg.

Low-Molecular-Weight Heparin

LMWHs are produced by depolymerizing UFH polysaccharide chains. LMWHs range from 2,000 to 10,000 Daltons and although they contain the pentasaccharide sequence necessary to bind to antithrombin, LMWHs are too short to crosslink antithrombin and thrombin. Therefore, the primary effect of LMWHs is limited to antithrombin-dependent factor Xa inhibition. In comparison to UFH where the ratio of factor Xa:thrombin inhibition is 1:1, LMWHs preferentially inhibit factor Xa and have a factor Xa:thrombin inhibition ratio that varies from 2:1 to 4:1. The most commonly used LMWHs enoxaparin and dalteparin have respective anti-Xa:antithrombin ratios of 3.8:1 and 2.7:1. Compared to UFH, LMWHs bind less avidly to plasma and cell surface proteins and therefore have more predictable pharmacokinetics profiles. Laboratory monitoring of LMWH anticoagulant effect is not routinely required although the therapeutic effect can be assessed by measuring anti-Xa levels. Following subcutaneous injection, LMWHs are 90% bioavailable and the measured anti-Xa effect peaks 3 to 5 hours after administration. LMWHs are cleared by kidney-dependent mechanisms and the drug accumulates in a linear fashion in patients that have impaired renal function. In patients with normal renal function, the half-life of LMWHs is 3 to 6 hours after subcutaneous administration.

**Figure 5.5**

Pathways of Blood Coagulation during Hemostasis and Thrombosis. Tissue factor forms a complex with circulating factor VIIa. This complex, which plays a major role in coagulation, has three substrates: factor VII, factor IX, and factor X. Factor IXa binds to factor VIII. This complex activates factor X to form factor Xa. Factor Xa, generated by the tissue factor–factor VIIa complex or the factor IXa–factor VIII complex, binds factor V on membrane surfaces. This complex converts prothrombin to thrombin. TF, indicates encrypted tissue factor; PDI, protein disulfide isomerase. (From Furie B, Furie BC. Mechanisms of thrombus formation. *N Engl J Med* 2008;359:938–949.)
Factor Xa Inhibitors
Fondaparinux, which is a selective factor Xa inhibitor, is a synthetic 1,728 Dalton LMWH that contains an antithrombin inhibitory pentasaccharide sequence, but because fondaparinux is not long enough to bridge antithrombin to thrombin, it has no thrombin-inhibitory activity. After subcutaneous injection, fondaparinux is 100% bioavailable. The half-life of fondaparinux is 17 hours and because the primary mechanism of clearance is renal, fondaparinux is contraindicated in patients with severe renal dysfunction. Similar to LMWHs, the anticoagulant effect of fondaparinux can be assessed by measuring anti-factor Xa levels. However, due to the minimal nonspecific binding to plasma and cell surface proteins and the predictable anticoagulant effect, routine anticoagulation monitoring is not required.\(^\text{142}\)

Direct Thrombin Inhibitors
The direct thrombin inhibitors (DTIs) (lepirudin, argatroban, and bivalirudin) have been used during PCI in lieu of UFH.\(^\text{143-145}\) Of these agents, bivalirudin has been the most extensively studied.\(^\text{144,146-148}\) DTIs do not require antithrombin and they exert their anticoagulant effect by directly binding to and inhibiting thrombin catalytic activity. In addition to inhibiting thrombin-dependent fibrin production, DTIs also reduce thrombin-mediated platelet activation and aggregation.\(^\text{149}\) Compared to other antithrombotic agents used for PCI, DTIs bind to and inhibit clot-bound thrombin in addition to circulating free thrombin, which provides a theoretical advantage in the treatment of atherosclerotic ACS.

The original DTI hirudin was isolated from the salivary gland of leeches. Lepirudin is a recombinant form of hirudin, which is a 65-amino acid polypeptide that has a plasma half-life of 60 minutes following intravenous injection.\(^\text{150}\) Renal clearance is the primary mechanism of elimination and dose reduction is required in patients with renal dysfunction.\(^\text{150}\) Lepirudin is mainly used as an anticoagulant in patients with HIT. Argatroban is a competitive small molecule thrombin inhibitor that undergoes hepatic clearance with a plasma half-life of 45 minutes.\(^\text{151}\) No dose adjustment is required for patients with renal dysfunction although argatroban should be used cautiously in patients with liver dysfunction.\(^\text{152}\) Similar to lepirudin, argatroban is primarily used as an anticoagulant in patients with HIT. Bivalirudin is the best validated and most commonly used DTI for PCI. Bivalirudin is a synthetic 20-amino acid polypeptide derivative of hirudin. Bivalirudin interacts with thrombin in a 1:1 ratio and after thrombin cleaves the amino terminal portion of bivalirudin, bivalirudin is released and thrombin enzymatic activity returns.\(^\text{153}\) Bivalirudin undergoes hepatic metabolism with some dependence on renal excretion and the half-life of the drug is 25 minutes.\(^\text{154,155}\) Because of the partial renal excretion, bivalirudin is administered at reduced doses in patients with severe renal dysfunction.\(^\text{156}\) Clinical data support the use of bivalirudin in UA/NSTEMI prior to initiation of cardiac catheterization,\(^\text{157}\) instead of UFH plus GP IIb/IIIa inhibitor during primary PCI for STEMI,\(^\text{158}\) and for anticoagulation treatment of patients with HIT.\(^\text{159}\)

Dosing for Percutaneous Coronary Intervention
Guideline-based dosing recommendations for common antithrombotic agents used during PCI are summarized in Table 5.3. UFH dosing is guided by ACT monitoring during PCI because the required level of anticoagulation is beyond the linear range that can be measured using the activated partial thromboplastin time (aPTT).\(^\text{160,161}\) At least two studies have retrospectively related ACT values to clinical outcomes after PCI.\(^\text{162,163}\) A third retrospective analysis of data from 5,216 patients receiving heparin during PCI suggested that ischemic complications at 7 days were 34% lower with an ACT in the range of 350 to 375 seconds than they were with an ACT between 171 and 295 seconds (P = 0.001).\(^\text{164}\) Although ischemic complications were reduced at higher levels of ACT, this was at the cost of progressively increased bleeding from 8.6% at ACTs <350 seconds to 12.4% at ACTs 350 to 375 seconds. A substantial increase in bleeding events was observed when ACT values exceeded 400 seconds.\(^\text{164}\) Importantly, these studies were performed in patients given heparin without adjunctive GP IIb/IIIa inhibitors that require lower ACT targets (see below).

The dosing regimen for heparin was evaluated in two small randomized trials comparing empiric and weight-adjusted heparin dosing. Both approaches showed comparable results.\(^\text{165-168}\) Based on these data, heparin is given in doses of 70 to 100 IU/kg to achieve a target ACT between 250 and 350 seconds in the absence of adjunctive GP IIb/IIIa inhibition. In contrast, the target ACT is 200 to 250 seconds when heparin (bolus dose of UFH 40 to 60 IU/kg) is given in conjunction with a GP IIb/IIIa inhibitor. Removal of the femoral sheath should be delayed until the ACT is between 150 and 180 seconds, unless a puncture closure device is used. Heparin is no longer used routinely after PCI because several randomized studies have showed that prolonged heparin infusion increases bleeding at catheter insertion sites and has no ischemic benefit.\(^\text{167}\)

Enoxaparin dosing during PCI is dependent on whether patients received a dose prior to initiation of the procedure, and in patients that received enoxaparin prior to the initiation of PCI, the administration of additional anticoagulation therapy is dependent on the timing of the last dose of enoxaparin. If the last dose of enoxaparin was administered 8 hours prior to PCI, no additional anticoagulant therapy is recommended. If the last dose of enoxaparin was administered between 8 hours and 12 hours before PCI, a 0.3 mg/kg bolus of IV enoxaparin at the time of PCI is suggested. If the last enoxaparin dose was administered more than 12 hours before PCI, conventional anticoagulation therapy during PCI is advised. Routine procedural anticoagulation monitoring is not recommended.
Table 5.3  Dosing of Parenteral Anticoagulants During Percutaneous Coronary Intervention

<table>
<thead>
<tr>
<th>Drug</th>
<th>Patient Has Received Prior AnticoagulantTherapy</th>
<th>Patient Has Not Received Prior AnticoagulantTherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>UFH</td>
<td>■ IV GPI planned: additional UFH as needed (e.g., 2,000–5,000 U) to achieve an ACT of 200–250 s</td>
<td>■ IV GPI planned: 50–70 U/kg bolus to achieve an ACT of 200–250 s</td>
</tr>
<tr>
<td></td>
<td>■ No IV GPI planned: additional UFH as needed (e.g., 2,000–5,000 U) to achieve an ACT of 250–300 s for HemoTec, 300–350 s for Hemochron</td>
<td>■ No IV GPI planned: 70–100 U/kg bolus to achieve target ACT of 250–300 s for HemoTec, 300–350 s for Hemochron</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>■ For prior treatment with enoxaparin, if the last SC dose was administered 8 to 12 h earlier or if only 1 SC dose of enoxaparin has been administered, an IV dose of 0.3 mg/kg of enoxaparin should be given.</td>
<td>0.5–0.75 mg/kg IV bolus</td>
</tr>
<tr>
<td></td>
<td>■ If the last SC dose was administered within the prior 8 h, no additional enoxaparin should be given.</td>
<td></td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>For patients who have received UFH, wait 30 min, then give 0.75 mg/kg IV bolus, then 1.75 mg/kg/h IV infusion.</td>
<td>0.75 mg/kg bolus, 1.75 mg/kg/h IV infusion</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>For prior treatment with fondaparinux, administer additional IV treatment with an anticoagulant possessing anti-IIa activity, taking into account whether GPI receptor antagonists have been administered.</td>
<td>N/A</td>
</tr>
<tr>
<td>Argatroban</td>
<td>200 mcg/kg IV bolus, then 15 mcg/kg/min IV infusion</td>
<td>350 mcg/kg bolus, then 25 mcg/kg/min IV infusion</td>
</tr>
</tbody>
</table>

ACT, activated clotting time; IV, intravenous; GPI, glycoprotein inhibitor; N/A, not applicable; PCI, percutaneous coronary intervention; SC, subcutaneous; and UFH, unfractionated heparin. (Adapted from 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, Circulation 2011; 124:e574-e651.)

Fondaparinux administered at 2.5 mg daily subcutaneously has been shown to have the best efficacy/safety profile when compared to higher doses in ACS patients.168 Fondaparinux has not been effectively studied in patients with severe renal impairment (creatinine clearance < 30 mL/minute); however, in patients with moderate renal impairment (creatinine clearance 30 to 50 mL/minute), fondaparinux dose should be reduced in half.169 Although fondaparinux is an acceptable anticoagulant regimen for ACS patients, it is not suitable for use as a primary anticoagulant for PCI because it is associated with a significant increase in intraprocedural catheter thrombosis.1 For this reason, fondaparinux-treated patients require additional procedural anticoagulation during PCI, and fondaparinux is preferred for patients being managed with a conservative rather than early invasive treatment strategy as outlined below.1

Lepirudin is typically administered intravenously as a 0.4 mg/kg bolus followed by a 0.15 mg/kg/hour infusion which is titrated to achieve an aPTT 1.5 to 3 times control.169 Bivalirudin is administered intravenously for PCI procedures as a 0.75 mg/kg bolus followed by 1.75 mg/kg/hour infusion which is continued for the duration of the PCI procedure. In patients with severe renal dysfunction the half-life of bivalirudin may be increased, and sheath removal should be delayed for 2 hours for patients with normal renal function and up to 8 hours for patients on dialysis. Bivalirudin increases the ACT in a nonlinear fashion and routine monitoring of the anticoagulant effect is not required. However, it is still recommended to obtain an ACT after the intravenous bolus to confirm that it has been appropriately administered.

Evidence for Use in Percutaneous Coronary Intervention Patients

Evidence for Unfractionated Heparin Use in Percutaneous Coronary Intervention

Guideline recommendations for UFH use in ACS are based on metaanalyses of placebo-controlled trials with UFH for treatment of UA/NSTEMI.170-176 In these studies, treatment...
with aspirin and UFH compared to aspirin alone resulted in a 54% reduction in death and MI; however, bleeding was increased in the heparin-treated group. As noted above, the data for heparin use during PCI are derived from retrospective studies where ACT values between 300 and 350 were associated with improved clinical outcomes in patients undergoing PCI.162-164

Evidence for Low-Molecular-Weight Heparin Use in Percutaneous Coronary Intervention

The use of the LMWH as an alternative anticoagulant to UFH in the PCI setting has been largely driven by trials showing superiority of enoxaparin compared to UFH in the medical treatment (i.e., noninterventional) of patients with ACSs. The Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events (ESSENCE) trial compared enoxaparin (1 mg/kg twice daily subcutaneous administration) with standard UFH (5,000 U bolus), followed by an infusion titrated to an aPTT of 55 to 86 seconds. The composite outcome of death, MI, or recurrent angina was reduced by 16.2% at 14 days with enoxaparin (19.8% UFH versus 16.6% enoxaparin, \( P = 0.019 \)) and by 19% at 30 days (23.3% versus 19.8%, \( P = 0.017 \)). Similarly, the TIMI 11B trial randomized patients with UA/NSTEMI to enoxaparin (30 mg intravenous initial bolus immediately followed by subcutaneous injections of 1 mg/kg every 12 hours) or UFH (70 U/kg bolus followed by an infusion of 15 U/kg/hour) titrated to a target aPTT 1.5 to 2.5 times control.177 The composite endpoint of death, MI, or need for an urgent revascularization was reduced at 8 days from 14.5% to 12.4% (\( P = 0.048 \)) and at 43 days from 19.6% to 17.3% (\( P = 0.048 \)). The risk of minor bleeding, however, was increased both in and out of hospital with enoxaparin.178

In contrast to enoxaparin, the superiority of the other LMWHs dalteparin and nadroparin compared to UFH was not observed in the FRagmin In unstable Coronary artery disease (FRIC)179 and FRAXiparine in Ischaemic Syndrome (FRAXIS)180 trials, respectively. These heterogeneous results may be explained by different populations, study designs, various heparin dose regimens, or properties of specific LMWH preparations related to their different molecular weights and variable anti-factor Xa/antithrombin ratios.

Four randomized studies181,182 have compared the safety and efficacy of UFH to enoxaparin during PCI. In the Coronary Revascularization Using Integrilin and Single Bolus Enoxaparin (CRUISE) study, patients undergoing elective or emergent PCI were randomized to epiftibatide and enoxaparin or epiftibatide plus UFH.184 The primary endpoint of the study, the bleeding index (change in hemoglobin corrected for blood transfusions), was 0.8 in the patients randomized to enoxaparin and 1.1 in patients randomized to UFH (\( P = 0.15 \)). The rate of vascular access site complications was 9.3% in the enoxaparin arm versus 9.8% in the UFH arm (\( P = NS \)). There were no significant differences in the composite of death, MI, or urgent TVR at 30 days (enoxaparin 8.5% versus UFH 7.6%, \( P = NS \)). CRUISE demonstrated comparable safety and efficacy of enoxaparin to UFH during PCI in a randomized controlled study.

The Integrilin and Enoxaparin Randomized Assessment of Acute Coronary Syndrome Treatment (INTERACT) study randomized 746 patients with high-risk ACS to receive epiftibatide plus either enoxaparin (1 mg/kg twice daily subcutaneously for 48 hours), or weight-adjusted UFH for 48 hours.182 Cardiac catheterization and coronary revascularization were performed at the discretion of the investigator (63% of patients underwent angiography, 28.5% underwent PCI). The primary safety endpoint was the incidence of major non–CABG-related bleeding at 96 hours. Compared with UFH, enoxaparin significantly reduced the rate of non–CABG-related major bleeding: 3.8% versus 1.1% at 48 hours (\( P = 0.014 \)) and 4.6% versus 1.8% at 96 hours (\( P = 0.03 \)), respectively. The rate of the secondary endpoint, death or MI, was significantly lower in the enoxaparin group than in the UFH group (3% versus 9%, respectively; \( P = 0.03 \)). Recurrent ischemia, determined by continuous electrocardiographic monitoring, was significantly lower in the enoxaparin group compared with the UFH group, both during the initial 48 hours (14.3% versus 25.4%; \( P = 0.0002 \)) and from 48 to 96 hours following study entry (12.7% versus 25.9%; \( P < 0.0001 \)).

The Aggrastat to Zocor (A to Z) study was designed to assess efficacy and safety of the combination of enoxaparin and tirofiban compared with UFH and tirofiban in patients with non–ST-elevation ACS.183 The primary endpoint of death, recurrent MI, or refractory ischemia occurred in 8.4% of patients randomized to enoxaparin compared to 9.4% of patients randomized to UFH (HR, 0.88; 95% CI, 0.71 to 1.08). This met the prespecified criterion for noninferiority. Rates for any TIMI grade bleeding were low (3.0% for enoxaparin and 2.2% for UFH; \( P = 0.13 \)).

In Superior Yield of the New strategy of Enoxaparin Revascularization and Glycoprotein Ilb/Ilia inhibitors (SYNERGY) trial, 10,027 high-risk ACS patients were randomized to enoxaparin (1 mg/kg twice daily subcutaneously) or UFH (60 U/kg bolus followed by 12 U/kg/hour infusion) with a goal of early invasive therapy. The primary composite clinical endpoint of all-cause death or nonfatal MI during the first 30 days occurred in 14% of patients assigned to enoxaparin and 14.5% of patients assigned to UFH (OR, 0.96; 95% CI, 0.86 to 1.06). No differences in ischemic events during PCI were observed between enoxaparin and UFH groups, respectively, including similar rates of abrupt closure, threatened abrupt closure, unsuccessful PCI, or emergency CABG surgery. More bleeding was observed with enoxaparin, with a statistically significant increase in TIMI major bleeding (9.1% versus 7.6%, \( P = 0.008 \)) but nonsignificant excess in Global Utilization of Streptokinase and t-PA for Occluded Arteries (GUSTO), severe bleeding (2.7% versus 2.2%, \( P = 0.08 \)), and transfusions (17.0% versus 16.0%, \( P = 0.16 \)). Subgroup analysis suggested that crossover therapy and protocol violations contributed adversely to bleeding complications.
In summary, enoxaparin appears to be equally effective as UFH during PCI at preventing MACE with modest excess of major bleeding. Difficulties associated with monitoring the anticoagulation intensity of enoxaparin during PCI have led to empiric dosing algorithms and consensus statements guiding its use based on pharmacokinetic and registry data.\textsuperscript{1,184} It is important to note that steady state anticoagulation without intravenous bolus of enoxaparin (0.3 mg/kg) requires three subcutaneous doses.

\section*{Evidence for Direct Thrombin Inhibitor Use in Percutaneous Coronary Intervention}

DTIs offer a number of theoretical advantages over UFH such as direct action, predictable pharmacokinetics, and inhibition of clot-bound thrombin and thrombin-mediated platelet activation. The Bivalirudin Angioplasty Trial (BAT) randomized 4,098 high-risk patients with ACS undergoing PCI to high-dose heparin bolus (175 IU/kg bolus followed by a 15 IU/kg/hour infusion for 18 to 24 hours) or to bivalirudin (1.0 mg/kg bolus followed by an infusion of 2.5 mg/kg/hour for 4 hours, reduced to 0.2 mg/kg/hour for the next 14 to 20 hours).\textsuperscript{147} Bleeding complications were reduced with bivalirudin and ischemic complications were lower in the subset of patients with post infarction angina. Reanalysis of this data using a post infarction angina. Reanalysis of this data using a treating analysis demonstrated lower rates of death (2.1\% versus 3.1\%, \(P = 0.047\)) and major bleeding (4.9\% versus 8.3\%; \(P < 0.001\)) at 30 days compared to the heparin plus GP IIb/IIIa group. Reduced bleeding resulted in a significantly lower rate of the net adverse clinical event endpoint which included death, ischemic, and bleeding events (9.2\% bivalirudin versus 12.1\% UFH/GP IIb/IIIa, \(P = 0.005\)). The bivalirudin group however had a 1\% absolute increase in the rate of acute stent thrombosis. Bivalirudin treatment was associated with reduced 1-year rates of cardiac mortality (2.1\% versus 3.8\%, HR 0.57, 0.38 to 0.84, \(P = 0.005\)) and all-cause mortality (3.5\% versus 4.8\%, HR 0.71, 0.51 to 0.98, \(P = 0.037\)), respectively, compared to UFH/GP IIb/IIIa treatment group.\textsuperscript{148} Figure 5.6 presents data from a metaanalysis evaluating the efficacy and safety of bivalirudin compared with UFH or enoxaparin plus GP IIb/IIIa inhibitors in patients undergoing PCI. The metaanalysis data demonstrate that anticoagulation with bivalirudin monotherapy results in similar ischemic adverse events and a significant reduction in major bleeding.\textsuperscript{185} Due to the growing appreciation of the adverse effect of bleeding on near and later term morbidity and mortality,\textsuperscript{186-188} bivalirudin has largely replaced UFH-GP IIb/IIIa inhibitor regimens in both elective and ACS PCI in the United States. Due to cost considerations, UFH and oral ADP receptor antagonists remain the dominant regimens outside of North America.

\section*{Adverse Reactions}

Antithrombotic agent administration increases bleeding and some of the key differences in bleeding risk between...
The anticoagulant effect of enoxaparin can be partially reversed with protamine. Protamine attenuates the antithrombin effect of enoxaparin; however, it has a limited effect on enoxaparin inhibition of factor Xa.192 The reversal dose for patients treated with enoxaparin is 1 mg of protamine for each 1 mg of enoxaparin.193 Compared to UFH, enoxaparin is less likely to induce antiplatelet factor-4 antibodies193 and is less likely to induce HIT in patients with preformed antiplatelet factor-4 antibodies.193,194 In the presence of HIT, LMWHs can worsen thrombocytopenia and increase risk of thrombosis; therefore LMWH cannot be used in HIT patients.

Because of its specific factor Xa activity, protamine does not reverse the anticoagulant action of fondaparinux. In the setting of severe, life-threatening bleeding, recombinant factor VIIa can be given to reverse fondaparinux anticoagulation.195 Fondaparinux does not induce the formation of platelet-factor-4 antibody complexes and it does not cross-react with HIT antibodies.196 Although it is not specifically approved for HIT therapy, fondaparinux has been used successfully to treat patients with HIT.197

Although the anticoagulant effect of bivalirudin dissipates quickly because of its fast elimination (25 minute half-life), there is no reversal agent available in the event of life-threatening bleeding. Lepirudin is immunogenic and will induce antibody formation in approximately 40% of patients. Hypersensitivity and anaphylaxis to lepirudin can occur.
when sensitized patients are reexposed. Bivalirudin, which is a smaller molecule than lepirudin, is not immunogenic and does typically cause hypersensitivity.

**Guideline Recommendations**

The 2011 ACCF/AHA/SCAI Guidelines for Percutaneous Coronary Intervention specifically address antithrombotic agent use in patients undergoing PCI. The recommendations are as follows:

- **Use of Parenteral Anticoagulants during PCI**
  1. An anticoagulant should be administered to patients undergoing PCI. (Class 1, level of evidence: C)

- **UFH: Recommendations**
  1. Administration of IV UFH is useful in patients undergoing PCI. (Class 1, level of evidence: C)

- **Enoxaparin: Recommendations**
  1. An additional dose of 0.3 mg/kg IV enoxaparin should be administered at the time of PCI to patients who have received fewer than 2 therapeutic subcutaneous doses (e.g., 1 mg/kg) or received the last subcutaneous enoxaparin dose 8 to 12 hours before PCI. (Class 1, level of evidence: B)
  2. Performance of PCI with enoxaparin may be reasonable in patients either treated with “upstream” subcutaneous enoxaparin for UA/NSTEMI or who have not received prior antithrombin therapy and are administered IV enoxaparin at the time of PCI. (Class 2, level of evidence: B)
  3. UFH should not be given to patients already receiving therapeutic subcutaneous enoxaparin. (Class 3, level of evidence: B)

- **Fondaparinux: Recommendations**
  1. Fondaparinux should not be used as the sole anticoagulant to support PCI. An additional anticoagulant with anti-IIa activity should be administered because of the risk of catheter thrombosis. (Class 3, level of evidence: C)

- **Bivalirudin and Argatroban: Recommendations**
  1. For patients undergoing PCI, bivalirudin is useful as an anticoagulant with or without prior treatment with UFH. (Class 1, level of evidence: B)

**Other Pharmacologic Agents**

Although a review of vasoactive, sedative, and antiarrhythmic drugs used in the cardiac catheterization laboratory is beyond the scope of this book, the following table of drug doses used at the Brigham and Women's Hospital is provided as a quick reference (Table 5.4). As always, the doses and contraindications for all drugs should be confirmed from a primary source (package insert, PDR, etc.) before administration.

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Agent</th>
<th>Dosing and Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulants</td>
<td>Heparin, unfractionated (UFH)</td>
<td>IV bolus and infusion:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Initial bolus 70–100 IU/kg for PCI without IIb/IIa, to ACT 250–300 s</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Reduce bolus to 50–60 IU/kg for PCI with IIb/IIa blocker, to ACT 200–250 s</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- If procedure longer than 1 h, recheck ACT and rebolus (1,500–2,000 units) as needed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- May be reversed with protamine sulfate (1 mL = 10 mg, reverses 1,000 units of heparin); maximum dose 50 mg</td>
</tr>
<tr>
<td></td>
<td>Low–molecular-weight heparin (Enoxaparin)</td>
<td>Subcutaneous dose:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 1 mg/kg BID SC for 2 to 8 days, administered with aspirin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Reduce to 0.5 mg/kg BID if renal insufficiency</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IV dose for PCI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- For full anticoagulation without IIb/IIa blocker: 1.0 mg/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- With a IIb/IIa blocker: reduce bolus to 0.5–0.75 mg/kg for full anticoagulation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- To supplement SC dose given 8–12 h previously: 0.3 mg/kg IV bolus; also consider 0.3 mg/kg IV bolus if patient not at steady state anticoagulation with SC dosing (i.e., &lt; 3 doses)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Does not prolong ACT owing to high Xa/IIa ratio</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Partial reversal with protamine: 1 mg protamine/1 mg enoxaparin &lt;8 h last SC dose; 0.5 mg protamine/1 mg enoxaparin 8–12 h</td>
</tr>
</tbody>
</table>
Table 5.4
Continued

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Agent</th>
<th>Dosing and Comments</th>
</tr>
</thead>
</table>
| Antiplatelet Agents         | Aspirin 160–325 mg tablets | ■ 325 mg oral loading dose
■ 81–100 mg QD maintenance   |
| ADP Receptor Antagonists    | Clopidogrel 75 mg tablets  | ■ 600 mg oral loading dose
■ 75 mg QD maintenance
■ 4 wk for bare-metal stents; 12 mo for drug-eluting stents; lifetime for brachytherapy |
|                             | Prasugrel                  | ■ 60 mg oral loading dose
■ 10 mg QD oral maintenance
■ FDA approved for ACS patients
■ Duration as for clopidogrel above |
|                             | Ticagrelor                 | ■ 180 mg oral loading dose
■ 90 mg BID oral maintenance
■ FDA approved for ACS patients
■ To be used with low-dose aspirin only (81–100 mg aspirin QD)
■ Duration as for clopidogrel above |
|                             | Ticlopidine 250 mg tablets (Ticlid) | ■ 750 mg oral loading dose
■ 250 mg BID oral maintenance
■ Duration as for clopidogrel above
■ Monitor for thrombocytopenia and neutropenia if duration >2 wk
■ Plavix/prasugrel/ticagrelor are preferred |
| IIb/IIIa inhibitors         | Abciximab (ReoPro)         | PCI or acute coronary syndromes with planned PCI within 24 h:
■ 0.25 mg/kg IV bolus (10–60 min before procedure), then 0.125 µg/kg/min (maximum of 10 µg/min) IV infusion, × 18–24 h
■ Check platelets at 4 h of infusion to monitor for thrombocytopenia |
|                             | Eptifibatide (Integrilin)  | For PCI:
■ 180 µg/kg IV bolus
■ Repeat the same dose in 10 min
■ Infuse 2 µg/kg/min for 18 h
■ Reduce infusion to 1 µg/kg/min for creatinine clearance <50 mL/min
■ Maximum dose (reached at patient weight of 121 kg): 22.6 mg IV bolus × 2, then maximum infusion of 242 µg/min |
|                             | Tirofiban (Aggrastat)      | Acute coronary syndromes
■ 0.4 µg/kg/min IV for 30 min, then 0.1 µg/kg/min IV infusion
■ Not recommended for PCI |
| Arrhythmia Bradycardia      | Atropine sulfate          | For vasovagal or symptomatic sinus bradycardia
■ 0.5 to 1.0 mg IV every 3–5 min as needed
■ Do not exceed total dose of 0.04 mg/kg |

(Continued)
### Table 5.4
Commonly Used Cath Lab Pharmacology at the Brigham and Women’s Hospital (Continued)

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Agent</th>
<th>Dosing and Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Isoproterenol</strong></td>
<td></td>
<td>IV Infusion for bradycardia owing to infranodal block with slow ventricular escape:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ Mix 2 mg in 250 mL D5W</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ Infuse at 2–10 μg/min, titrated to adequate heart rate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ In torsade de pointes, titrate to increase heart rate until VT rhythm is suppressed</td>
</tr>
<tr>
<td><strong>Atrial fibrillation or flutter</strong></td>
<td>Dofetilide</td>
<td>IV infusion dose for atrial fibrillation or flutter</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ Single infusion of 8 μg/kg over 30 min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ Not approved for use in the United States</td>
</tr>
<tr>
<td><strong>Ibutilide</strong></td>
<td></td>
<td>IV dose for atrial fibrillation or flutter (for adults ≥60 kg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ 1 mg (10 mL) administered IV (diluted or undiluted) over 10 min. A second dose may be administered at the same rate 10 min after completion of first dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ For atrial fibrillation or flutter</td>
</tr>
<tr>
<td><strong>Supraventricular tachycardia</strong></td>
<td>Adenosine</td>
<td>IV rapid push to convert SVT (see vasodilator below for use in no-reflow or FFR measurement)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ Initial bolus of 6 mg given rapidly over 1–3 s followed by normal saline bolus of 20 mL; then elevate the extremity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ Repeat dosage of 12 mg in 1–2 min if needed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ A third dose of 12 mg may be given in 1–2 min if needed</td>
</tr>
<tr>
<td><strong>Ventricular</strong></td>
<td>Lidocaine</td>
<td>For stable VT, wide-complex tachycardia or uncertain type, significant ectopy:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ 1.0 to 1.5 mg/kg IV push</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ Repeat 0.5–0.75 mg/kg every 5–10 min; maximum total dose: 3 mg/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ Maintenance infusion 1–4 mg/min (30–50 μg/kg/min)</td>
</tr>
<tr>
<td><strong>Amiodarone</strong></td>
<td></td>
<td>For VF</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ IV push 300 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ Repeat 150 mg over 2–5 min, if necessary</td>
</tr>
<tr>
<td><strong>Procainamide</strong></td>
<td></td>
<td>For VEA or stable VT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ Rapid infusion: 150 mg in 50 mL over 10 min, repeat every 10 min as needed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ Slow infusion: 360 mg IV over 6 h (1 mg/min)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ Maintenance infusion: 540 mg IV over 18 h (0.5 mg/min)</td>
</tr>
<tr>
<td><strong>Magnesium sulfate</strong></td>
<td></td>
<td>Recurrent VF/VF:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ 20 mg/min IV infusion (maximum total dose: 17 mg/kg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ In urgent situations, up to 50 mg/min may be administered to total dose of 17 mg/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ Suspend loading infusion if one of the following occurs:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ Arrhythmia suppression</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ Hypotension</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ QRS widens by &gt;50%.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ Maintenance infusion 1–4 mg/min</td>
</tr>
<tr>
<td><strong>Cardiac arrest</strong></td>
<td></td>
<td>Cardiac arrest (for hypomagnesemia or torsade de pointes):</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ 1–2 g (2–4 mL of a 50% solution) diluted in 10 mL of D5W IV push</td>
</tr>
<tr>
<td></td>
<td></td>
<td>torsade de pointes (not in cardiac arrest):</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ Loading dose of 1–2 g mixed in 50–100 mL of D5W over 5–60 min IV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ Follow with 0.5 to 1.0 g/h IV (titrate dose to control the torsade) for up to 24 h</td>
</tr>
</tbody>
</table>
### Table 5.4

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Agent</th>
<th>Dosing and Comments</th>
</tr>
</thead>
</table>
| Sodium bicarbonate   |       | For prolonged cardiac arrest—IV bolus  
|                      |       | - 1 mEq/kg IV bolus  
|                      |       | - Repeat half this dose every 10 min thereafter  
|                      |       | - If rapidly available, use arterial blood gas analysis to guide bicarbonate therapy (calculated base deficits or bicarbonate concentration)  
|                      |       | - An acute change in PaCO₂ of 1 mmHg is associated with an increase or decrease in pH of 0.008 U (relative to normal pH of 7.4)  |
| Beta blockers        | Esmolol| 0.5 mg/kg over 1 min, followed by continuous infusion at 0.05 mg/kg/min (maximum: 0.3 mg/kg)  
|                      |       | - Titrate to effect—note esmolol has a very short half-life (2–9 min)  |
|                      | Atenolol| Initial IV dose: 5 mg slow IV (over 5 min)  
|                      |       | - Wait 10 min, then give second dose of 5 mg slow IV (over 5 min)  
|                      |       | - In 10 min, if tolerated well, may start PO; then give 50 mg PO BID  |
|                      | Metoprolol| Initial IV dose: 5 mg slow IV, repeat at 5 min intervals to a total of 15 mg  
|                      |       | - Oral regimen to follow IV dose: 50 mg BID for 24 h, then increase to 100 mg BID  |
|                      | Propranolol| Total dose: 0.1 mg/kg by slow IV push, divided in 3 equal doses at 2–3 min intervals  
|                      |       | - Do not exceed 1 mg/min, watching for excessive bradycardia or hypotension  
|                      |       | - Nonselective beta-1 and beta-2 agent (use with care in asthmatic patients)  |
|                      | Labetalol| For severe hypertension:  
|                      |       | - 10 mg labetalol IV push over 1 to 2 min  
|                      |       | - May repeat or double labetalol every 10 min to a maximum dose of 150 mg, or give initial bolus dose and start labetalol infusion at 2 to 8 mg/min  |
| Calcium channel      | Diltiazem| Acute rate control (see vasodilator section for use in no-reflow):  
| blockers             |       | - 15 to 20 mg (0.25 mg/kg) IV over 2 min  
|                      |       | - May repeat in 15 min at 20–25 mg (0.35 mg/kg) over 2 min  
|                      |       | - Maintenance infusion 5 to 15 mg/h, titrated to heart rate  |
| Verapamil            |       | Acute rate control (see vasodilator section for use in no-reflow)  
|                      |       | - 2.5–5.0 mg IV bolus over 2 min  
|                      |       | - Second dose: 5 mg bolus every 15 min to total dose of 30 mg  |
| Conscious sedation   | Fentanyl| 25–50 µg intravenously  
|                      |       | - Repeat as needed every 5 min  
|                      |       | - Monitor vital signs, oximetry, and state of consciousness as per conscious sedation guidelines  |
|                      | Versed| 0.5–1.0 mg IV  
|                      |       | - Repeat as needed every 5 min  
|                      |       | - Monitor vital signs, oximetry, and state of consciousness per conscious sedation guidelines  |
|                      | Morphine sulfate| 2–4 mg IV (over 1 to 5 min) every 5–30 min  
|                      |       | - Monitor vital signs, oximetry, and state of consciousness as per conscious sedation guidelines  |

(Continued)
<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Agent</th>
<th>Dosing and Comments</th>
</tr>
</thead>
</table>
| Reversal agents  | Flumazenil (Romazicon, “Re-versed”)       | For oversedation with benzodiazeines  
|                  |                                             | - Dosage: 0.2 to a maximum dose of 1 mg  
|                  |                                             | - Administer in 0.2 mg increments over 15 s; may repeat in 1-min intervals to 1 mg  
|                  |                                             | - Maximum dose: 1 mg/dose and 3 mg/h  
|                  |                                             | - Monitor closely for re-sedation for at least 2 h  
|                  | Naloxone hydrochloride (Narcan)           | For oversedation with narcotics  
|                  |                                             | - Dilute 0.4 mg (1 mL) with 9 mL NS (0.04 mg/mL)  
|                  |                                             | - Administer 0.04 mg or 1 mL every 2–3 min PRN to increase respiratory rate and alertness  
|                  |                                             | - Onset 1 min, duration 30–40 min  
|                  |                                             | - Monitor closely for re-sedation for at least 2 h  
| “Unconscious”    | Propofol (Diprivan)                        | Induction of general anesthesia:  
| sedation*        |                                             | - Healthy adults <55 years of age: 40 mg every 10 s until induction onset (2.0–2.5 mg/kg)  
|                  |                                             | - Elderly, debilitated, ASA III/IV patients: 20 mg every 10 s until induction onset (1.0–1.5 mg/kg)  
|                  | Cisatracurium besylate (Nimbex)           | Maintenance of general anesthesia:  
|                  |                                             | - Healthy adults <55 years of age: 100–200 µg/kg/min (3–6 mg/kg/h)  
|                  |                                             | - Elderly, debilitated, ASAIII/IV patients: 50–100 µg/kg/min (3–6 mg/kg/h)  
| Neuromuscular     | Vecuronium bromide (Norcuron)             | Skeletal muscle relaxation: initial, 0.15–0.20 mg/kg IV bolus as component of a propofol/nitrous oxide/oxygen induction-intubation technique  
| blocker*         |                                             |  
|                  |                                             | Skeletal muscle relaxation: maintenance, 0.03 mg/kg IV  
|                  |                                             | Skeletal muscle relaxation: maintenance, initial continuous IV infusion rate of 3 µg/kg/min may be required to rapidly counteract spontaneous recovery from initial bolus dose; thereafter, 1–2 µg /kg/min continuous IV infusion; in ICU, infusion range of 0.5–10.2 µg /kg/min  
|                  |                                             |  
|                  | Hydration                                  | For prevention of contrast-induced nephropathy  
| Contrast          |                                             | - Normal saline 1 mL/kg/h for 12 h pre- and 12 h post-contrast exposure  
| nephropathy       |                                             | - Alternative normal saline 3 mL/kg over 1 h preprocedure, then 1 mL/kg/h for 6 h postprocedure  
|                  |                                             | - Limit infusion and monitor closely in CHF patients  
|                  |                                             | - Do not add Lasix, mannitol, dopamine, fenoldopam (systemic)  
|                  |                                             | - Limit contrast volume  
| Contrast allergy  | Prednisone                                 | Pretreat 60 mg PO daily for 24–48 h  
| or toxicity       |                                             | May use Solu-Medrol 100 mg IV just before the procedure  
|                  |                                             |
### Drug Class

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Agent</th>
<th>Dosing and Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benadryl</td>
<td></td>
<td>H1 blocker</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25-50 mg PO before the procedure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>May also be given as 25 mg IV for intraprocedural allergic reactions</td>
</tr>
<tr>
<td>H2-blocker</td>
<td></td>
<td>Needed to prevent histamine-induced vasodilation</td>
</tr>
<tr>
<td>Ranitidine (Zantac)</td>
<td></td>
<td>150 mg PO prior to procedure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alternative, 50 mg IV, given over 5 min</td>
</tr>
<tr>
<td>Epinephrine</td>
<td></td>
<td>For anaphylaxis, bronchospasm, cardiovascular collapse</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.1 mg (1 mL of 1:10,000) epinephrine given in small divided doses until response</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Monitor closely for tachycardia or hypertensive overshoot</td>
</tr>
<tr>
<td></td>
<td></td>
<td>May repeat or use IV infusion as noted below</td>
</tr>
<tr>
<td>Ondansetron HCl (Zofran)</td>
<td></td>
<td>For prevention or treatment of periprocedural nausea and vomiting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2-4 mg undiluted IV over 4 min</td>
</tr>
<tr>
<td>Diuretic</td>
<td>Furosemide (Lasix)</td>
<td>IV infusion:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.5-1.0 mg/kg given over 1-2 min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If no response, double dose to 2.0 mg/kg, slowly over 1-2 min</td>
</tr>
<tr>
<td>Bumetanide (Bumex)</td>
<td></td>
<td>IV infusion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bolus 0.5-1.0 mg is equivalent to 40 mg of furosemide</td>
</tr>
<tr>
<td>Inotrope</td>
<td>Dobutamine (Dobutrex)</td>
<td>IV infusion:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dilute 500 mg (20 mL) in 250 mL D5W</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Usual infusion rate is 2-20 μg/kg per min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Titrate so heart rate does not increase by &gt;10% of baseline</td>
</tr>
<tr>
<td></td>
<td>Dopamine</td>
<td>IV infusion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mix 400-800 mg in 250 mL normal saline, lactate Ringer solution, or D5W</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Continuous infusions (titrate to patient response)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low dose: 1-5 μg/kg/min—gamma (dopaminergic) stimulation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate dose: 5-10 μg/kg/min (“cardiac doses”—beta stimulation)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High dose: 10-15 μg/kg/min (“vasopressor doses”—alpha stimulation)</td>
</tr>
<tr>
<td>Milrinone (Primacor)</td>
<td>IV loading dose and infusion for severe pump failure:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Supplied as 200 μg/mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Loading dose 50 μg/kg over 10 min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Follow with infusion 0.5-0.75 μg/kg/min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduce infusion for renal insufficiency (e.g., 0.33 μg/kg/min for Cr 30 mL/min)</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>Cardiac arrest:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Note: Available in 1:1,000 (1 mg/mL) and 1:10,000 (0.1 mg/mL) concentrations!</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IV dose: 1 mg (10 mL of 1:10,000 solution) every 3-5 min during resuscitation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Higher doses (up to 0.2 mg/kg) may be used if 1 mg dose fails</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Continuous infusion: 30 mg epinephrine (30 mL of 1:1,000 solution) to 250 mL normal saline, run at 100 mL/h and titrate to response</td>
</tr>
</tbody>
</table>

(Continued)
Table 5.4  Commonly Used Cath Lab Pharmacology at the Brigham and Women’s Hospital (Continued)

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Agent</th>
<th>Dosing and Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Profound bradycardia or hypotension:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 2 mg in 500 mL NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 2–10 µg/min infusion (add 1 mg of 1:1,000 to 500 mL normal saline; infuse 1–5 mL/min)</td>
</tr>
<tr>
<td>Pressor agents</td>
<td>Glucagon</td>
<td>To treat excessive bradycardia from beta blockers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 1–5 mg over 2–5 min</td>
</tr>
<tr>
<td></td>
<td>Calcium chloride</td>
<td>IV slow push in cardiac arrest:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 100 mg/mL in 10 mL vial (total equals 1 g; a 10% solution)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 8–16 mg/kg (usually 5–10 mL) IV for hyperkalemia and calcium channel blocker overdose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- May be repeated as needed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 2–4 mg/kg (usually mL) IV for prophylaxis before IV calcium channel blockers</td>
</tr>
<tr>
<td></td>
<td>Digoxin</td>
<td>IV infusion (for rate control in atrial fibrillation/flutter (note beta or calcium channel blocker preferred):</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 0.25 mg/mL or 0.1 mg/mL supplied in 1 or 2 mL ampule (totals equal 0.1–0.5 mg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Loading doses of 10–15 µg/kg lean body weight—therapeutic effect with minimum toxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Maintenance dose is affected by body size and renal function</td>
</tr>
<tr>
<td></td>
<td>Phenylephrine (Neo-Synephrine)</td>
<td>For severe refractory hypotension bolus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 0.04–0.1 mg IV, can be repeated in 10 min if needed infusion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Mix 20 mg in 500 mL of D5W or NS (40 µg/mL)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Infuse 100–180 µg/min until blood pressure stabilizes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Reduce to 40–60 µg/min adjusted to maintain desired blood pressure</td>
</tr>
<tr>
<td></td>
<td>Metaraminol (Aramine)</td>
<td>For severe refractory hypotension</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Loading dose: 0.5–1.0 mg, IV push</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Infusion: 15 mg (1.5 mL) in 500 mL normal saline; adjust to maintain desired blood pressure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Indirect-acting sympathomimetic amine—mixed alpha and beta, action delayed by 5 min</td>
</tr>
<tr>
<td></td>
<td>Norepinephrine (Levophed)</td>
<td>For severe refractory hypotension</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 4 mg in 250 mL of D5W to yield 4 µg/mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Initial dose 0.5–1.0 µg/min (usual range 0.5–30 µg/min)</td>
</tr>
<tr>
<td></td>
<td>Vasopressin</td>
<td>Doses for cardiac arrest (option to epinephrine)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 40 U IV push × 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Wait 10 min before initiating epinephrine protocol</td>
</tr>
<tr>
<td></td>
<td>Vasodilator</td>
<td>For refractory hypotension</td>
</tr>
<tr>
<td></td>
<td>Nitroglycerin</td>
<td>- 20 U in 250 mL D5W</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Infuse at 0.01–0.10 U/min</td>
</tr>
<tr>
<td>Systemic arterial</td>
<td></td>
<td>IV infusion:</td>
</tr>
<tr>
<td></td>
<td>Nitroglycerin</td>
<td>- IV bolus: 12.5–25 µg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Infuse at 10–20 µg/min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Titrate to effect</td>
</tr>
<tr>
<td></td>
<td>Systemic arterial</td>
<td>Intracoronary (for vasospasm—do not use for no-reflow!)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Dilute to 100–200 µg/mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Administer 100 µg through guiding catheter or selectively into distal coronary</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Repeat as needed</td>
</tr>
</tbody>
</table>
### Table 5.4

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<tr>
<th>Drug Class</th>
<th>Agent</th>
<th>Dosing and Comments</th>
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| Coronary         | Nitroprusside (Sodium nitroprusside) | IV infusion:  
- Mix 50 mg in 250 mL D5W  
- Begin at 0.10 μg/min titrated to improve blood pressure (up to 10 μg/min)  
- Do not administer in same IV line as alkaline solutions |
|                  | ACE inhibitors: Enalapril (IV: Enalaprilat) | IV: 1.25 mg IV initial dose over 5 min  
Repeat dose: 1.25–5.0 mg IV every 6 h  
IV ACE inhibitors not approved in STEMI |
| Coronary         | Nitroglycerin              | For epicardial vasodilation or treatment of coronary spasm  
- Dilate to 200 μg/mL  
- Administer 100–200 μg intracoronary  
- Note: Nitroglycerine is primarily an epicardial vasodilator, and should not be used in situations like no-reflow where small vessel (arteriolar) dilation is required—see below |
| Adenosine        |                            | For measurement of fractional flow reserve (FFR)  
- Dilate to 10 μg/mL  
- For RCA 18–24 μg through guiding catheter or selectively into distal coronary  
- For LCA 24–36 μg through guiding catheter or selectively into distal coronary  
- Alternatively, 140–180 μg/kg/min peripheral intravenous infusion for 3 min |
| Coronary         | Nitroprusside (Sodium nitroprusside) | For reversal of no-reflow  
- 100 μg selective into distal involved vessel  
For reversal of no-reflow  
- Dilate to 100 μg/mL (in nonheparinized saline)  
- Administer 100 μg through guiding catheter or selectively into distal coronary  
- Repeat as needed |
| Coronary         | Nicardipine                | For reversal of no-reflow  
- Dilate to 100–200 μg/mL  
- Administer 200 μg selectively into involved coronary |
| Coronary         | Diltiazem                  | For reversal of no-reflow  
- Dilate to 0.25–1.0 mg/mL  
- Administer 1 mg through guiding catheter or selectively into distal coronary  
- Repeat as needed up to total of 2.5 mg |
| Coronary         | Verapamil                  | For reversal of no-reflow  
- Dilate to 100 μg/mL  
- Administer 100–200 μg through guiding catheter or selectively into distal coronary  
- Repeat as needed  
- Monitor for bradycardia in the right and circumflex coronary |
| Pulmonary arteriolar | Epoprostenol (Flolan) | IV infusion for pulmonary hypertension  
- Start at 2 ng/kg/min  
- Increase by 2 ng/kg/min every 15 min until reduction in pulmonary resistance of dose-limiting toxicity (nausea, headache, hypotension) |

Additional Abbreviations: FFR, fractional flow reserve; VT, ventricular tachycardia; VEA, ventricular ectopic activity; ASA, American Society Anesthesia; CHF, congestive heart failure; LCA, left coronary artery; RCA, right coronary artery. Prepared in Conjunction with Peg Angel, RN.
Risk of myocardial infarction and death during treatment with
cardiac infarction: a report of the American College of Cardiology
Foundation/American Heart Association Task Force on Practice
Guidelines and the Society for Cardiovascular Angiography and Interventions.
Circulation 2011;124:e574–e651.


70. Yusuf S, Zhao F, Mehta SR, Chrolavics S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute


In contrast to other cutdown techniques (see Chapter 8), the percutaneous approach to left and right heart catheterization uses a needle puncture to achieve vascular access and thus obviates the need for surgical isolation of the vessels during either the insertion or the subsequent removal of cardiac catheters. Once the needle has been positioned within the vessel lumen, a flexible guidewire is advanced through the needle and well into the vessel being accessed. This guidewire remains in an intravascular position as the needle is withdrawn to allow direct insertion of an appropriately sized sheath that is equipped with a back-bleed valve and a side-arm port. The desired catheters can then be placed through the sheath and into the vasculature. This modification reduces patient discomfort and eliminates repetitive local arterial trauma during catheter exchanges, although it does increase the size of the puncture slightly since the outer diameter of the sheath is IF size (0.33 mm) larger than the corresponding bare catheter. At the termination of the percutaneous catheterization procedure, the catheters and introducing sheaths are withdrawn, and bleeding from the puncture sites is controlled by the application of direct pressure or the use of one of several vascular closure devices (see below).

Because of its speed and simplicity, percutaneous entry via the femoral approach continues to be the dominant approach to cardiac catheterization. More than 90% of the procedures contained in the 2011 CathPCI Registry of the National Cardiovascular Data Registry were performed via this route. With appropriate skills and knowledge of regional anatomy, moreover, the same percutaneous techniques used for femoral artery and vein cannulation can be adapted to allow catheter insertion from a variety of other entry sites. Venous catheterization can thus be performed via the internal jugular, subclavian, or median antecubital vein, whereas arterial catheterization can be performed via the brachial, axillary or radial arteries, or even via the lumbar aorta.
**Patient Preparation**

After palpation of the femoral arterial pulse within the inguinal area, a safety razor is used to shave an area approximately 10 cm in diameter surrounding this point. Although most catheterizations can be performed quickly and easily from a single groin, it is generally routine to have both groins prepared. The right groin is commonly used, since it is more easily accessed by the operator standing on that side of the table. If difficulties in catheter advancement force a switch to the other groin once the procedure has begun, however, having the left groin already prepared saves time and inconvenience. In the past, the shaved areas were traditionally scrubbed with a povidone-iodine/detergent mixture and then painted with povidone-iodine solution. More recently, most laboratories (including ours) have replaced povidone-iodine solution with chlorhexidine-alcohol–based antiseptic preparations, which have been shown to be more effective and less irritant. The patient is then draped from clavicles to below the feet, leaving only the sterile prepared groin areas exposed. Most laboratories now use disposable paper drapes with adhesive-bordered apertures for this purpose, frequently packaged together with other disposable supplies (syringes, needles, bowls, and so on) in a custom kit available from any of several vendors.

**Selection of Puncture Site**

The adjacent common femoral artery and vein (Figure 6.1A and B) are the most commonly used vessels for percutaneous diagnostic cardiac catheterization. It is important to puncture these vessels at the correct level, that is, at the mid common femoral artery, above the arterial bifurcation into the profunda and superficial femoral artery and 1 or 2 cm below the inguinal ligament. Identification of the correct puncture site facilitates vessel entry and effective compression to minimize local vascular complications. The position of the skin crease itself is not a reliable marker for the puncture site and it can instead be misleading in obese patients. The appropriate localization of the skin puncture should be first identified by fluoroscopic landmarks; a radiopaque marker (i.e., mosquito forceps which routinely come within the sterile instrument package) should be placed on top of the inguinal area where the pulse appears stronger, and adjusted by fluoroscopy in the anteroposterior view so that it is positioned overlying the inferior quadrant of the femoral head (Figure 6.1C and D). Making the skin nicks at this level increases the chance that needle puncture will take place in the common femoral segment (overlying the middle of the femoral head) rather than either too high (above the inguinal ligament) or too low (in the superficial femoral or profunda branches of the common femoral artery). The femoral artery should be easily palpable over a several-centimeter span above and below the skin site. The femoral vein will lie approximately one fingerbreadth medial to the artery along a parallel course. It should be recognized that there are anatomical variations to this course. Thus, more recently the use of intraprocedure vascular ultrasound guidance has emerged as an alternative method to identify each vessel and select the puncture site. After initial fluoroscopic delineation of the landmarks, using a sterile plastic cover, the ultrasound vascular probe is positioned over the strongest pulse area to scan the femoral artery and vein (Figure 6.2A and B). The femoral artery appears as a pulsatile circle, usually with thicker and brighter delineation of the walls and on occasion with atherosclerotic and calcific plaques. Upon gentle pressure with the vascular probe, the artery is not compressible and the pulsations become more evident. The arterial bifurcation is identified by scanning north to south, in order to prevent puncture at this level (Figure 6.2A). A needle guide can be used to fix the angle of the needle and to intersect the ultrasound plane at the desire depth and avoid the bifurcation. By keeping the needle and the artery in the center of the image, one can reduce the number of puncture attempts and the incidence of unwanted venipunctures, reducing time to access and the risk of potential vascular complications.

Medial to the femoral artery (or occasionally underneath) lays the femoral vein, which can be identified because of its thinner and smoother walls as well as the compressibility upon gentle pressure with the vascular probe. Once the vessels are identified, an anterior wall stick can be visualized with the ultrasound as the needle enters the vessel.

Most difficulties in entering the femoral artery and vein—and most vascular complications—are as the result of inadequate identification of the landmarks prior to attempted vessel puncture. Once the catheter is introduced, a femoral angiogram (15 to 30 degrees ipsilateral) can be performed to confirm the position of the sheaths. A high puncture of the artery at or above the inferior epigastric artery or above the inguinal ligament makes catheter advancement difficult and predisposes to inadequate compression, hematoma formation, and/or retroperitoneal bleeding following catheter removal (see Chapter 4). A low puncture of the artery (at or below the femoral bifurcation or >3 cm below the inguinal ligament) increases the chance that the puncture will be at the bifurcation of the profunda and superficial femoral branches and will fail to enter the arterial lumen. Puncture of either one of the branches increases the risk of false aneurysm formation or thrombotic occlusion owing to smaller vessel caliber. Because the superficial femoral artery frequently overlies the femoral vein, low venous punctures may pass inadvertently through the superficial femoral artery, leading to excessive bleeding and possible arteriovenous (A-V) fistula formation. (see Chapter 4).

**Local Anesthesia**

Adequate subcutaneous local anesthesia is essential for a successful catheterization. Inadequate anesthesia leads to poor patient cooperation and makes the time in the catheterization
Regional anatomy relevant to percutaneous femoral arterial and venous catheterization: **A.** Schematic diagram showing the right femoral artery and vein coursing underneath the inguinal ligament, which runs from the anterior superior iliac spine to the pubic tubercle. The arterial skin nick (indicated by X) should be placed approximately 3 cm below the ligament and directly over the femoral arterial pulsation, and the venous skin nick should be placed at the same level but approximately one fingerbreadth more medial. Although this level corresponds roughly to the skin crease in most patients, anatomic localization relative to the inguinal ligament provides a more constant landmark (see text for details). **B.** Corresponding radiographic anatomy as seen during abdominal aortography. **C.** Fluoroscopic localization of skin nick (marked by clamp tip) to the inferior border of the femoral head (ibfh). **D.** Catheter (open arrow) inserted via this skin nick has entered the common femoral artery (cf), safely above its bifurcation into the superficial femoral (sfa) and profunda branches. (For further details, see Kim D, Orron DE, Skillman JJ, et al. Role of superficial femoral artery puncture in the development of pseudoaneurysm and arteriovenous fistula complicating percutaneous transfemoral cardiac catheterization. *Cathet Cardiovasc Diagn* 1992;25:91.)

laboratory unpleasant for both patient and operator. Once the inguinal ligament and femoral artery have been identified, the femoral artery is palpated along its course using the three middle fingers of the left hand, with the uppermost finger positioned just below the inguinal ligament. Without moving the left hand, a linear intradermal wheal of 1% or 2% lidocaine is raised slowly by tangential insertion of a 25- or 27-gauge needle along a course overlying both the femoral artery and vein at the desired level of entry. The smaller needle is then replaced by a 22-gauge 1.5-inch needle, which is used to infiltrate the deeper tissues along the intended trajectory for arterial and venous entry. As this needle is advanced, small additional volumes of lidocaine are infiltrated.
by slow injection. Each incremental infiltration should be preceded by aspiration so that intravascular boluses can be avoided. To avoid unnecessary injury to the femoral artery, we sometimes intentionally infiltrate medially and laterally to the pulse. If the anesthetic track passes through the artery, infiltration should be suspended until the tip of the needle has passed out of the back wall of the vessel and then continued to the full length of the needle or to the point where the needle tip contacts the periosteum. Approximately 10 to 20 mL 1% or 2% Xylocaine administered in this fashion usually provides adequate local anesthesia. The patient should be warned that he or she may experience some burning as the anesthetic is injected, but that the medication will prevent any subsequent sharp sensations.

Once local anesthesia has been achieved, with the left hand remaining in place, transverse skin punctures can be made over the femoral artery and vein, using the tip of a #11 scalpel blade. This procedure can decrease the resistance that is encountered during subsequent advancement of the vascular sheath and increases the likelihood that any vascular bleeding will manifest as oozing through the puncture rather than being hidden in the formation of a deep hematoma, although some operators prefer inserting small diameter vascular sheaths (5F or 6F) without a skin nick.

**Femoral Vein Puncture**

If right heart catheterization is to be performed, or secure venous access is desired (for administration of fluids and medications or rapid placement of a temporary pacing catheter), the femoral venous puncture is usually performed prior to arterial puncture. With the left hand palpating the femoral artery along its course below the inguinal ligament, the needle is introduced through the more medial aspect. If vascular ultrasound is available, this makes venous access easier by rapidly identifying the vein and visualizing the anterior wall stick.

Classically, an 18-gauge thin-walled Seldinger needle was used in the past; this needle consists of a blunt, tapered external cannula through which a sharp solid obturator projects (Figure 6.3). The needle is to be grasped so that the index and middle fingers lie below the lateral flanges of the needle and the thumb rests on the top of the solid obturator as the needle is advanced along the sagittal plane angled approximately 45° cephalad (depending on the degree of obesity of the patient). Although this needle can occasionally be advanced up to its hub, the tip of the needle will usually stop more superficially as it encounters the periosteum of the underlying pelvic bones. The periosteum is well innervated and may be quite tender if the initial lidocaine infiltration fails to reach this level. Accordingly, forceful contact with the periosteum is neither necessary nor desirable. If the patient experiences significant discomfort, some operators would remove the obturator from the Seldinger needle and infiltrate additional lidocaine into the deep tissues through the outer cannula. At this point, the Seldinger needle should have transfixed the femoral vein. The obturator is removed, and a 10-mL syringe is attached to the hub of the cannula. The syringe and cannula are then depressed so that the syringe lies closer to the anterior surface of the thigh (Figure 6.4) and the needle is more parallel (rather than perpendicular) to the vein. Gentle suction is applied to the syringe, and the whole assembly is slowly withdrawn toward the skin surface. In doing so, it is helpful to control the needle with both the left hand (which also rests on the patient's leg for support) and the right hand (which also controls the aspirating syringe). As the tip of the cannula is withdrawn into the lumen, venous blood will flow freely into the syringe.

However, nowadays the technique most widely used is a modified Seldinger, where instead an 18- to 21-gauge single-wall puncture needle with a sharpened tip and without the inner obturator is used (Figure 6.3). Placement of a fluid-filled syringe on the needle's hub allows direct front-wall entry of the vein without the need to first exit the back wall and then pull back. Otherwise, the technique used is identical after entry of the venous lumen has been achieved.

With the left hand stabilizing the needle, the right hand is used to remove the syringe and to advance a 0.018 to 0.038-inch J guidewire into the hub of the needle under fluoroscopy or ultrasound guidance. The curved wire tip may be straightened by hyperextension of the wire shaft in the right hand or by leaving the tip of the wire within the plastic introducer supplied by the manufacturer; when using a 0.018 wire for the 21-gauge needle, the wire has a straight or slightly curved soft tip. The wire should slide through the needle and 30 cm into the vessel with no perceptible
Figure 6.3 Percutaneous needles and guide wire. A. 18-gauge thin-wall needle B. Seldinger needle with its sharp solid obturator in place. C. Micropuncture® Introducer Set (Cook, Inc, Bloomington, IN, USA): 21 gauge needle, 5F introducer and dilator and 0.018-inch nitinol wire. D. A Doppler-guided SmartNeedle. (Reproduced with permission from Vascular Solutions Inc, Minneapolis, MN.)

resistance. Fluoroscopy should then show the tip of the guidewire just to the left (patient's right) of the spine.

If difficulty is encountered in advancing the guidewire, it should never be overcome by the application of force. Fluoroscopy may reveal that the tip of the wire has lodged in a small lumbar branch; it can be drawn back slightly and redirected or gently prolapsed up the iliac vein. When resistance to advancement is encountered at or just beyond the tip of the needle, however, even greater care is required. This resistance may be caused by apposition of the tip of the needle to the back wall of the vein, which can be corrected by further depression of the needle hub or slightly reorienting the hub to one side or the other, with or without slight withdrawal of the needle shaft. If this maneuver fails to allow free advancement of the wire, however, the wire should be removed, and the syringe should be reattached to the needle hub to ensure that free flow of venous blood is still present before additional wire manipulation is attempted—the wire should not be reinserted unless free flow is obtained. If it is necessary to withdraw the wire, this should always be done gently, since it is possible for the wire to snag on the tip of the needle.

To prevent this, the needle and wire should be removed as a unit. If the wire still cannot be advanced after these maneuvers, the needle should be withdrawn and the puncture site should be compressed for 1 to 3 minutes. The anatomic landmarks should be reconfirmed and puncture reattempted. In some cases, puncturing the vein during a Valsalva maneuver or after giving a bolus of intravenous fluids may help by distending the femoral vein and making clean puncture more likely.

After the wire has freely entered the vein, the needle is removed, leaving the wire well within the vein and secured at the skin entry site by the left hand. At this point, a small skin nick can be enlarged and deepened, using the tips of a curved mosquito forceps. The protruding wire is wiped with a moistened gauze pad, and its free end is threaded into the lumen of a sheath and dilator combination adequate to accept the intended right-sided heart catheter (Note: if a micropuncture kit is used, a 4F or 5F sheath and dilator are used over the 0.018-inch wire in order to exchange for an 0.035–0.038 inch wire, over which the intended sheath appropriate for the right heart catheter is then inserted). All current sheaths are equipped with a back-bleed valve and side-arm connector (Figure 6.5) to control bleeding around the catheter shaft and to provide a means of administering drugs or extra intravenous fluids during the right-sided heart catheterization. The operator must make sure that he or she has control of the proximal end of the guidewire and that it is held in a fixed position as the sheath and dilator are introduced through the skin. Insertion is eased if the sheath and dilator are rotated as a unit while they are advanced progressively through the soft tissues. If excessive resistance is encountered, it may be necessary to remove the dilator from the sheath and to
introduce the dilator alone before attempting to introduce the combination. If inspection shows that initial attempts have created significant burring at the end of the sheath, a new sheath should be obtained.

Once the sheath is in place, the wire and dilator are removed, and the sheath is flushed by withdrawal of blood and injection of heparinized saline solution. If needed, this sheath can be connected via a sterile length of intravenous extension tubing to provide a carrier for drug administration by the nurse. Although drug administration can also take place via a peripheral intravenous line, the side arm of the sheath avoids any concerns about how quickly volume can be administered or whether infiltration of the peripheral line might jeopardize drug delivery in an emergency. Even if right heart catheterization is not planned, the femoral sheath makes it easy to place a right heart catheter or a temporary transvenous pacemaker lead if hemodynamic instability or bradycardia ensue.

Catheterizing the Right Heart from the Femoral Vein

A right (as well as a left) heart catheterization is needed to obtain a full profile of the hemodynamic state. Right heart catheterization can provide data regarding mean left heart filling pressures (the pulmonary capillary wedge, rather than just the post-A wave left ventricular [LV] end diastolic pressure), detect pulmonary arterial hypertension, measure the cardiac output, and detect left-to-right intracardiac shunts. Leaving the right heart catheter in the pulmonary artery during a complex interventional procedure also gives an ongoing measure of changes in the hemodynamic state as fluid and contrast loading take place, various medications (nitrates, diuretics, and so on) are given, and as episodes of ischemia develop and are treated.
For these reasons, it was once common to perform a right heart catheterization in every patient who came to the cardiac catheterization laboratory. However, the 1990 SCA&I survey showed that the practice was to perform right heart catheterization in only 28% of procedures. The use of right heart catheterization has fallen further after several standard-setting and regulatory agencies ruled that a left heart catheterization alone is adequate for most patients undergoing evaluation for coronary artery disease. The time (<5 minutes), added expense (<$100), and added risk (<1/10,000) of right heart catheterization alone is adequate for most patients undergoing evaluation for coronary artery disease. The time (<5 minutes), added expense (<$100), and added risk (<1/10,000) of right heart catheterization alone is adequate for most patients undergoing evaluation for coronary artery disease. In such patients, however, we still believe that the quantitation of overall hemodynamic function provided by right heart catheterization justifies performance of this low-risk adjunctive part of the overall catheterization evaluation.

If right heart catheterization is to be performed, the desired right heart catheter (Figure 6.6) is flushed, attached to the venous manifold, introduced into the sheath, and advanced up the inferior vena cava. Although conventional woven Dacron (Goodale-Lubin or Courand) catheters provide excellent torque control, their inherent stiffness makes them poorly suited for routine use in a training laboratory. It is considerably safer to use 7F balloon flotation catheters to exploit their ease of passage, low risk of injury to the rightsided heart chambers, and (with a suitably equipped catheter) their ability to perform thermodilution measurements of cardiac output. Unfortunately, such soft catheters with smaller internal diameters tend to have poor frequency response (see Chapter 10), may not adequately transmit the torque required for easy catheterization of the right-sided heart from the femoral approach, and accept only <0.025-inch guidewires. To bridge this gap, stiffer, balloon-tipped catheters (PWP monitoring catheter, Medtronic) have been developed that combine the safety of the Swan-Ganz catheter with the catheter control and frequency response previously found only in the woven Dacron catheters. The larger lumen diameter also allows the passage of conventional 0.035- and 0.038-inch diameter guidewires when necessary.

Deviation of the catheter tip from its paraspinous position during advancement from the leg suggests entry into a renal or hepatic vein, which can be corrected by slight withdrawal and rotation of the catheter. Once the catheter is above the diaphragm and within the right atrium, it is rotated counterclockwise to face the lateral wall of the right atrium (Figure 6.7). Additional counterclockwise rotation and gentle advancement allow passage of the catheter tip into the superior vena cava, which is contiguous with the posterolateral wall of the right atrium. In contrast, anterior orientation of the catheter tip at this point may result in its entrapment in the right atrial appendage and inability to
reach the superior vena cava. If passage to the superior vena cava is difficult, the tip of the catheter can be withdrawn to the inferior vena cava, where a 0.035-inch J guidewire can be introduced to traverse the straight-line path from the inferior to the superior vena cava along the back wall of the right atrium. Once in position, a baseline superior vena caval blood sample is obtained for measurement of oxygen saturation and comparison with the subsequently
measured pulmonary arterial blood oxygen saturation to screen for unsuspected left-to-right shunts. The catheter is then flushed with heparinized saline solution and withdrawn to the right atrium for pressure measurement.

To advance a catheter from the femoral vein to the pulmonary artery, the tip of the catheter is positioned in the lower portion of the right atrium, directed toward its lateral border. If a balloon flotation catheter is being used, the balloon is inflated at this point. Clockwise rotation is applied, which causes the catheter tip to sweep the anterior and anteromedial wall of the right atrium, along the location of the tricuspid valve (Figure 6.7). As the catheter tip passes over the tricuspid orifice, a slight advancement causes it to enter the right ventricle, where pressure is again recorded. If the right atrium is enlarged, greater curvature of the catheter may be necessary, i.e., a large J loop. Such a loop may be formed by bending the tip of the catheter against the lateral right atrial wall or by engaging in the ostium of the hepatic vein (just below the diaphragm). This larger loop can then be rotated clockwise in the atrium as described above, causing the tip of the catheter to enter the right ventricle. Right ventricular pressure is then recorded.

Simple advancement of the catheter in the right ventricle causes the tip to move toward the apex of that chamber and usually does not result in catheterization of the pulmonary artery. To catheterize the pulmonary artery, the catheter must be withdrawn slightly so that its tip lies horizontally and just to the right (patient’s left) of the spine. In this position, clockwise rotation causes the tip of the catheter to point upward (and slightly posterior) in the direction of the right ventricular outflow tract (Figure 6.7). The catheter should be advanced only when it is in this orientation to minimize the risk of ventricular arrhythmias or injury to the right ventricle. Advancement may be facilitated if performed as the patient takes a deep breath.

If these maneuvers fail to achieve access to the pulmonary artery owing to enlargement of the right atrial and ventricular chambers, the catheter may be withdrawn to the right atrium and formed into a large reverse loop, which allows the tip of the catheter to cross the tricuspid valve in an upward orientation (similar to that when right heart catheterization is performed from above), which makes it more likely to enter the outflow tract (Figure 6.7, bottom right). When manipulated appropriately, the catheter tip should cross the pulmonary valve and advance to a wedge position without difficulty. Having the patient take a deep breath and cough during advancement often helps to achieve a wedge position. Alternatively, a small amount of air may be released from the balloon to decrease its size and facilitate wedging in a smaller, more distal branch of the pulmonary artery. Catheters advanced from the leg are more likely to seek the left pulmonary artery, whereas catheters advanced from above tend to seek the right pulmonary artery as they make a continuous counterclockwise curve through the right heart chambers. If needed, either pulmonary artery can be catheterized by appropriate manipulation or careful introduction of a curved J guidewire, but extending guidewires into the thin-walled pulmonary arteries should be avoided unless absolutely necessary.

Following measurement of the wedge pressure, the balloon (if a balloon-tip catheter is being used) is deflated and the catheter is withdrawn into the more proximal left or right pulmonary artery. There, pulmonary arterial pressure is measured and another blood sample for measurement of oxygen saturation is obtained. If a more simultaneous “snapshot” of the hemodynamic state is desired, these entry pressures can be rerecorded during a right-sided heart pullback. For practical reasons, we now tend to rerecord only the wedge pressure (simultaneous with the LV pressure) and pulmonary artery pressure, coincident with the measurement of the cardiac output. When baseline hemodynamics are abnormal, we commonly leave the right heart catheter in the proximal pulmonary artery for the duration of the case to allow continuous monitoring of the pulmonary artery diastolic pressure as an index of volume status and ischemic LV dysfunction.

Attempts to perform right heart catheterization occasionally result in entry into other structures. If a woven Dacron catheter is advanced in the right atrium with a posteromedial orientation, it may cross a patent foramen ovale and enter the left atrium. This is sometimes hard to detect by catheter position alone because the catheter appearance in the left atrium or ventricle may be indistinguishable (in the anteroposterior view) from its course during usual right heart catheterization. It can, however, be recognized by a change to a left atrial pressure waveform, position of the catheter tip across the spine and frequently out into the left lung field (i.e., into a pulmonary vein, Figure 6.8A and B), and the ability to withdraw fully oxygenated blood from the catheter tip. Although more unusual, a woven Dacron catheter can also enter the ostium of the coronary sinus, located inferiorly and posteriorly to the tricuspid orifice. There will be continued presence of a right atrial waveform, but blood sampling will disclose far lower oxygen saturation (20% to 30%) than was present in the superior vena cava. In the right anterior oblique (RAO) projection, the catheter will be seen to remain in the atroventricular groove rather than passing rightward into the ventricle. Anatomic abnormalities can also be suspected when the catheter takes an unusual position or course during attempted right heart catheterization. Figure 6.8C, D, and E depict the appearance of the right-sided heart catheter course in three such congenital abnormalities (persistent left superior vena cava, patent ductus arteriosus, and anomalous pulmonary venous return). The most important points about these side trips off the beaten path to the right ventricle are that the operator should recognize that the tip of the catheter is not in the right ventricle (i.e., one should not attempt to get to the pulmonary artery) and should decide where the catheter is (by pressure monitoring, saturation analysis, or hand...
Figure 6.8 Alternative paths occasionally encountered while attempting to advance the right heart catheter from right atrium to ventricle. A and B. A J-tipped guidewire has crossed a patent foramen ovale into the left atrium and left upper pulmonary vein; the right anterior oblique view confirms that the guidewire has remained on the atrial side of the atrioventricular plane and thus could not be in the pulmonary artery. C. The course of a catheter passed from the femoral vein to the inferior vena cava (IVC), right atrium (RA), coronary sinus (CS), and up into an anomalous left superior vena cava (LSVC). D. The catheter crossing from the pulmonary artery (PA) to the descending aorta (Ao) by way of a patent ductus arteriosus. E. The catheter entering an anomalous pulmonary vein that drains into the right atrium.

Injection of a small amount of contrast agent before withdrawing the catheter to the right atrium and proceeding with the right heart catheterization.

In patients with elevated right heart pressures or prior placement of an inferior vena caval filter or umbrella, those undergoing specialized procedures (endomyocardial biopsy, coronary sinus catheterization), or those in whom prolonged postprocedural monitoring with a balloon flotation catheter is desired, the right upper extremity (subclavian or median basilic vein) or the right internal jugular vein offers an excellent alternative to the femoral vein. The technique for jugular puncture is described in Chapter 26, and the method of advancing the
right-sided heart catheter to the pulmonary artery from the median basilic vein is described in Chapter 7.

**Femoral Artery Puncture**

The original Seldinger technique for cannulation of the femoral artery consists of advancing the Seldinger needle completely through the artery until the periosteum is encountered. The obturator is then removed, and the hub of the needle is depressed slightly toward the anterior surface of the thigh. Arterial pressure makes it unnecessary to attach a syringe to the cannula, so that both hands can be used to stabilize the needle as it is slowly withdrawn. When the needle comes back into the lumen of the femoral artery, as evidenced by vigorous pulsatile flow of arterial blood, a 0.035- or 0.038-inch J guidewire is advanced carefully into the needle. This technique has largely been replaced by an anterior wall puncture or modified Seldinger technique described above. Once the fluoroscopic landmarks have been identified, vascular ultrasound can help visualize a single anterior wall stick above the bifurcation and in the common femoral artery as explained above. When the artery is accessed without ultrasound imaging guidance, the needle is inserted at approximately 45° along the axis of the femoral artery (depending on degree of obesity of patient) as palpated by the three middle fingers of the left hand. Occasionally, the “bounce” technique can be used. With this technique, the proximity to the artery can be confirmed based on the pulsation transmitted to the needle; if the needle is on top of the artery the movement is north to south, while when the needle is lateral to the artery the pulsation is transmitted laterally and the movement of the needle is from side to side. This technique is more obvious when using a 21-gauge needle.

There are several needle options used for the modified Seldinger technique (Figure 6.3). The Potts-Cournand needle has an obturator with a small lumen that transmits a flashback of arterial blood as the vessel is entered, while the 18-gauge single-wall puncture needle described for venous entry does not include an obturator. When the femoral pulse is difficult to palpate or numerous needle insertions have been fruitless, it may be easiest to use the 18-gauge SmartNeddle (Vascular Solution, Maple Grove, MN; see Figure 6.3, bottom panel). The obturator of this device contains a Doppler crystal that picks up pulsatile arterial or more continuous venous flow, and thereby helps aim the needle tip toward the center of the desired vascular lumen. In addition, the use of ultrasound guidance in conjunction with a micropuncture kit can facilitate the identification of the optimal puncture site. It should be noted that when a 21-gauge needle is used, the amount of blood that exteriorizes has less pressure than when a larger bore needle is used. However, pulsatile bright blood will still be noted. The Femoral Micropuncture or Routine Introducer Study (FEMORIS), a randomized multicenter study, is assessing whether the use of the micropuncture technique provides a clinical benefit when compared with the standard 18-gauge needle front-wall technique.

Whichever needle is used to enter the arterial lumen, the guidewire introduced through the needle should move freely up the aorta (located to the right [patient’s left] side of the spine on fluoroscopy) up to the level of the diaphragm. When difficulty in advancing the guidewire is encountered at or just beyond the tip of the needle and is not corrected by slight depression or slight withdrawal of the needle, the guidewire should be withdrawn to ensure that brisk arterial flow is still present before any further wire manipulation is attempted. If flow is not brisk or if the wire still cannot be advanced, the needle should be removed and the groin should be compressed for 5 minutes. The operator should verify the correctness of the anatomic landmarks and attempt repuncture of the femoral artery. If the second attempt is also unsuccessful in allowing wire advancement, a third attempt on the same vessel is unwise, and an alternative access site should generally be selected.

If wire motion is initially free, but resistance is encountered after several centimeters (particularly if the patient complains of any discomfort during wire advancement), extensive iliac disease or subintimal wire position are distinct possibilities. The wire should be pulled back slightly under fluoroscopic control, and the needle should be removed as the left hand is used to stabilize the wire and control arterial bleeding. After the wire is wiped with a moist gauze pad, a small (4F or 5F) dilator can be cautiously introduced to a point just below where wire movement became difficult. The wire is then withdrawn from the dilator, blood is aspirated to ensure free flow, and a small bolus of diluted low-osmolar contrast medium is then injected gently under fluoroscopic monitoring. This should disclose the anatomic reason for difficult wire advancement—generally iliac tortuosity, stenosis, or dissection. Problems advancing the wire above the aortic bifurcation may also suggest the presence of an abdominal aortic aneurysm.

Either can usually be overcome by use of a floppy steerable (Whooley wire, Malinckrodt, Hazelwood, MO) or hydrophilic (Glidewire, Terumo) guidewire, carefully reintroduced through the dilator in an attempt to reach the descending aorta, using extreme care to avoid perforation, dissection, or dislodgment of atherothrombotic debris (Figure 6.9A). In an era when the obstructing lesion can be quickly and effectively treated by angioplasty or stent placement (see Chapter 34), iliac stenosis is no longer a firm indication to abandon transfemoral left heart catheterization.

If contrast injection through the small dilator reveals that subintimal wire passage has occurred or that the ipsilateral iliac artery is occluded, retrograde left heart catheterization should be relocated to the other femoral artery, the radial, or brachial artery. Patients with retrograde dissection should be observed for signs of progressive dissection or arterial compromise, both of which are fortunately rare with retrograde guidewire dissections.

In an aging population with diffuse atherosclerotic disease, the question of performing left heart catheterization via a prosthetic (e.g., aortobifemoral) graft arises frequently. This is not an ideal approach because the graft wall is tough
**Figure 6.9**

A. Entry of the right femoral artery was straightforward, but guidewire advancement stopped in the iliac system. **Left.** Contrast injection through a 5F dilator shows severe iliac stenosis with extensive cross-pelvic collaterals. This was crossed with a Terumo Glidewire to allow completion of the diagnostic angiography and a right coronary artery angioplasty (not shown). **Center.** Injection in the abdominal aorta shows the proximal extent of the iliac stenosis. **Right.** Iliac stenosis then dilated and treated by placement of a Palmaz-Schatz iliac stent, with restored antegrade iliac flow. 

B. Retrograde left heart catheterization in a patient with previous aortic-bifemoral grafting. **Left.** Entry of the graft hood has resulted in passage of the wire into the blind native iliac. **Right.** In an RAO projection, the more anterior pathway to the central aorta (Ao) via the graft can be seen overlying the native iliac, with the bifurcation of the common femoral artery into the profunda and superficial femoral artery (SFA) just below.

C. Difficult wire passage led to placement of a 5F dilator and hand injection of contrast, showing distal aortic aneurysm (negotiated with Whooley wire).

D. In another patient, hand injection through a 5F dilator showed occlusion of both iliac arteries (only the right is shown here) leading to conversion to the percutaneous radial approach for completion of the procedure.
(making sheath insertion difficult), such grafts may contain diffuse atherosclerotic or thrombotic debris, and graft closure or serious graft infection may occur. The graft should be identified as a separate structure from the adjacent native femoral artery and punctured using a front-wall approach, ideally under vascular ultrasound. Even if the graft hood is punctured correctly, the guidewire may pass through the anastomosis and into the native femoral artery rather than proximally up the graft. In that event, contrast injections through a small dilator in an RAO projection (ipsilateral) will disclose the problem. Partial withdrawal of the dilator and the use of special steerable guidewires may then allow the wire to be redirected into the graft lumen and thereby reach the descending aorta (Figure 6.9B). A vascular introducing sheath should always be used to avoid excessive friction during catheter movement or excessive traction on catheter tips during withdrawal, but serial dilators may be needed to facilitate sheath passage through the tough graft wall. Hydrophilic sheaths can also be used in order to facilitate sheath insertion. This approach via a vascular graft can thus be used with care, particularly when other alternatives (e.g., brachial, axillary, or radial artery) are less than desirable. Some operators choose to administer prophylactic antibiotics (Kezol 1 g every 8 hours for 24 hours) when achieving vascular access via a prosthetic graft.

Catheterizing the Left Heart from the Femoral Artery

Once the guidewire has been advanced to the level of the diaphragm and the needle has been removed, the operator's left hand is used to stabilize the wire and control arterial bleeding while the wire is wiped with a moistened gauze pad to remove any adherent blood. If the catheter is to be introduced directly into the artery, the soft tissues are predilated by brief introduction of a Teflon arterial dilator one F size smaller than the intended catheter before insertion into the left heart catheter itself. Essentially all left heart catheterizations from the femoral approach, however, are now performed using an appropriate-sized vascular sheath (e.g., a 6F sheath for a 6F catheter) that is equipped with a back-bleed valve and side-arm tubing as described above. The 15-cm-long sheath is commonly used for diagnostic catheterization, but can reach only the midiliac. In the presence of severe tortuosity, it may be preferable to use the 23-cm-long sheath designed for interventional procedures, which is sufficiently long to enter the distal aorta above the bifurcation. This helps improve the torque responsiveness of diagnostic catheters under those circumstances.

The chosen sheath is introduced over the guidewire (the proximal end of which is held in a straightened, fixed position) with a rotational motion, following which the guidewire and dilator are removed and the sheath is aspirated and flushed. The sheath can be connected to a pressurized flush system (Intraflo II [30 mL/h], Abbott Critical Care, North Chicago, IL) to avoid clot formation in the sheath. Alternatively, this side arm can be connected to a manifold for monitoring arterial pressure at a separate site (e.g., during passage of a pigtail catheter across a stenotic aortic valve). This sheath should be flushed before insertion and after removal of each catheter.

In the classic approach as described above, the guidewire was removed once the sheath had been inserted. This required that the desired left heart catheter be flushed and loaded with a 145-cm J guidewire before its nose was introduced into the back-bleed valve of the sheath. The soft end of the guidewire was then advanced carefully through the catheter, out the end of the sheath, and to the level of the diaphragm before the catheter itself was advanced. One concern, however, is that readvancement of the guidewire out the end of the sheath can cause vascular injury in the presence of severe iliac tortuosity or disease. We therefore adopted a modified technique in which a short exchange length (175 cm) Newton J (Cook, Inc.) is placed through the access needle, and its tip is left at the level of the diaphragm as the dilator is removed from the sheath, the sheath is flushed, and the left heart catheter is inserted over the wire and through the sheath lumen. This obviates the need to renegotiate complex iliofemoral anatomy with the guidewire.

Once the catheter has been advanced to the desired level (either above the diaphragm or into the ascending aorta), the guidewire is removed so that the catheter can be connected to the arterial manifold and double-flushed (withdrawal and discarding of 10 mL of blood, followed by injection of heparinized saline solution). All subsequent left heart catheters are then introduced by reinserting this wire to the level of the diaphragm (allowing one catheter to be removed and the second to be reintroduced safely), rather than withdrawing the first catheter completely and then inserting the second catheter and wire through the sheath de novo. Of course, if the left heart catheterization is being performed without the aid of a sheath, the operator must leave the tip of the wire in the abdominal aorta during the removal of the first catheter and the introduction of a second catheter to retain access to the vessel. These over-the-wire catheter exchanges are facilitated by extending the back end of the wire straight down the patient's leg and holding it fixed there to ensure that the wire remains in constant position within the aorta as the newer catheter is advanced.

A Word About Heparin

As described in Chapters 4 and 8, early catheterizations from the femoral artery had a higher incidence of major complications than catheterization from the brachial artery. One difference was that brachial catheterization used systemic heparinization to avoid thrombosis in the smaller diameter brachial artery. When systemic heparinization was adopted in femoral procedures, the rates of complications became equivalent, and it became standard practice to achieve full intravenous heparinization (5,000 U) immediately after the left-sided sheath was inserted. Lesser amounts of heparin (2,500 to 3,000 U) were used,
particularly in smaller patients, and additional heparin (up to a total of 50 to 70 U/kg) was given if the procedure went on to a coronary intervention. This type of higher heparin dosing is routinely monitored by an activated clotting time (ACT) machine in the cardiac catheterization laboratory, and titrated to an ACT of roughly 300 seconds. If it is planned to use an intravenous IIb/IIIa receptor blocker, lower levels of heparin anticoagulation (target ACT > 200 seconds) may be desirable to prevent excessive bleeding risk; on the other hand, if direct thrombin inhibitors are used (i.e., bivalirudin) the goal is to confirm that the ACT is above 200 seconds before introducing coronary wires to confirm that the drug has been administered, and from then the ACT is monitored to confirm that the patient is receiving the drug through the continuous intravenous infusion. Most of the times the ACT is > 300 seconds while the infusion is maintained.

Although the use of heparin is mandatory for interventional or prolonged diagnostic procedures, most laboratories have abandoned the use of systemic heparinization for simple diagnostic catheterization, where the complications today are extremely low with or without heparin. For this issue to be decided scientifically, more than 100,000 patients would have to be randomized to undergo diagnostic catheterization with versus without systemic heparinization. Without such trial data, we now withhold systemic heparinization for simple procedures, although we still feel that systemic anticoagulation is appropriate for more prolonged or complex diagnostic catheterizations, during transseptal catheterization (after the transseptal puncture has been completed), during mitral or aortic valvuloplasty, and (absolutely) for all percutaneous coronary or peripheral interventions.

If systemic heparinization is used, its effects can be reversed at the termination of the left heart catheterization and associated angiography. This was previously accomplished by the administration of protamine (1 mL equals 10 mg of protamine for every 1,000 IU of heparin). The operator should be watchful for potential adverse reactions to protamine, characterized by hypotension and vascular collapse. Protamine reactions appear to be more common in insulin-dependent diabetics and patients with previous protamine exposure, who are more likely to have elevated levels of IgG or IgE antiprotamine antibodies. With the decreasing use of heparin during diagnostic catheterization and the increasing use of vascular closure devices, protamine is now rarely used to reverse heparin. When bivalirudin is used (not reversible) the sheaths are routinely removed 2 hours after discontinuation of the drip due to its short half-life.

**Catheter Selection**

The initial left heart catheter in most cases is a pigtail catheter with end- and multiple side holes (Figure 6.10). This catheter usually can be flushed in the descending aorta and then advanced to the ascending aorta without difficulty. If LV and femoral arterial (sheath side arm) pressures are being monitored (as in catheterization to evaluate aortic stenosis), the rough equality of central aortic and femoral arterial pressure should be confirmed at this time (Figure 6.11). As described in Chapters 10, 13, and 14, the systolic peak in the femoral waveform may be slightly delayed and accentuated compared with the ascending aortic pressure trace, but the diastolic and mean pressures should be virtually identical. A greater difference in mean pressure between the catheter and the sheath may be seen in patients with small or extensively diseased iliac arteries, which may require the use of a longer sheath, as described above. For the highest-pressure fidelity, the sheath size should be one F size larger than the intended left heart catheter (e.g., a 5F pigtail advanced though a 6F sheath). Alternatively, catheters can be advanced from separate arterial entry sites to record LV and ascending aortic pressure; a specially designed pigtail with a separate end-hole lumen and side-hole lumen (dual-lumen pigtail) is preferably used to perform simultaneous aortic and LV pressure recordings in patients with aortic stenosis, and a straight dual-lumen catheter is used when evaluating intraventricular gradients (as in the cases of hypertrophic cardiomyopathy). In patients without known aortic valve disease, the traditional pigtail catheter can be pullback for pressure recording from the left ventricle apex to the ascending aorta.
in the length of protruding wire or the orientation of the pigtail catheter. Alternatively, some operators prefer to leave the pigtail catheter fixed and move the guidewire independently in attempts to cross stenotic aortic valves. In either case, the wire should be withdrawn and cleaned and the catheter should be double-flushed vigorously every 3 minutes despite systemic heparinization. If promising wire positions are not obtained, the process should be repeated using a different catheter: a left Amplatz (AL1) catheter if the aortic root is normal or dilated or a Judkins right coronary catheter if the aortic root is unusually narrow together with a straight wire. Other catheters have been proposed for this purpose, but we have found these standard catheters to suffice in virtually all cases. As of today, the left Amplatz (AL1) catheter is the preferred catheter by most operators to cross a stenotic aortic valve.

When the tip of the guidewire is across the aortic valve, additional wire should be inserted before any attempt is made to advance the catheter itself. Otherwise the catheter may be diverted into a sinus of Valsalva, causing the wire to flip out of the left ventricle. The straight wire should be advanced carefully, since there is a potential (admittedly small in the hypertrophic left ventricle of a patient with aortic stenosis) to perforate the LV wall if the guide wire is advanced farther when it has become trapped in an endocardial surface feature. It is important to note that when crossing the aortic valve with catheters other than the pigtail, a left anterior oblique (LAO) or anteroposterior view should be used in order to prevent inadvertent advancement of the straight wire in the coronary ostium. Once the tip of the wire has crossed the valve, the RAO angle should be used to visualize the position of the wire in the ventricular cavity and prevent perforations. Once the catheter is in the left ventricle, the wire is immediately withdrawn and the catheter is aspirated vigorously, flushed, and hooked up for pressure monitoring, so that a gradient can be measured even if the catheter is rapidly ejected from the left ventricle or must be withdrawn because of arrhythmias. When using a left Amplatz catheter to cross a stenotic valve, however, we prefer to cross the valve with a full exchange length (260 cm) guidewire. Once the tip of this wire has entered the left ventricle, it is left in position as the Amplatz catheter is removed, and a conventional dual-lumen pigtail catheter is substituted before an attempt is made to measure LV pressure.

The same approach applies to retrograde catheterization across a porcine aortic valve prosthesis, although it is more common to use a J-tip guidewire to help avoid the area between the support struts and the aortic wall. Ball valves (Starr-Edwards) can be crossed retrograde with this approach, but use of a small (4F or 5F) catheter will minimize the amount of aortic regurgitation resulting from catheter interference with diastolic ball seating. Tilting disc valves (Bjork-Shiley, St. Jude, Carbomedics), however, should not be crossed retrograde because of the potential for producing torrential aortic regurgitation, catheter entrapment, or even disc dislodgement if the catheter passes across the smaller (minor) orifice. Although safe passage through the major orifice may be possible under careful fluoroscopic

Crossing the Aortic Valve

After measurement of the ascending aortic pressure, the pigtail catheter is then advanced across the aortic valve and into the left ventricle. If the aortic valve is normal and the pigtail is oriented correctly, it will usually cross the valve directly. In many cases, however, it may be necessary to advance the pigtail down into one of the sinuses of Valsalva to form a secondary loop (Figure 6.12). As the catheter is withdrawn slowly, this loop will open to span the full diameter of the aorta, at which point a very subtle further withdrawal will often cause the pigtail to fall across the valve.

If significant aortic stenosis is present, the pigtail must be advanced across the valve with the aid of a straight 0.038-inch guidewire. Approximately 6 cm of the guidewire is advanced beyond the end of the pigtail catheter, and the catheter is withdrawn slightly until the tip of the guidewire is leading (Figure 6.12). The position of the tip of the guidewire within the aortic root can then be controlled by rotation of the pigtail catheter and adjustment of the amount of wire that protrudes; less wire protruding directs the wire tip more toward the left coronary ostium, whereas more wire protruding directs the wire more toward the right coronary ostium. With the wire tip positioned so that it is directed toward the aortic orifice, the tip of the wire usually quivers in the systolic jet. Wire and catheter are then advanced as a unit until the wire crosses into the left ventricle. If the wire buckles in the sinus of Valsalva instead of crossing the valve, the catheter–wire system is withdrawn slightly and readvanced with or without subtle change

Figure 6.11 Central aortic pressure (Ao) measured through a 7.3F pigtail catheter (Cook) and femoral artery (FA) pressure measured from the side arm of an 8F arterial sheath (Cordis). Only minimal damping of the femoral artery pressure is seen, blunting its systolic overshoot, which frequently exceeds central aortic systolic pressure (see Chapter 10). With larger (8F) catheters, more damping may occur in the side-arm pressure.
control,\textsuperscript{21} we still prefer a transseptal or even apical puncture approach (see below) when it is necessary to enter the left ventricle in a patient who has a tilting disc valve in the aortic position.

**Control of the Puncture Site Following Sheath Removal**

Originally, standard groin management required the effect of heparin to wear off or be reversed by protamine to an ACT <160 seconds before the arterial catheter and sheath were removed and manual pressure applied, except in the case of bivalirudin as mentioned above. Manual pressure method is best applied using three fingers of the left hand that are positioned sequentially up the femoral artery beginning at the skin puncture. With the fingers in this position, there should be no ongoing bleeding into the soft tissues or through the skin puncture, and it should be possible to apply sufficient pressure to obliterate the pedal pulses and then release just enough pressure to allow them to barely return. Pressure is then gradually reduced over the next 10 to 15 minutes, at the end of which time pressure is removed completely. The venous sheath is usually removed 5 minutes after compression of the arterial puncture has begun, with gentle pressure applied over the venous puncture using the right hand. To avoid tying up the catheterization laboratory during this period, patients were usually taken to a special holding room in the catheterization laboratory or back to their hospital beds before the sheaths were removed. If such relocation is
to be performed prior to sheath removal, it is important that the sheaths are secured in place (suture, or at least tape) to prevent them being pulled out during transport.

When procedures are performed using larger arterial sheaths or with thrombolytic agents or Hb/IIa receptor blockers, more prolonged (30- to 45-min) compression is typically required. To avoid fatigue of the operator or other laboratory personnel performing compression, occasionally a mechanical device (Compressor [Applied Vascular Dynamics, Portland, OR], The Clamp Ease device [Pressure Products Inc., Rancho Palos Verdes, California] or Femostop [Radi Medical, Wilmington, MA]) can be used to apply similar local pressure. These devices can be equally or even more effective in prolonged holds, but are uncomfortable for the patients and human supervision is required while in place; hence manual compression is preferred for removal of smaller (6F) sheaths or in patients with peripheral vascular disease or prior peripheral grafting surgery where occlusive compression or flow restriction might cause arterial occlusion. In every case, however, it should be emphasized that a trained person must be in attendance throughout the compression to ensure that the device is providing adequate control of puncture site bleeding and is not compromising distal perfusion.

After compression has been completed, the puncture site and surrounding area are inspected for hematoma formation and active oozing, and the quality of the distal pulse is assessed before application of a bandage. The patient is usually kept at bed rest with the leg straight for 4 to 6 hours following a diagnostic percutaneous femoral catheterization. The use of a sandbag over the puncture site for the first few hours after catheter removal is no longer routine since it has not been shown to decrease the incidence of hematoma formation. Nevertheless, in patients at higher risk for rebleeding (those with hypertension, obesity, or aortic regurgitation), application of a pressure bandage together with a sandbag may still be of some value. Elevation of the head and chest to 30° to 45° by the electrical or manual bed control, without muscular effort by the patient, will greatly increase the patient’s comfort and will not increase the risk of local bleeding. The only reason to insist that the patient lie completely flat is if there is significant orthostatic hypotension. Before ambulation and again before discharge, the puncture site should be reinspected for recurrent bleeding, hematoma formation, development of a bruit suggestive of pseudoaneurysm or A-V fistula formation, or loss of distal pulses.

### Puncture Closure Devices

The technique described above relies on manual or mechanical pressure for initial control of arterial bleeding and then on local hemostasis for ongoing plugging of the arterial puncture site. The potential for ongoing bleeding (with formation of hematoma, false aneurysm, or A-V fistula) has already been described in Chapter 4 and tends to be more common with interventional procedures that require larger sheath size or more aggressive antithrombotic therapy. This has prompted the development of a variety of new devices that seek to provide more positive closure of the arterial puncture site (Figure 6.13 and Table 6.1). These closure devices allow sheath removal in the catheterization laboratory in even a fully anticoagulated patient and shorten the time to hemostasis and ambulation.

There are different types of vascular closure devices; they can be grouped into passive or active, depending on their mechanism. The simplest devices are the passive ones, which enhance hemostasis by providing prothrombotic material at the time of mechanical compression. The most common of this type are the hemostasis pads coated with procoagulant material: Chito-Seal (Abbott Vascular, Redwood City, California), Clo-Sur PAD (Scion Cardiovascular, Miami, Florida), SyvekPatch (Marine Polymer Technologies, Inc., Dankers, Massachusetts), Neptune Pad (Biotronik, Berlin, Germany), D-Stat Dry (Vascular Solutions, Minneapolis, Minnesota). Nevertheless, small-randomized trials with patients undergoing diagnostic or interventional procedures have not demonstrated that the use of these pads shorten the time to ambulation, and the influence on hemostasis appears to be small; hence they are currently not considered true closure devices, but tools to aid manual compression to obtain hemostasis.

The Cardiva Catalyst (II and III) previous Boomerang (Cardiva Medical, Inc., Sunnyvale, California) is also a passive closure device that consists of a nitinol-braided mesh disk. The last generation is coated with protamine sulfate and attached to a 0.037-inch wire. This is introduced through the arteriotomy sheath and once the tip is within the arterial lumen, the disk is deployed and the sheath removed. The disk is gently pulled against the arterial wall where it is held in place by a tension clip in the skin to provide temporary intravascular tamponade, facilitating physiologic vessel contraction and thrombosis. After 15 minutes (120 min for interventional cases) the device is withdrawn and light manual compression can be done. Nothing is left behind once the device is removed, but a few minutes of manual compression are required once the device is pulled out in view of the potential rebleeding at the time of removal. This device appears to reduce time for ambulation and the Catalyst III is used in patients who have received heparin.

The Exoseal (Cordis Corporation, Bridgewater, NJ) is also considered a passive closure device that consists of deployment of a polyglycolic acid plug (absorbed within 90 days) over the arteriotomy site for hemostasis, delivered through the procedural sheath after diagnostic or interventional procedures. It should not be used in vessels of diameters <5 mm. Time taken to achieve hemostasis and ambulation appeared to be lower when compared to manual compression.

The MynxGrip device (AccessClosure, Mountain View, California) consists of a polyethylene glycol matrix (degrades by hydrolysis in less than 30 days) that deploys outside the artery while a balloon occludes the arteriotomy site within the artery. This is introduced through the existing procedural sheath and a small semicompliant balloon
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is inflated within the artery and pulled back to the arterial wall, serving as an anchor to ensure proper placement. The sealant is delivered just outside the arterial wall where it expands to achieve hemostasis. The balloon is deflated and removed through the tract leaving the expanded sealant. Limited experience supports efficacy to obtain hemostasis but with a higher rate of device failure compared with other closure devices.\textsuperscript{18,29}

Active vascular closure devices range from simple to more complex mechanism of action.

The Angio-Seal closure device (St Jude Medical, Inc, Minnetonka, Minnesota) combines active and passive techniques. It is currently one of the devices most commonly used.\textsuperscript{30} It consists of positioning a rectangular absorbable intraarterial polymer anchor tethered by a polymer filament to an extravascular small collagen plug pushed against the outside of the artery, which provides a procoagulant state. The existing arterial sheath is exchanged for a specially designed 6F or 8F sheath with an arteriotomy locator. Once blood return confirms proper positioning within the arterial lumen, the sheath is held in place while the guidewire and arteriotomy locator are removed. The Angio-Seal device is inserted into the sheath until it snaps in place. The anchor is deployed and pulled back against the arterial wall. As the device is withdrawn further the collagen plug is exposed just outside the arterial wall and the remainder of the device is removed from the tissue track. Finally, the suture, which connects all the elements of the device is cut below skin level leaving behind the anchor, collagen plug, and suture, all of which are absorbable by hydrolysis within 90 days. The Angio-Seal has been shown to reduce time to hemostasis and ambulation compared with manual compression, with a modest decrease in hematoma formation. The latest version of the device is called Evolution, and is designed to overcome some of the procedural limitations while retaining the mechanism of hemostasis.\textsuperscript{31,32}

The FISH device (Morris Innovative, Bloomington, Indiana) is an active closure device that uses a combined procedural sheath and bioabsorbable extracellular matrix “patch” made from porcine small intestinal submucosa,
which is inserted through the arteriotomy so that it straddles the arterial wall. After insertion, a wire is pulled to release the “patch” from the device, creating a reabsorbable plug in the artery wall. This device at the time of this writing has been approved only for diagnostic procedures. More data are still needed regarding the safety of the FISH device given that a portion of the patch remains intravascular.

The StarClose SE device (Abbott Vascular, Redwood City, California) is another active closure device that achieves hemostasis by deploying a 4-mm nitinol clip that approximates the edges of the arteriotomy. The device is inserted into the arterial lumen, and the clip is deployed just outside the arterial wall, grasping the edges of the arteriotomy and drawing them together for closure. The StarClose device improves patient comfort and bed rest time, but its utility may be limited in patients receiving anticoagulation because of persistent oozing.

The Perclose ProGlide (Abbott Vascular, Redwood City, CA) consists of suture-mediated active closure. The device is inserted over a guidewire until blood return indicates positioning within the lumen. A lever is then pulled to deploy a “foot” within the arterial lumen. The device is pulled back positioning the foot against the anterior arterial wall. Two simultaneous needles are deployed through the anterior wall of the femoral artery engaging a nonbiodegradable polypropylene suture that is then pulled back through the arterial wall to form a suture loop. The device (containing the needles) is then removed, leaving behind the two suture tails. A knot is tied and pushed toward the arteriotomy to achieve hemostasis. This device has been shown to decrease time taken to achieve hemostasis and bed rest. Using the “preclosure” technique, the ProGlide can be used to close larger arteriotomies. In this case, after placing a 6F sheath and performing a femoral angiogram, the sheath is replaced with two subsequent ProGlides, the needles are deployed using perpendicular angles on the artery, and the ProGlides are removed leaving behind only the suture. A larger sheath can then be placed for the procedure and at the conclusion of the procedure the sutures are tied and pushed toward the arteriotomy for closure.

The Prostar XL (Abbott Vascular, Redwood City, CA) relies on the use of a sheath-like device to perform suture-mediated closure of the arterial puncture site. This device has undergone several design updates to improve the ease of delivery, and it relies on the passage of fine nitinol needles through the margins of the arterial puncture and out through the skin tunnel, where they can be tied to provide surgical hemostasis. It is currently mainly used for large sheaths. It shortens the time from the end of the procedure to hemostasis and ambulation with a comparably low incidence of major complications.

The Axera device (Artstasis, Redwood City, CA) is an active closure device that does not leave any foreign material behind, and it is approved only for diagnostic cases with still limited data. It consists of creating an optimal predetermined shallow angle puncture allowing native hemodynamic pressure to close the access channel.
Randomized studies consistently have demonstrated that vascular closure devices shorten time to hemostasis and ambulation when compared to manual compression without any benefit in reducing vascular complications. Current recommendations are that it is reasonable to use closure devices after percutaneous interventions to improve comfort and reduce time to ambulation, but the use of closure devices is considered a class III indication for the reduction of vascular complications.

Given this array of devices, the use of femoral closure devices is expected to increase together with the increase in outpatient percutaneous interventions, which require safe and early ambulation, as well as with the use of larger sheath for transcatheter therapies. As these devices continue to evolve and the demand for early ambulation offsets the moderate cost of a closure device, they may ultimately replace prolonged local manual or mechanical pressure in the control of postprocedural bleeding from the femoral artery. The conversion to puncture-sealing devices will be accelerated if they can consistently reduce the incidence of hemorrhagic complications at the arterial puncture site, which constitute one of the most common morbidities associated with catheterization from this route. Of course, the success of these puncture-sealing approaches rests on the premise that a single, accurate, front-wall puncture of the common femoral artery (above the bifurcation and below the inferior epigastric artery) has been performed and that favorable conditions prevail within the vessel and the surrounding soft tissue. Each also requires a modest level of skill and training on the part of the operator and the realization that difficulties encountered in performing a clean closure, once the sheath has been removed and wire access has been given up, may increase rather than decrease the incidence of complications requiring vascular surgery or transfusion, or resulting in the development of deep infection. Metaanalysis of groin-closure devices suggest that early generations of these devices may have slightly increased complications such as pseudoaneurysm or infection compared with manual or mechanical compression, but they are now used with good results in most femoral catheterizations. Antibiotic prophylaxis should be considered in high-risk patients, especially in those with diabetes mellitus.

Contraindications to Femoral Approach to Left Heart Catheterization

As discussed in Chapter 1, the choice of catheterization approach is usually a function of operator, institution, and patient preference. Because of technical ease, however, data from recent large registries still show that the majority of catheterizations are performed via the femoral approach. In patients with peripheral vascular disease (femoral bruits or diminished lower extremity pulses), abdominal aortic aneurysm, marked iliac tortuosity, prior femoral arterial graft surgery, or gross obesity, however, catheter insertion and manipulation may present technical challenges even for experienced operators. Recognition of these relative contraindications may favor the use of the percutaneous radial, brachial, axillary, or even translumbar aortic approaches (see Chapters 7 and 8). Each laboratory should thus have one or more operators skilled in these alternative percutaneous routes.

Beyond the limitations of access to the central arterial circulation, one important parameter in the selection of a percutaneous access site is the ability to obtain hemostasis after catheter removal. In the femoral arterial entry technique, this is usually obtained easily after removal of a percutaneous arterial catheter, but patients with a wide pulse pressure (e.g., severe aortic incompetence or systemic hypertension), gross obesity, or ongoing anticoagulation have more problems with bleeding after femoral catheterization than do patients without these factors. The vascular complications of percutaneous retrograde arterial catheterization have already been discussed in Chapter 4. In the final analysis, however, there are relatively few patients who absolutely cannot be catheterized from the femoral approach.

**ALTERNATIVE SITES FOR LEFT HEART CATHETERIZATION**

The techniques described above for percutaneous insertion of a femoral catheter also can be used successfully from the axillary, brachial, or radial arteries, or even the lumbar aorta, with the use of an introducing sheath. In certain cases, access to the left heart may be gained by transseptal puncture from the right atrium to the left atrium, or even by direct percutaneous entry via the left ventricular apex. Although these other access sites may use needle puncture, guidewire advancement, and sheath insertion skills similar to those outlined above for the femoral approach, the operator wishing to use one of the alternative percutaneous routes must master the local anatomy, details of maximal allowable catheter size, limitations on catheter selection, techniques for achieving postprocedural hemostasis, and the range of complications that may ensue from bleeding or thrombosis at that anatomic location. Individuals interested in mastering one or more of these approaches are referred to the growing body of literature and to Chapters 7 and 8 in this textbook.

**Percutaneous Entry of the Axillary, Brachial, or Radial Arteries**

Axillary puncture has long been used as an alternative to femoral entry by the vascular radiologist. The patient's hand is brought behind his or her head to expose the axillary fossa, in which the artery can be felt to course. Using local anesthesia and needle puncture and guidewire techniques like those described above, the axillary artery is entered over the head.
of the humerus. The left axillary artery is generally preferred to allow use of preformed Judkins catheters and to avoid the brachiocephalic trunk. Effective control of the puncture site after catheter removal is critical, since accumulation of even modest amounts of hematoma around the artery can cause nerve compression.\(^4\)

The brachial artery is, of course, readily approached by surgical cutdown (see Chapter 8) but may also be approached using percutaneous (needle and guidewire) techniques.\(^6\) The antecubital fossa is prepared and anesthetized as for the cutdown approach. A 21-gauge arterial needle, a special 0.021-inch heavy-duty guidewire, and a 5F or 6F sheath (MicroPuncture set, Cook) can be used to gain access, after which traditional percutaneous catheter techniques are used. Working from the right brachial artery, Amplatz coronary curves are preferred (see Chapters 8 and 15). At the end of the procedure, the sheath is removed and the area is compressed manually. Alternatively, proximal occlusion can be obtained by inflation of a blood pressure cuff while a gauze pad and a clear intravenous infusion pressure bag is inflated to above systolic pressure over the puncture site.\(^7\) Pressure is then released gradually over 20 to 25 minutes. Comparisons of this percutaneous brachial technique to brachial cutdown show a shorter procedure time (without the need for dissection or repair) and no increase in complications, although surgical repair may be needed occasionally.\(^8\) Nevertheless, due to the associated vascular complications, this approach has been largely replaced by the radial approach (see Chapter 7), and it is used only when no femoral or radial approach is available.

### Lumbar Aortic Puncture

Percutaneous puncture of the lumbar aorta is a technique that had been used by radiologists to study patients with extensive peripheral vascular disease since the early 1980s and was then adapted to the performance of coronary angiography.\(^9\) This approach has even been used for coronary stent placement,\(^10\) although the fact that the procedure must be done with the patient prone complicates angiographic views and limits resuscitative efforts. The inability to apply direct pressure over the arterial entry site (the posterior wall of the aorta) also limits aggressive anticoagulation. Because of these negative factors, this approach has not gained any popularity.

### Transseptal Puncture

With refinements and improvements in techniques for retrograde left heart catheterization, the use of transseptal puncture for access to the left atrium and left ventricle\(^11\)\(^12\) had become an infrequent procedure in most adult cardiac catheterization laboratories.\(^13\) In these laboratories, transseptal puncture was reserved for situations in which direct left atrial pressure recording was desired (pulmonary venous disease), in which it was important to distinguish true idiopathic hypertrophic subaortic stenosis from catheter entrapment, or in which retrograde left-sided heart catheterization had failed (e.g., owing to severe peripheral arterial disease or aortic stenosis) or was dangerous owing to the presence of a certain type of mechanical prosthetic valve (e.g., Bjork-Shiley or St. Jude valves). The infrequency with which the procedure was performed made it difficult for most laboratories to maintain operator expertise and to train cardiovascular fellows in transseptal puncture and thus gave the procedure an aura of danger and intrigue. More recently, the development of catheter-based treatment of arrhythmias and of interventions for structural heart disease (including mitral valve procedures, antegrade aortic valvuloplasty, and antegrade transcatheter aortic valve replacement) has led to a resurgence of this approach.\(^14\)\(^15\) Table 6.2 summarizes current indications for transseptal catheterization.

The goal of transseptal catheterization is to cross from the right atrium to the left atrium through the fossa ovalis. In approximately 10% of patients, this maneuver is performed inadvertently during right heart catheterization with a woven Dacron catheter because of the presence of a probe-patent foramen ovale, but in the remainder, mechanical puncture of this area with a needle and catheter combination is required to enter the left atrium. Although puncture of the fossa ovalis itself is quite safe, the danger of the transseptal approach lies in the possibility that the needle and catheter will puncture an adjacent structure (i.e., the posterior wall of the right atrium, the coronary sinus, or the aortic root). To minimize this risk, the operator must have a detailed familiarity with the regional anatomy of the atrial septum (Figure 6.14). As viewed from the feet with the patient lying supine, the plane of the atrial septum runs from 1 o’clock to 7 o’clock. The fossa ovalis is posterior and caudal to the aortic root and anterior to the free wall of the right atrium. The fossa ovalis is located superiorly and posteriorly to the ostium of the coronary sinus and well posterior of the tricuspid annulus and right atrial appendage. The fossa ovalis itself is approximately 2 cm in diameter and is bounded superiorly by a ridge—the limbus.

This anatomy can be distorted somewhat by the presence of aortic or mitral valve disease.\(^16\) In aortic stenosis, the plane of the septum becomes more vertical and the fossa may be located slightly more anteriorly. In mitral stenosis, the intraatrial septum becomes flatter with a more horizontal orientation and the fossa tends to lie lower. Combined with the fact that the septum (and fossa) may then bulge into the right atrium, this makes detailed familiarity with the anatomy even more important when transseptal catheterization is attempted in patients with advanced valvular heart disease. Several algorithms using fluoroscopic landmarks determined by right and left atrial angiography, or the position of a pigtail catheter in posterior (noncoronary) aortic sinus of Valsalva, have been developed to aid localization of the best site for transseptal puncture\(^17\) (Figure 6.15). Alternatively, intraprocedural transthoracic,\(^18\) transesophageal,\(^19\) or intracardiac\(^20\) ultrasound may aid in identifying the optimal location for puncture of the intraatrial septum (Figure 6.16).

Classically, transseptal catheterization is performed from the right femoral vein, although transcervical or left femoral
### Table 6.2 Complications of Transseptal Puncture

<table>
<thead>
<tr>
<th>Complications During Transseptal Puncture</th>
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<tbody>
<tr>
<td><strong>Perforation:</strong></td>
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<tr>
<td>• Roof of the LA</td>
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<tr>
<td>• Posterior LA wall</td>
</tr>
<tr>
<td>• LAA</td>
</tr>
<tr>
<td>• SVC or IVC</td>
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<tr>
<td>• Aorta</td>
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<tr>
<td>• Pulmonary vein perforation</td>
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<tr>
<th><strong>Arrhythmias</strong></th>
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<tr>
<td><strong>Puncture or dissection of coronary sinus</strong></td>
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<th><strong>Embolization</strong></th>
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<tbody>
<tr>
<td><strong>From:</strong></td>
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<tr>
<td>• Layered thrombus in the LA wall</td>
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<tr>
<td>• LA myxoma</td>
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<tr>
<td>• Air</td>
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<tr>
<td><strong>To:</strong></td>
</tr>
<tr>
<td>• Brain</td>
</tr>
<tr>
<td>• Coronaries</td>
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<tr>
<td>• Systemic</td>
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<table>
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<tr>
<th><strong>Instrumental fracture due to breakage of the 21-gauge needle tip at its junction with the 18-gauge</strong></th>
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<tbody>
<tr>
<td><strong>Bezold-Jarisch–like vasovagal response: ST-segment elevation in the inferior leads without chest pain, associated with hypotension, bradycardia, and normal coronary arteries and reversed by atropine</strong></td>
</tr>
<tr>
<td><strong>Transient migraine</strong></td>
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<tr>
<td><strong>Thrombophlebitis and pulmonary embolism after complicated venous access</strong></td>
</tr>
<tr>
<td><strong>Pericarditis after injection of dye into the pericardium</strong></td>
</tr>
<tr>
<td><strong>Serious bleeding into posterior pericardial space</strong></td>
</tr>
<tr>
<td><strong>Inferior ST elevation</strong></td>
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<tr>
<td><strong>Residual atrial septal shunt</strong></td>
</tr>
<tr>
<td><strong>Hemothorax</strong></td>
</tr>
<tr>
<td><strong>Puncturing of the posterior RA creating a stitch phenomenon by reentering the LA</strong></td>
</tr>
<tr>
<td><strong>Atrial–aorto fistula</strong></td>
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Vein approach is feasible but more complicated. For the right femoral approach we use a 71-cm curved Brockenbrough needle, which tapers from 18-gauge to 21-gauge at the tip (Figure 6.17). The needle is introduced via a matching Brockenbrough catheter or 8F Mullins sheath and dilator combination⁴⁶; that has been inserted into the superior vena cava over a flexible 0.032-inch, 145-cm J guidewire. Once the wire has been removed and the catheter has been flushed, the Brockenbrough needle is advanced through the catheter, with an obturator (Bing stylet) protruding slightly beyond the tip of the needle to avoid abrasion or puncture of the catheter wall during needle advancement. As the needle and its stylet are advanced through the catheter, the patient may experience a slight pressure sensation owing to distortion of the venous structures by the rigid needle. During needle advancement, it is thus essential to allow the needle and its direction indicator to rotate freely so that it may follow the curves of the catheter and venous structures; the hub of the needle should
never be grasped and rotated at this point. The progress of the needle tip should be monitored fluoroscopically, looking for any sign of perforation of the catheter by the needle. The stylet is then removed at the diaphragm, and the needle hub is connected to a pressure manifold, using a stopcock with a short length of tubing, and is carefully flushed. The needle is then advanced to lie just inside the tip of the catheter or sheath, as indicated by measurements made by comparing the distance between the needle flange and the catheter hub to similar measurements made with a sterile ruler before insertion (Figure 6.18). Alternatively, current high-quality fluoroscopy can be used to visually monitor advancement of the needle to the catheter tip.

The superior vena caval pressure should then be recorded through the needle, with the needle rotated so that the direction indicator points anteriorly. Under continuous fluoroscopic and pressure monitoring, the needle and catheter are then held in constant relationship as they are withdrawn slowly, using both hands. The direction indicator is firmly controlled with the right hand and used to rotate the needle clockwise during this withdrawal from the superior vena cava until the arrow is oriented posteromedially (4 o’clock when looking from below). As the tip of the catheter enters the right atrium, it moves slightly rightward (toward the patient’s left). The needle and catheter are maintained in their posteromedial orientation, and they continue to be withdrawn slowly. As the catheter tip slips over the bulge of the ascending aorta, it again moves rightward to overlie the vertebrae in the anterior projection. Further slow withdrawal maintaining the 4 o’clock orientation will be associated with a third rightward movement as the catheter tip “snaps” into the fossa ovalis. This is confirmed by the fact that advancement will cause the catheter tip to flex slightly (rather than move back up the atrial septum) if its tip is lodged in the fossa. Clear fluoroscopic evidence of fossa engagement is thus essential to successful transseptal puncture.

If the foramen is patent, the catheter may actually cross into the left atrium spontaneously at this point, as indicated by a change in atrial pressure waveform and the ability to withdraw oxygenated blood from the needle. Otherwise, the
Figure 6.15  Fluoroscopic landmarks for localizing the fossa ovalis. Left. As described by Inoue, right atrial injection can be used to locate the upper corner of the tricuspid valve (point A), which is marked on the TV monitor. Right. Continued filming during the levophase fills the left atrium. A horizontal line is drawn from point A to the back wall of the left atrium, defining point B. That line is divided in half, and a vertical line is dropped to the floor of the left atrium, defining point C. The location of the fossa (X) is along this vertical line, approximately one vertebral body height above point C. When the borders of the left atrium are visible fluoroscopically, the position of a pigtail catheter in the noncoronary sinus of Valsalva can be substituted for point A, allowing localization of the ideal puncture site without contrast injection. A similar localization scheme (not shown) has been proposed in the 40° RAO projection by Croft and associates (reference 59), using the aortic pigtail and the posterior border of the left atrium. Puncture is made 1 to 3 cm below the midpoint of a line connecting the posterior wall of the aorta to the back wall of the left atrium.

Figure 6.16  Intracardiac echo from within the right atrium shows the fossa ovalis and the left atrium clearly. Images during positioning of the transseptal needle show clear tenting of the foramen by the needle and reduce the uncertainty regarding correct puncture position. (Reproduced with permission from Moscucci M, Dairywala IT, Chetcutí S, Mathew B, Li P, Rubenfire M, Vannan MA. Balloon atrial septostomy in end-stage pulmonary hypertension guided by a novel intracardiac echocardiographic transducer. *Catheter Cardiovasc Interv: Official J Soc Cardiac Angiogr Interv* 2001;52:530–534.)
Equipment for transseptal puncture. The Brockenbrough needle (far left) and Bing stylet (left) can be used in conjunction with the traditional Brockenbrough catheter (center) and Mullins sheath/dilator system (right).

The Brockenbrough system with the needle and stylet inserted into the catheter. Ruler measurement of the distance from the catheter hub to the needle flange is shown with the tip of the stylet at the tip of the catheter (position 1) and with the stylet withdrawn and the needle tip extended to the tip of the catheter (position 2). (Redrawn from Ross J Jr. Considerations regarding the technique for trans-septal left heart catheterization. Circulation 1966;34:391.)

The catheter is advanced slightly to flex its tip against the limbus at the superior portion of the foramen ovale. Once the operator is satisfied with this position, she or he advances the Brockenbrough needle smartly so that its point emerges from the tip of the catheter and perforates the atrial septum. Successful entry into the left atrium can be confirmed by recording left atrial pressure waveform and the withdrawal of oxygenated blood or the demonstration of the typical fluoroscopic appearance of the left atrium during a contrast puff through the needle. Once the operator is confident that the needle tip is across the interatrial septum, the needle and catheter are advanced as a unit a short distance into the left atrium, taking care to control their motion so that the protruding needle does not injure left atrial structures. When the catheter is across the atrial septum, the needle is withdrawn and the catheter is double-flushed vigorously and connected to a manifold for pressure recording.

The main risk during transseptal catheterization is inadvertent puncture of adjacent structures (the aortic root, coronary sinus, or posterior free wall of the right atrium) rather than the fossa ovalis. As long as the patient is not anticoagulated and perforation is limited to the 21-gauge tip of the Brockenbrough needle (i.e., perforation is recognized and the catheter itself is not advanced), this is usually benign. However, if the 8F catheter itself is advanced into the pericardium or aortic root, potentially fatal complications may occur, underscoring the need for the operator to monitor closely the location of the transseptal apparatus by fluoroscopy, pressure, and oxygen saturation at each stage of the procedure. Damped pressure waveform during attempted septal puncture may indicate puncture into the pericardium or simply incomplete penetration of a thickened interatrial septum. Injection of a small amount of contrast through the needle can be useful in this case by staining the atrial septum and allowing confirmation of an appropriate position in the LAO and RAO projection before more forceful needle advancement is attempted (Figure 6.19). If the initial attempt at transseptal puncture is unsuccessful, the operator may wish to repeat the catheter positioning procedure by removing the transseptal needle from the catheter, withdrawing the catheter slightly, and reinserting the 0.032-inch guidewire into the superior vena cava. In general, one should never attempt to reposition the catheter–needle combination in the superior vena cava in any other way, since perforation of the right atrium or atrial appendage is a distinct possibility during such maneuvers.

Once the catheter is safely in the left atrium, additional manipulation may be required to enter the left ventricle. If the tip of the catheter has entered an inferior pulmonary vein (as evident by its projection outside the posterior heart border in the RAO projection), the left ventricle can be approached by torquing the catheter 180° in a counterclockwise direction so that its tip moves anteriorly as it is withdrawn slightly. As the catheter tip moves anteriorly and downward, further advancement will usually allow it to cross the mitral valve and enter the left ventricle. If not, it may be necessary to
Figure 6.19 Steps of transseptal puncture as seen with fluoroscopy using common anatomical landmarks (spine, cardiac silhouette, left bronchus) and in this case prosthetic valves. 

A. Transseptal (TS) kit in the superior vena cava (SVC).  

B. Descent of the TS kit into the FO.  

C. Staining of the IAS.  

D. TS puncture and advancement into the LA.  

E. Advancement of the TS sheath into the LA.  

Apical Left Ventricular Puncture

Historically, a variety of direct puncture techniques were used to enter the cardiac chambers before the introduction of percutaneous left and right heart catheterization. These techniques included transbronchial and transthoracic approaches to the left atrium, the suprasternal puncture technique of Radner, and apical LV puncture. Of these, only the last has survived, and has gained much popularity as the preferred approach to measure LV pressure in patients where retrograde and transseptal catheterization of the left ventricle are precluded by the presence of mechanical aortic and mitral prostheses, as well as for the treatment of specific structural heart disease conditions that either do not have alternative access approach or due to better anatomical access (i.e., para-valvular leaks).

In preparation for an apical puncture, ideally preprocedure imaging with computed tomography can help identify the specific puncture site in relation to the bone structures in order to prevent inadvertent perforation of other structures including the lungs and coronary arteries. The site of the apical impulse is then located by palpation and confirmed by fluoroscopy of a hemostatic clamp placed at the intended puncture site. Alternatively, the true LV apex can be located using echocardiography and may be found to lie significantly more lateral than the palpated apical impulse in patients with right ventricular enlargement. After liberal local anesthesia, a 21-gauge needle is introduced at the apex and directed along the long axis of the left ventricle. This is accomplished by aiming the needle tip roughly toward the back of the right shoulder. Contact with the LV wall can usually be felt as a distinct impulse (and the onset of ventricular premature beats). Sharp advancement of the needle at this point will cause its tip to enter the left ventricular cavity, with pulsatile ejection of blood.

In the technique of Semple, an outer Teflon catheter was then advanced over the puncture needle and into the left ventricle (sometimes out through the aortic valve, as well). We, however, have preferred to advance a 0.035-inch 65-cm-long J guidewire through the needle and into the left ventricle under fluoroscopic guidance. This allows the advancement of a 4F dilator followed by a 4F pigtail catheter to allow pressure measurement and/or LV angiography (Figures 6.20 and 6.21).

One series describes excellent results of apical puncture in 102 patients, whereas a recent series from the Massachusetts General Hospital describes excellent results in 38 patients. A variation of the apical puncture is a subxiphoid approach through the right ventricle and septum into the left ventricle. Hemostasis at the end of the procedure will be obtained depending on the size of the sheath inserted. Small sheaths can be manually pulled without major complications and larger sheaths, up to 9F, have been removed by using off-label ventricular closure devices at the ventriculostomy site. When this fails, an open mini-thoracotomy may be required to stitch close or to patch the puncture site. Major complications (tamponade or pneumothorax) occur.
Apical left ventricular puncture. In this patient with Björk-Shiley aortic and mitral valve prostheses (arrow, upper left), percutaneous puncture of the left ventricular apex was performed to allow left ventricular pressure measurement and contrast ventriculography using a 4F angiographic pigtail catheter shown entering the LV apex (arrow, lower right). This catheter was advanced into the left ventricle over an 0.035-inch guide wire, following apical puncture with an 18-gauge thin-wall needle (see text for details).

Direct apical puncture and transseptal puncture in a patient with St. Jude valves in aortic and mitral position. Cine frame in RAO view. There is a pigtail catheter inserted in the left ventricle through a transthoracic apical LV puncture, a second pigtail catheter positioned in the ascending aorta, a Mullins catheter advanced into the left atrium through the trans-septal approach, and a Swan-Ganz catheter positioned in the pulmonary artery. The mitral and aortic St. Jude valve prosthesis are visible on the left of the spine (arrows). (Reproduced with permission from: Turgut T, Deeb M, Moscucci M. Left ventricular apical puncture: a procedure surviving well into the new millennium. Catheter Cardiovasc Interv: Official J Soc Cardiac Angiogr Interv 2000;49:68–73.)
in roughly 3% of patients, although tamponade is very rare in postoperative patients (who have adhesive pericardium). Other complications of apical puncture can include hemothorax, intramyocardial injection, and ventricular fibrillation, as well as pleuritic chest discomfort (approximately 10%) and reflex hypotension owing to vagal stimulation (approximately 5%). We thus reserve this technique for patients in whom it is essential to enter the left ventricle and in whom neither retrograde nor antegrade (transcaval) entry of the left ventricle is feasible.

REFERENCES


INTRODUCTION

In 1989, Lucien Campeau published his successful series of 100 coronary angiographies performed via the left radial artery with minimal occurrence of complications. Subsequently in 1993, Kiemeneij performed percutaneous coronary interventions (PCI) using 6F guiding catheters in a time when most interventional procedures were performed with larger 8F catheters. Since then, transradial access (TRA) has continued to gain popularity in some regions of Europe, Canada, South America, Japan, and other sites outside of the United States where TRA is used in more than 60% of the cases. The most compelling reason for adopting TRA is the increased patient safety that results from the virtual elimination of access site bleeding and vascular complications. In addition, TRA is associated with early sheath removal, improved patient comfort, faster recovery, and lower costs in comparison with transfemoral access. However, a relatively steep learning curve, increased radiation exposure, incompatibility of the radial artery with sheaths larger than 6F required for large rotablator burrs and complex bifurcation stenting, and higher access failure rates have been cited as reasons for not systematically adopting TRA. An early analysis of the American College of Cardiology National Cardiovascular Data Registry (ACC/NCDR) of procedures performed between 2004 and 2007 demonstrated a minimal use of TRA in the United States, with almost 90% of centers performing less than 2% of cases using the radial artery approach. However, interventional cardiologists have been more open to change and TRA has gained renewed momentum in the United States with the recognition of access site bleeding as a predictor of adverse outcomes post-PCI. Wider access to training opportunities, and the inception of dedicated micropuncture needles, hydrophilic-coated sheaths, and radial hemostasis devices. A more recent analysis including 1,776,625 patients treated at more than 1,200 U.S. hospitals demonstrated a significant uptake in TRA use from 1.3% in 2007 to 12.7% in 2011. The ACC/AHA/SCAI guidelines now include TRA as a class IIA recommendation with a level of evidence A to decrease access site complications. A class IIA recommendation for TRA is also included in the most recent European guidelines for the management of acute ST segment elevation myocardial infarction in the setting of primary PCI, if performed by an experienced radial operator.

ANATOMICAL CONSIDERATIONS

The radial artery arises together with the ulnar artery from the bifurcation of the brachial artery just below the bend of the elbow. The radial artery passes along the lateral side of the forearm from the neck of the radius to the forepart of the styloid process in the wrist and is smaller in caliber than the ulnar artery. It then winds backward, around the lateral side of the carpus. The distal portion of the artery in the forearm is superficial, being covered by the integument and the superficial and deep fascia, lying between the tendons of the brachioradialis and flexor carpi radialis over the prominence of the radius. With an average diameter of 2.8 mm in females and 3.1 mm in males, the radial artery is compatible with 6F sheaths. The artery is accompanied by a pair of venae comitantes throughout its whole course, which can be used to perform right heart catheterization (RHC). Several anatomic characteristics explain the marked safety advantage of the radial artery over the femoral artery approach. The flat, bony prominence of the radius provides ease of compression and hemostasis after sheath removal; the vast collateralization of the radial artery through the palmar arch prevents ischemia of the hand; because the puncture site is not overlying a joint, motion of the hand or the wrist does not increase the risk of bleeding; and because of the absence of major adjacent nerve structures, there is no risk of neurologic sequelae. In contrast, the ulnar artery is deep lying, mobile, adjacent to the ulnar nerve, and consequently not
ideal for first-line vascular access. Despite this, ulnar access has been used successfully for coronary procedures, without evidence of an increased rate of complications when compared with TRA. The ulnar artery should not be used after a failed ipsilateral radial attempt because of a possible small risk of complete obstruction of circulation to the hand.

The interventional cardiologist should be aware of relatively uncommon anatomic anomalies that may impede the advancement of catheters to the aorta or increase the risk of failure or complications. Variations include tortuous radial configurations, stenoses, hypoplasia, radioulnar loops, aberrant right subclavian artery (arteria lusoria), and abnormal origin of the radial artery. In a series of 1,540 transradial procedures, anatomic anomalies were found in about 15% of cases. A high radial artery origin at the level of the mid or upper humerus was found in 7% of cases and was associated with a failure rate of 4.6%, a loop in the proximal radial artery was found in 2.3% of cases and associated with a high failure rate of 37.1%, severe tortuosity was found in 2%, and other miscellaneous anomalies in 2.5% of cases. These anomalies are usually unilateral, therefore vascular access crossover to the left radial artery may be indicated in cases of extreme tortuosity or angulated radial loops. Significant subclavian or brachiocephalic tortuosity is present in about 10% of cases and is usually associated with advanced age, short stature, and long-standing history of hypertension. However, subclavian tortuosity is rarely a cause of procedural failure because it can be easily negotiated by the use of deep inspiration or supportive guidewires. In rare cases (<1%), the right subclavian artery arises directly from the distal segment of the posterior aspect of the aortic arch and has a retroesophageal course toward the right upper extremity. This anomaly is known as arteria lusoria and represents a formidable challenge for advancing a catheter from the subclavian artery to the ascending aorta. This anomaly is mostly asymptomatic but can be associated with dysphagia.

### TECHNICAL ASPECTS

#### Preprocedure Assessment—Testing for Dual Circulation to the Hand

All patients undergoing TRA procedures in the catheterization laboratory should be assessed and undergo preparation according to a standardized protocol. Depending on the operator's preference, the groins can be prepped along with the wrists. Placement of intravenous lines in the vicinity of the wrist should be avoided. Sedation is strongly recommended to decrease catecholamine release that can potentially contribute to radial spasm.

There is significant variability in the vascular anatomy of the hand. The superficial palmar arch that connects the ulnar and radial arteries is complete in approximately 80% of cases and the predominant blood supply to the hand is thought to be from the ulnar artery in the majority of cases. In 1929, Edgar Van Nuys Allen introduced a "compression test" to diagnose arterial occlusion resulting from thromboangiitis obliterans or Buerger disease. The test consists of simultaneously compressing the ulnar and the radial arteries at the level of the wrist for approximately 1 or 2 minutes, the patient closes the hand tightly to squeeze as much blood out as possible, then quickly opens the hand and extends the fingers; then the operator releases compression of the ulnar artery and waits for the hand to regain color. In individuals with integrity of the hand circulation and a patent palmar arch, the pallor of the hand is quickly replaced by blushing of higher intensity than normal in about 5 to 9 seconds. Because the Allen's test is largely subjective and yields more than 30% of falsely abnormal results, Barbeau and coworkers modified the test by attaching a pulse oximeter to the thumb to record oxygen saturation and plethysmography. In a study including 1,010 patients, Barbeau and colleagues described four reading patterns: no damping of the pulse waveform immediately after 2 minutes of radial compression, positive oximetry (Type A, frequency 15%); damping of the pulse waveform and positive oximetry, followed by complete recovery within 2 minutes of compression (Type B, frequency 75%); loss of pulse waveform, negative oximetry, with partial progressive recovery of the pulse waveform and oximetry within 2 minutes of compression (Type C, frequency 5%); loss of pulse waveform, negative oximetry, without recovery of either pulse waveform or oximetry after 2 minutes of compression (Type D, frequency 5%) (Figure 7.1). After analyzing these patterns in the right and left wrists of the study participants, only 1.5% showed a bilateral Type D pattern and these patients did not undergo TRA procedures.

In summary, this study suggests that almost all patients are eligible for TRA procedures without risk of ischemic complications to the hand. Some operators have challenged the utility of testing the collateral circulation of the radial artery, stating that the presence of a rich collateral system and the presence of interosseous branches that supply circulation to the hand could possibly allow to tolerate concomitant radial and ulnar artery occlusion. In addition, there is no evidence indicating that the modified Allen's test predicts hand ischemia after TRA procedures. However, as part of the catheterization laboratory routine in most sites, a modified Allen's test using pulse oximetry and plethysmography is usually performed and the results documented.

#### Patient Positioning—Right versus Left Radial Access

TRA can be performed through the left or the right radial artery. Due to ergonomic considerations, most operators prefer using right TRA. Regardless of the side of choice, a comfortable position for the patient and the operator is crucial for successfully performing TRA procedures. The patient is
positioned supine on the angiographic table. With right-sided TRA, an arm board extension is attached to the right hand side of the table. Importantly, there should be a platform that extends from the distal portion of the patient’s hand to the table controls so that equipment can be placed in this area. Arm boards are commercially available in different shapes and designs. Many laboratories have opted for trapezoid-shaped acrylic glass board, with the narrow end tucked under the mattress at the shoulder level and the broad area at the wrist level (Figure 7.2). The patient’s right arm is placed on the board and abducted at a 30° angle. The right wrist is placed in a hyperextended position using commercially available splints or a rolled towel behind the wrist with the fingers taped to the arm board. A pulse oximeter probe can be placed in the right thumb for continuous monitoring of the circulation to the hand throughout the procedure (Figure 7.3). Both groins may be prepped as well, depending on the anticipated need for femoral access.

For left TRA, the setup is completely different and varies widely across catheterization laboratories. As with right TRA, the operator stands on the right side of the patient for left TRA to avoid disruption of the traditional laboratory setup.

The patient is positioned supine on the table and a custom arm rest, made of foam or pillow material, is attached to the left side of the table to elevate and pronate the left arm and guide the forearm toward the midsection of the patient’s body and place the wrist over the leg where it can strapped to a splint (Figure 7.2).

It has been shown that the prevalence of subclavian tortuosity and radial loops is three times higher in the right upper extremity. With right TRA the catheter has to pass through the right subclavian artery and the brachiocephalic trunk before reaching the aortic root. These two areas of bifurcation can increase technical difficulty, especially when these vessels are atherosclerotic, tortuous, and calcified. Since the left subclavian artery arises directly from the aorta, the path followed by the catheter in the left radial route into the ascending aorta is more straightforward, often resulting in less complex catheter manipulation. In addition, left TRA should be strongly considered in patients who have undergone coronary artery bypass grafting (CABG), because it provides direct access to the left internal mammary artery (LIMA). Certainly, the LIMA can also be cannulated from the right radial route, but this
is significantly more challenging from a technical standpoint with a potential risk of embolic stroke due to catheter manipulation and exchanges in the aortic arch. Randomized data comparing right versus left radial access suggested that using left TRA during the learning curve may be advantageous as it allows novice operators to acquire the skills and confidence required for transradial procedures more quickly than the right radial route. In the TALENT trial (Transradial Approach [Left versus. Right] and Procedural Times during Percutaneous Coronary Procedures) 1,500 patients were randomized to right or left TRA. The study found that among trainees, left TRA was associated with a significantly shorter learning curve, with progressive reductions in cannulation and fluoroscopy times as the operator volume increased, compared to right TRA.28,29

**Radial Puncture**

There are a number of TRA kits available in the market. In general, these kits include a micropuncture needle, a short 0.018 to 0.021 inch wire, and an arterial sheath with or without hydrophilic coating of shorter (10 to 13 cm) or longer (23 cm) length. Some operators advocate the use of longer sheaths to avoid difficulties with catheter manipulation should spasm occur, but a randomized trial comparing sheath lengths on arterial spasm showed no effect of longer sheaths on reducing spasm.30 On the other hand, hydrophilic coating allows easier sheath removal and is clearly associated with less spasm and patient discomfort.31 However, in the past decade, Kozak and colleagues reported sterile abscesses in the wrist after the use of a particular transradial sheath brand. These abscesses were
Section II Basic Techniques

Transradial access technique (Step 1). After sterile preparation and draping, the wrist area is locally anesthetized with lidocaine using a 25G needle and a small 3 cc syringe.

Later found to be a foreign-body reaction to the hydrophilic coating of the sheaths. Conservative management ruling out the presence of infection, local wound care with drainage in case of abscess formation, and reassurance are recommended for the management of this complication. Sterile abscesses are rarely found in contemporary practice as the hydrophilic coating causing the problem has been modified, although a recent isolated case of sterile abscess has been reported with new sheaths. A recent study randomized 790 patients undergoing TRA PCI in a 2×2 factorial design to shorter (13 cm) or longer (23 cm) sheaths with or without hydrophilic coating. Hydrophilic-coated sheaths were associated with a significant reduction in radial spasm (19.0% versus 39.9%, \( P < 0.001 \)) and patient discomfort (15.1% versus 28.5%, OR 2.27, \( P < 0.001 \)), whereas sheath length did not have any effect in the occurrence of spasm or patient discomfort. In addition, the operator may consider using smaller diameter sheaths as 5F sheaths are associated with lower incidence of radial artery occlusion (RAO) than 6F sheaths. Therefore, in current practice, shorter 5F hydrophilic-coated sheaths are preferred.

It is important to administer sedation to avoid the release of catecholamines associated with the emotional stress and fear that patients usually experience before the procedure, which can contribute to radial artery spasm. The site of access is approximately 2 cm proximal to the radial styloid process, not at the wrist. The radial artery is most superficial in this area. Once the patient is prepped in sterile fashion, this area is anesthetized with approximately 2 to 3 cc of 1% lidocaine injected with a small syringe and a 25G needle (Figure 7.4). Usually, the arterial puncture is performed with either a short 2.5 cm, stainless steel, 21G needle or a micropuncture IV catheter that consists of a fine metal needle and a 22G Teflon catheter that allow the passage of a 0.018 to 0.021 inch guidewire. While feeling the pulse with one hand, the operator advances the needle into the radial artery at a 30° angle with the other hand (Figure 7.5). Most operators prefer one of two different
access techniques (single-wall versus double-wall or back-wall technique). With the single-wall technique, a stainless steel needle is advanced through the front wall of the artery into the lumen; once blood is noticed in the needle hub the wire can be advanced (Figure 7.6). Using this technique, the blood return is rarely brisk or pulsatile and sometimes the wire does not advance freely because the bevel may be directing the wire toward the vessel wall. If this happens, the operator should never force the wire because of the risk of arterial dissection. The needle should be carefully rotated clockwise or counterclockwise until the wire can be easily advanced without resistance (Figure 7.7). With the dual-wall or back-wall technique, a micropuncture catheter is advanced through the front wall into the lumen of the artery until blood is noticed in the hub and then intentionally pushed through the back wall of the artery (Figure 7.8). The fine needle is removed and the small Teflon microcatheter is slowly withdrawn until the appearance of brisk pulsatile flow (Figures 7.9 and 7.10). Then, the wire can be freely advanced and the microcatheter exchanged for the arterial sheath (Figure 7.11). The orifice in the back wall of the radial artery is sealed once the sheath is in place (Figure 7.12). This technique has not been reported to be associated with a higher incidence of wrist hematomas. Proponents of the back-wall technique argue that this method is simpler, more reproducible, easier to teach, allows easier advancement of the wire, and that the arterial pulsatile blood return is easier to recognize.

After several unsuccessful puncture attempts, there are instances in which the radial pulse disappears due to spasm. In this situation, the operator should reassess the sedation status of the patient, consider administering 200 to 400 mcg...
Figure 7.8 Transradial access technique–back-wall technique (Step 2). The microcatheter and needle are advanced in a 30° angle through the skin into the radial artery. The presence of blood in the hub of the needle indicates that the artery has been punctured. The needle is advanced forward through the back wall of the radial artery.

of subcutaneous nitroglycerin at the site of the lost radial pulse, and wait patiently for 5 to 10 minutes until the pulse reappears before attempting a new puncture.35

Even though TRA procedures can be successfully completed in more than 95% of cases, inability to puncture the radial artery has been one of the most frequent mechanisms associated with TRA failure.11 Therefore a consistent and meticulous radial artery puncture technique could not be emphasized more. A steep learning curve for TRA procedures has been well described. Spaulding et al., documented an initial access failure rate greater than 10% that decreased dramatically to about 2% after the first 80 cases. In addition, the time required for access and sheath insertion decreased from $10.2 \pm 7.6$ to $2.8 \pm 2.5$ minutes and the procedure time also decreased from $25.7 \pm 12.9$ to $17.4 \pm 4.7$ minutes after the first 80 cases.7 More recently, in a group of 28 operators, Ball and colleagues documented a stepwise reduction of TRA-PCI failure rates from 7% to 2% ($P = 0.01$), contrast volume use from $180 \pm 79$ to $168 \pm 79$ mL ($P = 0.05$), and fluoroscopy times from $15 \pm 10$ to $12 \pm 9$ minutes ($P = 0.02$) with increasing procedural volumes. The odds of TRA procedural failure showed a steep decline up to 50 cases, and after 100 cases the learning curve flattened. Figure 7.13 shows that reasons for failure are different according to operator volume. It is clear that with experience, the operator can overcome most hurdles and the major reasons for failure remain radial artery spasm and extreme vascular tortuosity.9

Prevention of Radial Artery Spasm

The radial artery has a high propensity to develop spasm due to its smaller caliber, large muscular media, and higher receptor-mediated vasomotion in comparison with similar arteries.36 Radial artery spasm is perhaps the most common TRA complication and a frequent reason for failure and crossover to transfemoral access.9,11 In the catheterization laboratory, spasm should be routinely prevented using a hydrophilic-coated sheath with the injection of a single vasodilator or a cocktail of vasodilators through the sidearm of the sheath immediately after obtaining access (Figure 7.14). Most
commonly used vasodilators in order of frequency include the combination of verapamil and nitroglycerin, verapamil or nitroglycerin alone, nicardipine, lidocaine, and papaverine. Radial spasm manifests with severe forearm pain and unusually difficult manipulation of the catheters and the sheath. Independent predictors of radial spasm include the presence of radial artery anomalies, multiple catheter exchanges, pain during radial cannulation, larger catheter diameter, and small radial artery caliber. In extreme cases, eversion radial endarterectomy has been reported after forceful removal of the radial sheath. When spasm occurs, additional doses of intraarterial vasodilators, sedation, and use of smaller 4F to 5F catheters to complete the procedure are usually recommended. If after these measures the patient still complains of substantial pain and the catheters are difficult to manipulate, a limited upper extremity angiography is recommended to rule out vascular anomalies such as a high radial origin in the proximal brachial artery or a radial loop.

Navigating the Upper Extremity
Arterial System

Once arterial access is obtained, a 0.035 inch guidewire and a catheter of choice are advanced into the ascending aorta traversing the upper extremity arterial system. Choice of guidewires differs across operators and local practices. A J-tip wire may follow the path of larger vessels and may not selectively

Figure 7.9 Transradial access technique–back-wall technique (Step 3). Once the tip of microcatheter and needle are through the back wall of the radial artery, the needle is removed and the microcatheter left in place across the radial artery.

Figure 7.10 Transradial access technique–back-wall technique (Step 4). The microcatheter is retrieved very slowly until the appearance of brisk pulsatile blood return that confirms that the distal tip is in the lumen of the radial artery.
Transradial access technique—back-wall technique (Step 5). A short 0.018 inch wire, usually included in the micropuncture transradial access kit, is advanced without resistance through the microcatheter into the proximal radial artery. In case of resistance, a limited angiogram can be performed through the microcatheter to verify the intraluminal position and rule out the presence of vascular anomalies.

Transradial access technique (Step 6). The sheath, preferably hydrophilic-coated, is advanced over the wire.
enter into small radial or brachial branches, but the diameter of the J tip is usually larger than the diameter of the radial artery and may cause vasospasm. Angled-tip hydrophilic guidewires with stiff shafts are ideal for negotiating tortuous anatomy, especially in the subclavian artery and brachiocephalic trunk, but these wires need to be advanced under close fluoroscopic surveillance, as they may inadvertently enter into and perforate small branches of the radial or brachial arteries. As full anticoagulation is usually administered during transradial procedures, a small branch perforation can result in significant hematoma formation.

In a small proportion of cases, the transradial operator will encounter anatomic variations that may prevent the advancement of guidewires or catheters into the ascending aorta. In these cases, the operator will meet resistance to the advancement of either guidewires or catheters. Due to the relatively small size of the upper extremity arterial system, the operator should never force any equipment against resistance. Instead, a limited retrograde angiographic assessment should be performed to identify a vascular anomaly or unusual tortuosity, plan a strategy, and avoid complications. Radioulnar loops and tortuosity in the radial or brachial arteries can be identified and negotiated with the 0.014 inch coronary wire of choice with the support of a 4F hydrophilic-coated Cobra or angled catheter compatible with a 0.035 inch guidewire. Once the tipped coronary wire is positioned

Figure 7.13  TRA experience and mechanisms of failure. (Adapted from Ball W, et al. Circ Cardiovasc Interv 2011;4:336–341.) PCI, percutaneous coronary interventions; TRA, transradial access.

Figure 7.14  Transradial access technique–prevention of radial spasm. Once the sheath is in place, the spasmolytic cocktail is administered through the sidearm.
beyond the loop, the hydrophilic catheter is advanced farther in the brachial artery, and then the coronary wire is exchanged for a regular 0.035 inch guidewire. The loop usually straightens as the 0.035 inch wire passes through or with gentle pullback and counterclockwise torque of the entire system (Figure 7.15). In the presence of unusual difficulty in advancing a catheter through a loop or if the patient complains of significant pain, the operator may consider an alternative vascular access route.

Occasionally, in the presence of a radioulnar loop, the guidewire will advance through a small accessory communicating vessel between the loop and the proximal brachial artery without resistance (the so-called accessory radial artery). Under fluoroscopy the wire will appear as it follows the expected trajectory, but upon advancement of the catheter the operator will encounter unusual resistance and the patient will experience severe pain due to spasm. Once this problem is identified, the operator may opt for downsizing the catheter size, but should recognize that the accessory radial artery is often extremely small and advancement of catheters into the artery carries the risk of dissection or perforation. Instead, it is recommended that the operator negotiates the radioulnar loop in the forearm, or go to the other radial artery in order to complete the procedure.

A true high origin of the radial artery in the upper segment of the brachial artery may present additional challenges to the operator. In this case, diagnostic catheterization can be performed without much difficulty and minimal discomfort to the patient. However, when ad hoc PCI is planned, unusual resistance may be felt by the operator when the leading edge of the guiding catheter encounters the angulated origin of the anomalous radial artery. Forceful advancement of the catheter will likely result in dissection, perforation, or avulsion. Faced with this situation, several options are available. One strategy is to maintain the guidewire in place, advance a long 125 cm 5F multipurpose or JR4 catheter through the guiding catheter to create a smooth transition between the wire and the guiding catheter eliminating the leading edge, and advance the whole assembly without resistance. Another option is to advance a 300 cm 0.014 inch coronary guidewire into the ascending aorta, then load a 2.0 × 15 mm angioplasty balloon on the wire through the guide with half of the balloon protruding from the distal end of the guide. The balloon is then deployed at nominal pressure and the entire assembly can be advanced through the arm (balloon-assisted tracking). With the guiding catheter across, the dissection or small perforation is usually sealed by the end of the procedure.

Significant subclavian tortuosity can be negotiated by careful manipulation of the catheter and the use of a stiff shaft hydrophilic-coated guidewire. Having the patient take a deep breath can also straighten the vessel. The tortuous segment usually straightens as the stiff part of the wire passes through. Maintaining the wire in the catheter while attempting to cannulate the coronaries can facilitate catheter manipulation and cannulation. The guidewire can be removed once the catheter is in stable position. It is emphasized that all catheter and wire manipulations to negotiate difficult anatomy must be performed under fluoroscopic guidance. The inexperienced operator may feel more comfortable using left TRA during the steep portion of the learning curve because the left subclavian artery is less tortuous with less areas of resistance compared with the right subclavian artery.

Forearm bleeding and hematoma formation should be suspected in the presence of significant pain and swelling.
during or after the procedure. Awareness and early detection in the catheterization laboratory or the holding area is important to prevent compartment syndrome, one of the most feared complications. Circumferential compression to the forearm should be applied as soon as the diagnosis is suspected. This is usually accomplished by wrapping the forearm with an elastic bandage or a blood pressure cuff inflated up to 15 mmHg below the systolic blood pressure, until the coagulation parameters return to normal values, usually after 1 or 2 hours (Figure 7.16). A pulse oximeter should be placed in the ipsilateral thumb to monitor for hand ischemia. In cases of large perforations, vascular ultrasound is recommended to rule out the presence of a pseudoaneurysm in the forearm. In extreme cases, compartment syndrome can develop with need for surgical fasciotomy of the forearm.42

CATHER SELECTION

Judkins catheters provide the easiest way to start the transradial learning curve and train fellows. For the left coronary it is recommended to downsize the curve of the JL catheter from 4.0 to 3.5 and for the right coronary to use either a JR4 or JR5. All catheter exchanges for TRA procedures should be performed over exchange length (260 cm) guidewires, especially in patients with tortuous radial or subclavian anatomy. More experienced operators may choose a single-catheter technique to selectively engage both coronary arteries with a dedicated catheter shape, thus eliminating an exchange step and decreasing procedure and fluoroscopy time. Shapes for single-catheter approach include the multipurpose, Kimney, MAC, Tiger, Sarah, and Jacky catheters, among others.43 In severe aortic stenosis cases, the Amplatz Right (AR-1) catheter provides the best central positioning in the root of the aorta to cross the aortic valve with the wire. Regardless of catheter selection, manipulation for diagnostic or interventional TRA cases should always be performed with small, finger-based, clockwise and counterclockwise torquing movements and active catheter holding due to the multiple friction points in the subclavian artery and the aorta.

For patients with prior CABG, the left radial approach is preferred because it allows easy cannulation of the LIMA, usually with an IMA or a VB-1 catheter. Of note, the time of LIMA cannulation is much faster using TRA compared to transfemoral access. The technique is to advance the catheter proximal to the LIMA take-off, then slowly pull back with clockwise torque. In case of bilateral mammary grafts, the left TRA approach can be used with crossover to the left subclavian (Figure 7.17). For saphenous vein grafts, the left TRA approach is more straightforward than the right TRA approach. The multipurpose or JR4 catheters can be used to cannulate right-sided grafts. Amplatz left catheters are well suited for grafts arising from the anterior or left walls of the aorta.44

TRANSRADIAL PERCUTANEOUS CORONARY INTERVENTION

For coronary interventions, the 3.5 extra-backup curves (EBU, XR, Voda) provide adequate support. Studies examining the physics of catheter engagement and positioning in the ascending aorta indicate that the Ikari catheter provides better and stabler support for PCI than Judkins catheters.45

Figure 7.16 Prevention and treatment of compartment syndrome after forearm hematoma formation. After a vascular perforation in the forearm with early hematoma formation, the forearm can be wrapped with elastic bandage to prevent compartment syndrome. Once compartment syndrome develops, it is treated with fasciotomy.
An argument sometimes used against TRA PCI is the lack of catheter support and inability to perform complex procedures involving bifurcation stenting or large rotational atherectomy burrs. Lack of backup support can be easily overcome by using a guide catheter extension such as a Guideliner® (Vascular Solutions Inc., Minneapolis, Minnesota, United States), a 5F soft-tipped 20 cm flexible catheter that is telescoped through a 6F guiding catheter to deeply intubate the target vessel. This device does not add complexity to the intervention and provides extraordinary backup support for complex interventions.46 Regarding the need for large bore catheters, it is important to keep in mind that most interventions nowadays can be performed through 6F guiding catheters, including complex bifurcations and calcified lesions requiring rotational atherectomy (maximum burr size ≈ 1.75 mm). However, in the minority of interventions that require simultaneous introduction of two stent delivery systems or rotational atherectomy burrs of 2.0 mm or larger, a 7F catheter can be introduced directly through the radial artery without an introducer sheath. This is possible because the outer diameter of a 7F guiding catheter is 2.31 mm, smaller than the outer diameter of a conventional 6F sheath (2.52 mm) (Figure 7.18). The sheathless technique can be performed using standard guiding catheters or specifically designed catheters with hydrophilic coating and a long central dilator that extends beyond the distal tip of the catheter and tapers down to the size of a 0.035 inch guidewire that allows foratraumatic and smooth insertion of the system through the skin.47-50 To apply this technique, radial access is obtained using best local practice with a 5F sheath, then an exchange length 0.035 inch wire is advanced to the root of the aorta. Then the sheath is removed and directly exchanged for the dedicated sheathless catheter-introducer system over the wire. Once the system reaches the aorta, the introducer and wire are removed and the target vessel cannulated with standard technique. In the United States, where sheathless systems are not available, From and colleagues have successfully performed TRA interventions using large-bore standard guiding catheters. To facilitate insertion and to avoid trauma to the skin or the radial artery by the leading edge of the guiding catheter, a “pseudo-taper” can be created with the insertion of a long (125 cm) 5F multipurpose diagnostic catheter or the dilator of a 110 cm Shuttle sheath through the 7F standard guiding catheter.47,48 Importantly, RAO is a significant limitation of using large-bore guiding catheters, even when using sheathless techniques.49

### RADIAL HEMOSTASIS—PREVENTION OF RADIAL ARTERY OCCLUSION

One important advantage of TRA is that the vascular sheath is always removed at the end of the procedure regardless of the intensity of anticoagulation or antiplatelet therapy. Multiple methods for radial hemostasis have been described. Gentle manual compression with one or two fingers at the arteriotomy site is an effective method. Alternatively, a rolled piece of gauze can be placed longitudinally at the arteriotomy
site and wrapped with an elastic bandage or a hemoband around the wrist to maintain prolonged hemostatic pressure. The disadvantage of these methods is the complete interruption of arterial flow because of the inability to gauge the hemostatic pressure. It has been demonstrated that the longer the occlusive pressure the higher the rates of RAO. In contrast, balloon-based hemostatic devices that apply selective pressure to the radial artery, such as the TR Band (Terumo Medical, Somerset, NJ) allow fine adjustments of the hemostatic pressure and direct visualization of the arteriotomy site through the transparent balloon material. In addition, elastic bandages and hemobands interrupt venous return resulting in venous congestion of the hand. After a few minutes, the hand becomes swollen and bluish, usually alarming the patient and staff. Applying a pulse oximeter to the ipsilateral thumb provides reassurance by demonstrating intact arterial circulation.

RAO occurs in approximately 5% to 10% of transradial procedures, most likely due to vessel injury and thrombosis, and usually manifests as asymptomatic loss of radial pulse due to the extensive collateral circulation in the hand from the ulnar and interosseus arteries that prevent ischemia. However, hand ischemia after TRA procedures can occur and has been described in a handful of cases. In most of these, RAO was successfully treated with antegrade angioplasty. In one unfortunate case, RAO resulted in amputation of the index finger. In other series, RAO has been associated with forearm and access site pain without hand ischemia. Empiric short courses of low-molecular weight heparin led to late recanalization. Lack of anticoagulation during the procedure, larger diameter sheaths, multiple procedures through the same radial artery, and prolonged occlusive compression for hemostasis increase the risk of RAO. However, approximately 25% to 50% of RAO cases recanalize spontaneously at 30 days.

RAO can be prevented by using full anticoagulation during the procedure, usually with 50 to 70 IU/Kg up to a maximum of 5,000 IU of unfractionated heparin, and by applying minimum pressure for less than 2 hours during hemostasis. The “patent” nonocclusive hemostasis technique described by Pancholy to minimize the occurrence of RAO has become increasingly popular. With this technique, a balloon-based device is positioned around the wrist with the sheath in place and a pulse oximeter is attached to the ipsilateral thumb. Then, while the sheath is being removed, the balloon is fully inflated with 15 to 18 cc of air to completely occlude the radial artery. Subsequently, the device is slowly deflated while occlusive manual pressure is applied to the ulnar artery located at the Guyon canal, lateral to the pisiform bone. Patent hemostasis is achieved when oximetry becomes positive and a plethysmographic waveform can be visualized. This technique assures the presence of antegrade flow in the radial artery during hemostasis. Two hours later, 5 cc of air can be released every 15 minutes until the device is completely deflated and then removed. Using this technique, late occlusion rates can be reduced to approximately less than 5%. As part of TRA best practices, radial artery patency should be confirmed with a reverse modified Allen’s test in all patients after hemostatic device removal and before patient discharge. In case of early RAO, occurring on the same day of the procedure and/or before discharge, Bernard and colleagues demonstrated that applying 1 hour of ulnar artery occlusive compression with a balloon-based hemostatic device can increase peak velocity flow into the radial artery with reestablishment of forward flow. In a study including 465 patients undergoing TRA catheterization, the rates of RAO were reduced from 5.9% to 2.9% in patients anticoagulated with 2,000 IU of unfractionated heparin and from 4.1% to 0.8% in patients anticoagulated with 5,000 IU of unfractionated heparin after applying ulnar compression. Hence, with intense procedural anticoagulation, meticulous patent hemostasis, and careful vigilance for early RAO managed with ulnar compression, RAO incidence can be reduced to less than 1%. (Figure 7.19). Even though most RAO
cases are asymptomatic, institutional best practices should be implemented to prevent this complication mainly because it limits the possibilities for future transradial procedures, especially in patients with difficult arterial access, and the remote possibility of hand ischemia. Unfortunately, in current practice, radial patency before discharge is confirmed in less than 50% of cases and about a third of transradial operators are unaware of the RAO rates in their own practices.38 Table 7.1 summarizes current strategies for RAO prevention.

TRANSRADIAL ACCESS AND RADIATION EXPOSURE

Even though procedural times tend to be similar between transradial and transfemoral procedures, most randomized trials have consistently shown longer fluoroscopy time (by approximately 1 to 2 minutes), and modestly increased radiation exposure to patients and operators for transradial diagnostic and interventional procedures. However, most studies did not correct for improved procedural dexterity and the shorter fluoroscopy times that may be realized with greater experience.52 A large observational study including 5,954 cases adjusting for patient factors (obesity and gender), technical difficulty (presence of peripheral vascular disease or bypass grafts), and operator experience demonstrated that radial access was an independent determinant of patient radiation exposure with an increase in fluoroscopy time from 3.82 minutes with femoral access to 5.57 minutes with radial access. However, the radiation dose was still below the threshold for deterministic effects with either approach in this study.53

Concerns have been raised about increased operator exposure with left TRA due to the position of the operator leaning forward over the patient and the radiation source located underneath the table to reach the left upper extremity. However, in the TALENT trial that randomized procedures to

| Table 7.1 Strategies Associated with a Reduced Risk for Radial Artery Occlusion |
|-----------------|-----------------|-----------------|-----------------|
| **Clearly Reduce Risk** | **Likely Reduce Risk** | **Limited Effect** |
| Full anticoagulation | Enoxaparin | Sheath length |
| Patent hemostasis | Hydrophilic sheaths | Sheathless guide catheters |
| Smaller sheath diameter (5F) | Routine use of spasmolytic drugs | |
| Limiting the number of times the same radial artery is accessed | Limited duration of arterial compression | |
the right or the left radial approach, the radiation exposure to the thyroid, trunk, and shoulder, were similar with either approach. Of note, there was increased radiation exposure to the wrist of the operator with right compared to left TRA.64

In summary, the data consistently show slightly increased fluoroscopy times and radiation doses with radial compared with femoral access, but overall exposure remains well below recommended thresholds. Diagnostic cases may demand higher fluoroscopy times due to potential challenges in navigating the upper extremity vasculature and in finding the right catheter for selective cannulation of the coronary arteries. However, once a guiding catheter is well positioned in the coronary ostium, an interventional procedure can proceed as if performed via transfemoral access.65 Radiation exposure to the operator can be further reduced with the use of a movable floor shield, a longer connecting tube between the manifold and the catheter, and by choosing left radial access in older patients and when procedures are performed by less experienced operators.28

**BRACHIAL VENOUS ACCESS FOR RIGHT HEART CATHETERIZATION**

One of the arguments used against TRA catheterization is the need for concomitant RHC. Interventional cardiologists are used to performing percutaneous RHC through the femoral vein, and therefore feel that if the groin is already accessed, it just seems easier to perform left heart catheterization through the femoral artery. There may be some safety concerns with this approach in anticoagulated patients with high thromboembolic risk, such as those with prosthetic heart valves, hypercoagulable state, or atrial fibrillation. Bridging from oral to parenteral anticoagulants is cumbersome and associated with increased risks, costs, and longer length of hospital stay. Similar concerns apply to cirrhotic patients with impaired coagulation who are usually catheterized in anticipation of liver transplant.

RHC through the upper extremity is a simple procedure and can be easily performed concomitantly with TRA left heart catheterization through one of the large veins located in the antecubital fossa. The operator needs to keep in mind that there is significant anatomic variability in the upper extremity venous system with multiple collaterals and redundant passages. In comparison with arteries, veins are distensible and spasm is not a problem.

Venous access with an 18G catheter can be obtained by a nurse in the holding area in anticipation of the procedure. In the catheterization laboratory, the IV catheter is exchanged for a 5F sheath using a short 0.021 inch wire. Then, a 5F 120 cm long balloon-tipped catheter is advanced into the superior vena cava with or without the use of a 0.025 inch guidewire. Once the tip of the catheter is located in the chest, the balloon can be inflated and the catheter is flow-directed into the pulmonary artery.19,66 Passage of the catheter is usually straightforward and can be performed without fluoroscopy by observing the hemodynamic waveforms. In case of venous anatomical variation or tortuosity, a 0.014 inch coronary guidewire can be used to facilitate catheter navigation. A comparison of right and left cardiac catheterizations performed through the femoral artery/vein versus radial artery/brachial vein showed that the latter vascular access approach was associated with significantly shorter procedural and fluoroscopy times with lower complication rates with the upper extremity approach.57 In a case series of 81 cirrhotic patients with high INR values, the median fluoroscopy time was 8.3 minutes and the volume of contrast used was 90 mL.68

If a peripheral vein cannot be cannulated before the procedure, the brachial vein can be punctured with a 2 inch long 18G stainless steel needle using ultrasound guidance in the catheterization laboratory (Figure 7.20). A tourniquet has to be placed in the upper arm to facilitate visualization of

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**Figure 7.20** Ultrasound-guided access and setup for brachial venous transradial catheterization.
the vein with ultrasound. Usually two brachial veins can be identified in close proximity to the brachial artery. The vein is usually elliptical and easily compressible in contrast to the artery, which is round and pulsatile.

TRANSRADIAL ACCESS AND OUTCOMES

Over the past two decades, the treatment of coronary disease has evolved significantly and PCI has become an integral management component along with modern pharmacological therapies. In the appropriate setting, PCI is associated with a reduction in morbidity and mortality, in particular in higher-risk patients with acute coronary syndromes. Advances in technology and antithrombotic therapies have allowed the application of PCI to a wide range of patients across the spectrum of risk, with high procedural success and minimal ischemic complications. Over the past decade, it has been recognized that bleeding after PCI has a significant unfavorable effect on short- and long-term outcomes. As a consequence, the management focus has shifted from the prevention of ischemic complications to the prevention of bleeding. Access site bleeding is an important source of bleeding after diagnostic and interventional catheterization. A number of clinical trials of relatively modest sample size have consistently demonstrated significantly decreased bleeding risk and vascular complication rates with TRA in comparison with transfemoral access. An early systematic overview of 12 randomized trials (n = 3,224) demonstrated a significant reduction in vascular access complications with the radial approach (odds ratio [OR] 0.20; 95% confidence interval [CI] 0.09 to 0.42), yet significantly higher procedural failure compared with femoral access (OR 3.30; 95% CI 1.63 to 6.71). However, with advancements in vascular access equipment and catheter technologies, more contemporary trials have shown significantly decreased failure rates. A large Canadian observational registry of PCI for broad indications suggested a significant reduction in transfusion by approximately 40% with TRA associated with a decrease in mortality at 30 days (adjusted OR 0.71, 95% CI 0.61 to 0.82) and 1 year (adjusted OR 0.83, 95% CI 0.71 to 0.98). More recently, the international multicenter Radial Versus femoral access for coronary intervention (RIVAL) trial randomized a large patient population with acute coronary syndromes undergoing PCI to radial (n = 3,507) versus femoral access (n = 3,514). There were no significant differences in the primary outcome, a composite of death, myocardial infarction, stroke, or non-CABG bleeding at 30 days with radial compared with femoral access (3.7% versus 4.0%, P = 0.50). Of note, all procedures were performed by high-volume operators at high-volume centers with very low rates of major bleeding complication of 0.5% in both arms, significantly lower than the bleeding rates reported in similar populations recruited in observational studies. Major vascular complications were significantly lower with transradial versus transfemoral access (1.4% versus 3.7%, P < 0.0001). Interestingly, subgroup analyses showed a statistical interaction for patients treated at the highest radial-per-operator volume centers (>146 PCI/year/operator) and ST-elevation myocardial infarction (STEMI) patients, favoring transradial over transfemoral access in these subgroups.

TRA has been also been tested in primary PCI for STEMI in a number of modestly sized studies that showed a similar mortality benefit as the RIVAL trial in this population. These results were confirmed in the Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome (RIFLE STEACS) trial. A total of 1,001 patients with STEMI undergoing primary or rescue PCI were randomized to radial versus femoral access at 4 high-volume centers. Inclusion criteria for RIFLE STEACS were broad. Approximately 10% of the patients were in acute pulmonary edema or cardiogenic shock, and 8% required intraaortic balloon pumps. Door-to-balloon time was 7 minutes longer with TRA but the difference was not statistically significant (53 versus 60 minutes, P = 0.175), and 5F catheters were used more frequently with TRA than transfemoral access (18.2% versus 9.2%, P < 0.001). Access failure rates were 6% in the radial arm and 1% in the femoral arm. Final TIMI flow grade 2 or 3 was achieved in more than 95% with both vascular access strategies. The study primary endpoint, net adverse clinical events, a composite of death, myocardial infarction, stroke, target lesion revascularization and non-CABG bleeding, occurred in 13.6% of patients in the radial arm and 21% in the femoral arm (P = 0.003). Unlike other studies comparing radial versus femoral access, where the difference in composite endpoints is usually driven by the reduction of access site bleeding afforded by TRA, in the RIFLE STEACS trial, ischemic and bleeding endpoints were equally reduced. Major adverse cardiac and cerebrovascular events were 7.2% and 11.4%, with radial and femoral access, respectively (P = 0.03), while non-CABG bleeding rates were 7.8% and 12.2% respectively (P = 0.03). Moreover, there was a cardiac mortality difference favoring radial access (5.2% versus 9.2%, P = 0.02), which was attributed to the significant reduction in access-related bleeding. Of note, in this trial, approximately 50% of bleeding events were not access related, similar to the bleeding patterns described in other studies including patients with acute coronary syndromes, who are usually exposed for longer time to potent antithrombotic agents.

In summary, outcome data suggests that TRA affords similar, if not better, PCI outcomes as transfemoral access. The benefit appears to concentrate in sicker patients, such as those with STEMI, and patient treated by operators at high-volume centers. It is expected that these results will translate into practice and more patients will be treated for STEMI using radial artery access. The potential concerns related to delays in obtaining radial access and cannulating the coronary arteries appear to be offset by the decreased incidence of major bleeding, vascular complications, and overall adverse effects. However, it is important to keep in mind that TRA for primary PCI in unstable patients should be performed by...
operators experienced in this approach, and that the femoral artery access site should be prepared in case of need for left ventricular assist devices.

**ECONOMIC ASPECTS—SAME-DAY DISCHARGE PERCUTANEOUS CORONARY INTERVENTIONS**

It has been estimated that a severe bleeding event has an incremental cost of $4,000 to $6,000, a unit of blood transfusion an approximate cost of $2,000, and a vascular complication a cost of $6,400, adding 3 additional days of hospital stay.76-80 By decreasing access-related bleeding and vascular injury, TRA can save costs for the health care system. Dedicated cost analyses comparing vascular access sites have consistently shown a significant reduction in hospital costs with TRA. In an early randomized study including diagnostic catheterization procedures, TRA was associated with a cost saving of approximately $290 per case, driven by lower nursing utilization and decreased pharmacy costs.4 The savings observed with diagnostic catheterization are even larger after PCI due to the higher risk of bleeding associated with potent antithrombotic therapies. In a small randomized study of 142 patients undergoing PCI for acute coronary syndromes, postprocedure length of stay was reduced by approximately 1.5 days and total hospital charges decreased from $23,389 to $20,476 with TRA.81 A recent metaanalysis including 14 studies examined the cost-benefit of TRA from the hospital standpoint. The main question was whether the savings associated with decreased procedural complications and shorter hemostasis times can offset the potentially higher cost of longer procedural times and higher access crossover rates observed with TRA. The overall result demonstrated that TRA resulted in an estimated cost saving of $275 per patient, which was mainly driven by a reduction in complication costs. According to this analysis, the risks of transfemoral catheterization would have to be reduced by 60%, in order to be cost-equivalent to TRA.82

In addition to direct cost savings, TRA can result in significant downstream savings by optimizing the flow and reducing the workload and staffing needs of the catheterization laboratory. Staffing requirements following TRA procedures can be reduced due to fewer access-related complications, immediate sheath removal, and faster and more independent patient mobilization.83 An added value of short patient recovery associated with TRA is the possibility of safe same-day discharge after elective PCI. Interventional procedures have become safer and the hazard of complication decreases abruptly within the first 4 to 6 hours after the procedure.84 Same-day discharge after transfemoral elective PCI has been studied in a Dutch study including 800 patients randomized to overnight stay versus same-day discharge after 4 hours of observation. Strict criteria established in the protocol to identify patients requiring extended observation included angiographic complications, clinical instability, and problems with hemostasis. Of patients randomized to same-day discharge, 18% required extended observation. More importantly, after hospital discharge no events occurred within 24 hours in the same-day discharge group. Only one patient had to be readmitted for a femoral access-related complication (pseudoaneurysm). The same-day discharge strategy resulted in significant cost savings.85 A Canadian study randomized 1,005 patients after TRA PCI to same-day discharge versus overnight stay. All patients were randomized after the procedure and received abciximab either as bolus alone or as bolus plus infusion. Same-day discharge patients were observed for 4 to 6 hours prior to discharge. All major bleeding events were unrelated to access and occurred in five (<0.5%) patients. Of patients assigned to same-day discharge, 88% were successfully discharged as planned and did not have higher repeat 30-day hospitalization rates compared to patients who stayed overnight (5% with same-day discharge versus 3% with overnight stay).86 A very detailed economic analysis of this study showed that postprocedural hospital care was significantly less costly for the same-day discharge group ($459) than the overnight stay group ($1,618). There were no differences in follow-up costs, physician services, or medications. The overall cost difference was $1,141 per patient and driven by the extra night stay post-PCI. This could result in over $1 million in savings per 1,000 outpatients.87 Analysis of Medicare beneficiaries including more than 100,000 stable patients demonstrated that across the United States, same-day discharge occurs very infrequently in only 1.25% of elective PCI cases. Of note, a higher proportion of patients discharged on the same day underwent TRA PCI or had vascular closure devices (3.14% versus 1.56%, P < 0.001).

In summary, implementation of a TRA catheterization offers significant cost-saving opportunities for individual institutions and the health care system as a whole.

**CONCLUSION**

TRA has become the standard approach for cardiac catheterization and PCI in many parts of the world, and is slowly gaining ground in the United States. TRA implementation requires a learning curve of approximately 50 to 100 cases and is associated with slightly increased fluoroscopy time and access crossover rates. However, once mastered and implemented as an institutional program, TRA is associated with less access-related bleeding, less vascular injury, improved patient comfort, and significant cost savings for the health care system.

Staff training and development of institutional policies and best practices are crucial for the implementation of a successful TRA program. A guidance document and multiple training opportunities are now available for established U.S. operators through efforts of professional societies.
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Although once the dominant technical approach to cardiac catheterization and angiography, the brachial cutdown (or Sones) approach has decreased progressively in popularity over the past 40 years as the percutaneous femoral and, more recently, radial approaches described in Chapters 6 and 7 have risen to dominance. The brachial cutdown approach is now used in only a few (<1%) cardiac catheterization procedures, and the skills required for brachial arterial and venous cutdown and vascular repair are rapidly vanishing among the invasive cardiology community. Because this approach may still be of value in occasional patients, this chapter summarizes the technique as a guide for those learning to perform it, or as a refresher for those previously trained in the brachial approach who need to use this technique in a particular patient. The brachial cutdown approach, however, should not be used by an inexperienced operator unless backed up by a vascular surgeon or a cardiologist with expertise in this technique.

**INDICATIONS**

The brachial approach may be indicated for patients with (1) severe peripheral vascular disease, making upper extremity vascular access preferable; (2) urgent or emergent cardiac catheterization with an increased risk for bleeding (owing to chronic oral anticoagulation or recent thrombolytic therapy); (3) a need for early ambulation or mobility (outpatient procedures, severe back pain, and so on). Many of these situations can also be addressed by percutaneous radial artery catheterization (see Chapter 7), but the brachial cutdown approach can provide the following additional advantages: (1) the ability to obtain upper extremity arterial access in patients without a patent radial artery or with a contraindication to radial artery access; (2) reliable venous access to perform concomitant right heart catheterization in patients with suspected or known valvular heart disease, congestive heart failure, intracardiac shunts, and so on; (3) assured arterial access for 7F or greater catheter sizes; and (4) access to large veins to allow for foreign body retrieval (from the superior and inferior vena cava, right ventricle, or pulmonary artery).

Relative contraindications to brachial artery cutdown are few. They include absence of a brachial pulse, presence of an arteriovenous fistula, overlying soft tissue infection, severe ipsilateral axillary or subclavian vascular disease, and inability to extend the arm at the elbow or supinate the hand.

**PREPROCEDURE EVALUATION**

Proper preprocedure patient evaluation is critical for a successful brachial catheterization. Inspection and identification of the antecubital folds, biceps tendon, and medial and lateral epicondyles of the humerus takes only a few seconds but is essential. This inspection should be performed with the patient’s arm extended and the hand supinated to assess for the ability to position the arm properly for the procedure. The general location for arterial cutdown will be approximated 2 to 3 cm above the antecubital skin folds, slightly superior to the level of the humeral epicondyles, and medial to the...
biceps tendon. A cutdown below this level is not recommended because the artery subsequently courses under the biceps tendons and bifurcates. A cutdown performed above this level is feasible, but may be awkward owing to the medial course of the artery.

The brachial pulses should be carefully palpated bilaterally. A weak unilateral pulse usually indicates proximal vascular occlusive disease. Auscultation should be performed over the brachial, axillary, and subclavian areas to assess for bruits. A diminished pulse and/or bruits should lead the operator to anticipate proximal vascular occlusive disease and plan accordingly with consideration for a contralateral procedure, femoral access, or the use of soft and steerable guidewires. If a prior cutdown has been performed, the brachial pulse should be assessed 1 to 2 cm from the scar (to avoid the need to dissect through scar tissue with potential adhesions to the previous arteriotomy site), with the new cutdown preferably performed proximally to the previous one.

INCISION, ISOLATION OF VESSELS, AND CATHETER INSERTION

With the direct brachial approach, a single cutdown is made in the right antecubital fossa, through which both the brachial artery and vein can be isolated and used to perform left and right heart catheterization, respectively. With the arm fully extended flat on the armboard and the hand supinated, the brachial artery (Figure 8.1) is identified by palpation and local anesthesia is induced in the overlying soft tissues using 1% to 2% lidocaine. This is first injected intradermally through a short 25 or 27 gauge needle to raise a bleb and then deeper using a long (1.5 inch) 22 gauge needle to infiltrate the subcutaneous, deep fascial, and periosteal tissues. Liberal amounts of 2% lidocaine are injected, 5 to 15 mL initially. During the course of the procedure, an additional four 4 mL aliquots of lidocaine may be applied topically within the incision. If anesthesia is achieved properly, the catheter insertion site ought to be virtually painless throughout the procedure.

Prior to starting the procedure, the proper instruments should be on hand, including the following: a no. 15 blade with handle, a no. 11 blade without a handle (or with a short handle) for improved control during arteriotomy, two or three curved hemostats, two straight hemostats, one self-retaining retractor, two soft tissue retractors, one small scissors, one needle holder, one toothless forceps, one small forceps, two segments of umbilical tape or vascular loops, 6.0 Prolene suture on a 3/8 inch needle, 3–0 absorbable suture with a curved needle, silk or chromic ties, and a vein lifter. These items are sufficient for almost all cases (Figure 8.2).

A transverse incision is made with a no. 15 surgical blade just proximal to (i.e., approximately 2 cm above) the flexor crease. If right and left heart catheterization is contemplated, the incision is wide and made over the palpable brachial artery; if a right heart study alone is planned, the incision is narrow and made directly over a previously identified medial vein. Even large veins of the lateral antecubital fossae usually drain into the cephalic system, through which it may be difficult to navigate the catheter into the right atrium, whereas the medial veins drain into either the basilic or brachial venous systems (which join the axillary vein by direct continuation and thus provide the easiest routes to the superior vena cava (SVC) and right atrium (Figure 8.3).

The operator performs blunt dissection through the subcutaneous fat with a curved hemostat, simultaneously

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**Figure 8.1** Anatomy of antecubital fossa illustrating course of the brachial artery. The artery is best sought at or slightly above the antecubital skin crease, medial to the bicipital aponeurosis. Care must be taken not to disturb the median nerve, which usually lies medial to the brachial artery. (From Clemente, C. Gray's Anatomy of the Human Body, 30th American ed. Philadelphia, PA: Lea & Febiger; 1985.)
performing lateral retraction, while the assistant retracts medially. As the handheld retractors are applied to the lateral ends of the incision, the self-retaining retractor is applied superoinferiorly. This provides optimal exposure, particularly when substantial amounts of adipose tissue are present. After the fascia overlying the brachial artery is exposed, the artery is palpated again and blunt dissection through the fascia is then performed immediately overlying or lateral to the artery. This further decreases the chance for median nerve injury. When the artery is partially exposed, dissection is continued to separate the artery from adjacent veins and other structures.

At this point, the artery is easily recognized by its pulsation and characteristic silvery white color. Veins, in contrast, are nonpulsatile, much darker in color, and usually of smaller caliber. The median nerve is yellowish with a slightly corrugated surface, and should not be further manipulated. A few patients have an accessory brachial artery, which is smaller and usually not suitable for catheterization. This vessel has a more superficial course and generally is not surrounded by veins, but deeper palpation will often reveal the location of the true brachial artery. The tissues are separated by blunt dissection with a curved Kelly forceps, and an appropriate vein is brought to the surface, separated from adjacent nerves and fascia, and tagged proximally and distally with a loop of 3–0 or 4–0 silk suture material. The brachial artery is similarly brought to the surface with a curved Kelly forceps, isolated from adjacent nerves, veins, and fascia, and tagged proximally and distally with moistened umbilical tape or silicone-elastomer surgical tape (Retract-o-tape, Med-Pro Division, Quest Medical, Dallas, TX; Figure 8.4).

After isolating the brachial artery and basilic or brachial vein, an appropriate right heart catheter is selected and flushed. A 1 to 2 mm longitudinal incision is made in the vein with a no. 11 blade, and the catheter is introduced with the aid of either curved tissue forceps or a small plastic catheter introducer. Alternatively, the vein may be placed over a bridge formed by straight forceps to enable better control and to diminish oozing during passage of the catheter. Once the catheter has been introduced and passed a short distance, blood is aspirated, and the catheter is again flushed with heparinized solution. The catheter may then be connected either directly or by means of flexible plastic tubing to the side port of a manifold with an appropriate pressure transducer (see Chapter 10).
After passage of the right heart catheter (discussed below), the brachial artery is cleaned and positioned by applying gentle pressure on the hemostats or umbilical tapes using thumb and index finger to stretch the artery longitudinally (Figure 8.5). This maneuver is critical because it allows for arterial positioning, stabilization, and (with adequate tension) excellent hemostatic control. Most operators incise it transversely by making a small (2 mm) nick in its anterior surface with a no. 11 surgical blade. Others favor a longitudinal arteriotomy with the no. 11 surgical blade held at a 30\(^\circ\) angle to the artery and the sharp edge facing upward (toward the ceiling) to minimize risk of injury to the posterior wall. The longitudinal direction requires a more cautious repair to avoid narrowing the lumen.

An appropriately selected left heart catheter (see the following section) is flushed. Tapered tip catheters, such as the Sones or multipurpose ones, can be inserted without a sheath (Figure 8.6), but a sheath may be preferable when multiple catheter exchanges are planned or when catheters with a nontapered tip, such as guiding catheters for percutaneous coronary interventions, are used. To minimize the risk for arterial dissection during insertion of a relatively rigid arterial sheath, it should be introduced over a wire and carefully aspirated and flushed after insertion.

Many laboratories administer heparin solution (e.g., 50 units/kg) to help prevent thromboembolic events to the hand. This can be given into the distal brachial artery, central aorta, or intravenously.

**CATHETER SELECTION**

### Right Heart Catheters

When right heart catheterization is being performed only for measurement of right atrial, right ventricular, pulmonary artery, and pulmonary capillary wedge pressures, any
of the end-hole catheters is adequate. Classic woven Dacron right heart catheters (e.g., Goodale-Lubin and Cournand, Figure 8.7) have now been replaced by flow-directed balloon flotation catheters. Passage of the right heart catheter may occasionally produce transient right bundle branch block.

Should this occur in a patient with preexisting left bundle branch block, bilateral or complete heart block will develop and may require emergency ventricular pacing. If right-sided angiography is planned, a closed-end catheter with multiple side-holes can be used (see Chapter 17).

**Left Heart Catheters**

When the direct brachial approach is used, potential catheters include both open-end and closed-end multiple side-hole designs (used for left ventricular pressure measurement and angiography). The classic Sones B or a multipurpose catheter can also be used for most coronary and left ventriculographic purposes, although they tend to recoil at injection rates greater than 8 mL/second and have to be positioned carefully within the left ventricle to avoid myocardial staining. Thus, from a safety perspective, it is preferable to use pigtail catheters for left ventriculography. In addition, pigtail catheters (6F or 7F) should be used whenever contrast flows greater than 10 mL/second are needed.

Coronary angiography can usually be completed with the Sones catheter. Alternatively, Castillo or Amplatz 1, 2, or 3 type curves are available (Cordis Corp, Miami, FL) and are very useful for angiography of coronary artery bypass grafts, coronary engagement in patients with large aortic roots, and in situations where more forceful torque must be applied (see below). The Sones A type curve is also useful for patients with a high take-off of the left coronary artery. Multipurpose type I and type II catheters have applications generally similar to the Sones. From the right brachial approach, the femoral mammary catheter is adequate for angiography of the right internal mammary artery, whereas the brachial mammary catheter or a multistep approach (1) gaining access to the left subclavian artery with a Castillo or Amplatz catheter; 2) advancing an exchange wire into the axillary artery; and 3) exchanging for the femoral mammary catheter) is required for angiography of the left internal mammary (see below).
ADVANCING THE RIGHT HEART CATHETER

Both right and left heart catheters should be advanced as soon as possible after introduction into the vascular system, because letting them sit in the bloodstream at body temperature may result in loss of catheter stiffness and also diminishes catheter control. The right heart catheter is advanced under fluoroscopic control to the SVC. If a balloon-tip catheter is used, advancement is generally straightforward. However, if the cephalic vein is entered rather than the brachial vein there may be resistance due to the angle of entry at the level of the subclavian vein. If there is difficulty entering the subclavian vein/SVC, it is sometimes helpful to try the following maneuvers: have the patient take a deep breath; raise the right arm and shoulder toward the head; ask the patient to shrug his or her right shoulder; turn the patient's head to the extreme left; remove the patient's pillow. On occasion, a guidewire may be helpful in passing from the subclavian vein into the SVC. Arterial or venous spasm may develop and inhibit catheter movement. It may resolve if the catheter is withdrawn by a distance of 10 to 20 cm, and the same cocktail of intravenous nitroglycerine and verapamil or other calcium channel blockers may be administered as used in radial artery catheterization. Intravenous papaverine (30 to 60 mg) may also be efficacious (note, it should never be given intraarterially because of intense local pain). Persisting in attempts to advance or manipulate the catheter in the presence of spasm produces pain, vagal reactions, and hypotension, and may convert a minor problem into a large one including dissection of the artery.

When the catheter tip has been advanced to the SVC, the operator should draw a blood sample for oximetry. If the SVC blood oxygen saturation is substantially lower than the pulmonary artery oxygen saturation, a full oximetry run should be done (Chapter 12). If a nonballoon catheter is used, a J loop technique should be initially tried to pass from the right atrium to right ventricle and pulmonary artery. The catheter is advanced so that its tip catches on the lateral right atrial wall and the catheter looks like the letter J on fluoroscopy (Figure 8.8). Next, the catheter is rotated counterclockwise so that the tip of the J sweeps the anterior right atrial wall (thus avoiding the coronary sinus, whose ostium lies posterior to the tricuspid valve) and jumps across the tricuspid valve into the right ventricle. Because the catheter usually still retains its J curve, its tip will now be pointing toward the right ventricular outflow tract and can easily be advanced into the pulmonary artery. Right ventricular pressure may be recorded during the transit or subsequently during the catheter pullback. It should never, however, be advanced against resistance, since perforation of the right ventricular outflow tract can occur.

The catheter is then advanced to the “wedge” position by having the patient take a deep breath and hold it while the catheter is advanced until its tip will go no farther and ceases to pulsate with the heart. Having the patient cough at this time will frequently advance the catheter tip into a true wedge position. The pressure waveform is examined, and if it has the appearance of a true wedge pressure, it is recorded. If there is any doubt that a true wedge position has been achieved, blood is sampled from the catheter. The pressure is confirmed as a true wedge pressure only if blood that is completely (≥95%) saturated with oxygen can be aspirated gently from the catheter.1 In patients who are hypoxemic, a wedge blood oxygen saturation of 90% or more may be accepted, especially if the oxygen saturation of pulmonary artery blood is much lower (e.g., ≤70%). When mitral stenosis is not expected to be present, the wedge pressure may be confirmed simply by observing its typical waveform and its match against the simultaneously recorded left ventricular diastolic pressure. After measuring (and possibly confirming) the wedge pressure, the right heart catheter is withdrawn into the pulmonary artery. There has been substantial debate on the usefulness of pulmonary capillary wedge pressure as a measure of pulmonary venous and left atrial pressure (2-10). In general, most studies have reported excellent agreement between left atrial and mean capillary wedge pressure (2-7, 10).

If a Swan-Ganz catheter is used to obtain pulmonary capillary wedge pressure, it is often necessary to aspirate and discard the 5 to 15 mL of pulmonary artery blood that lies between the balloon and the pulmonary capillary bed before bright red pulmonary capillary blood can be sampled.

ADVANCING THE LEFT HEART CATHETER

After the right heart catheter has been advanced to the pulmonary artery or wedge position, an appropriately selected left heart catheter is inserted into the brachial artery as described previously. This catheter is then advanced into the ascending aorta just above the aortic valve. Although the Sones and multipurpose shapes can sometimes be advanced gently without a guidewire, advancement over a J-tipped guidewire is safer and it is the preferred approach. Passage may be aided by deep and held inspiration while lifting the chin and rotating the head leftward and over the left shoulder, but severe tortuosity may then impair catheter control once the aortic root has been reached.

Once the catheter is in the ascending aorta, central aortic pressure is measured and recorded. The catheter is then advanced across the aortic valve into the left ventricle by probing the valve with small to-and-fro excursions while gradually rotating the catheter through 360° so that the catheter tip moves up and down on the aortic valve over its entire plane. The soft-tipped Cordis polyurethane Sones catheter may be advanced directly (tip first) into the left ventricle, or it may be prolapsed across the aortic valve, loop first, as illustrated
Figure 8.8 Advancing the right heart catheter. In navigating from right atrium to pulmonary artery, the J loop technique should be tried first. (Top left) The catheter is advanced so that its tip catches on the lateral right atrial wall and forms the letter J. (Top right) It is then rotated counterclockwise so that the catheter tip sweeps the anterior right atrial wall (thus avoiding the coronary sinus) and jumps across the tricuspid valve into the right ventricle. (Bottom left) The catheter tip, pointing toward the right ventricular outflow tract, can be easily advanced into the pulmonary artery. (Bottom right) The patient takes a deep breath, and the catheter is advanced to the “wedge” position (see text).

In Figure 8.9. In severe aortic stenosis, the Sones catheter usually crosses tip first, but can be aided by insertion of a 0.035 inch straight guidewire (see Chapter 6).

Once in the left ventricle, the full baseline hemodynamic measurements are made, including simultaneous pulmonary capillary wedge and left ventricular pressure recording. If a right heart catheterization was not performed, a special-purpose left heart catheter developed by Dr. Earl Shirey can be used for retrograde catheterization of the left atrium from the left ventricle. It can be prolapsed loop first into the left ventricle so that its tip faces the aortic and mitral valves (Figure 8.10) rather than the left ventricular apex. Withdrawal of the redundant loop frequently guides the catheter tip into the left atrium.

After completion of hemodynamic and cardiac output measurements (Chapter 11), most cardiac catheterization procedures today proceed to left ventriculography and coronary angiography. The details of these techniques as applied to both brachial and femoral approaches are discussed in Chapters 15 and 17, but some special brachial techniques are described below.
Section II Basic Techniques

Coronary Bypass Grafts

Aortocoronary vein grafts have a high takeoff compared with coronary arteries; therefore, a longer-curve Sones or multipurpose catheter (such as a Sones A or MP 2) should be used. However, in preshaped catheters such as the Castillo or Amplatz type 1 (vein grafts to the right coronary), 2 (vein grafts to the left coronary arteries) or 3 curves (widened aortic root) are generally preferable.

Internal Mammary Arteries

The mammary arteries usually originate from the subclavian arteries with inferior takeoffs opposite to the origin of the vertebral arteries. Although the internal mammary artery is best engaged from an ipsilateral brachial approach using performed femoral catheters, it is usually possible to engage the left mammary from the right brachial approach using one of two techniques. An Amplatz catheter (generally an AL 0.75, AL 1, or AL 2) is advanced into the descending aorta distal to the origin of the left subclavian artery. The catheter is manipulated into its natural configuration and as it is slowly withdrawn using gentle rotation the left subclavian artery is engaged. An exchange length wire is passed through this catheter into the axillary artery and used to exchange the Amplatz for a femoral mammary catheter. The second technique utilizes a preshaped brachial mammary catheter that is passed into the aortic root and secondary curve is banked off the aortic valve while the tip is advanced toward the subclavian artery. This is done with the support of an 0.35 inch or 0.38 inch wire. After the tip engages the subclavian artery the catheter is advanced and rotated to engage the mammary artery.

Anomalous Coronary Takeoff

Preshaped catheters with Castillo or Amplatz curves are preferable for anomalous origins not easily reached with the Sones or multipurpose curves. Some catheter recommendations for specific situations include the following:

1. Right coronary artery with inferior takeoff or horizontal heart—AR 2, Castillo/AL 1
2. Right coronary artery with anterior takeoff—Castillo/AL 1 or 2
3. Left coronary artery with a high takeoff—Castillo/AL 3, Sones A, MP 1
4. Left circumflex coronary originating from the right coronary—Sones or MP 1 or 2 curves are optimal with the tip directed inferiorly; AR 2, Castillo/AL 1 if the Sones catheter overshoots the origin of the circumflex that is very proximal or is immediately adjacent to the right coronary ostium.
5. Right coronary artery with anomalous takeoff from the left sinus of Valsalva or left coronary artery arising from the right sinus of Valsalva—Castillo/AL 2 or 3 to “scan” the aortic wall seeking the ostium. Kimny or JL 3.5 catheters can also be effective.

### Percutaneous Coronary Interventions

A sheath should always be inserted into the brachial artery for these procedures, as guiding catheters are nontapered and difficult to insert without causing arterial trauma. The sheath can be secured to the skin with a suture or by wrapping the umbilical tape loops around the hub. This helps to stabilize the sheath during catheter manipulations. Guiding catheters must always be inserted over a wire because of their reduced flexibility and sharp edges. The 6F or 7F catheter sizes are often useful for PTCA and stenting (see Chapters 28 and 31). Because of the size of the brachial artery, 8F catheters may be used for rotational atherectomy, kissing balloons, large-profile stents, or when extra support is needed.

The following guiding catheter shapes are suggested for the brachial approach:

**Right Coronary.** The secondary curve of guiding catheters advanced from the right brachial position necessarily lies against the left wall of the aorta yielding superior backup support when compared with catheters advanced from the femoral position. Therefore, we occasionally prefer the right brachial approach in cases of severe right coronary tortuosity, calcification, and so on. The hockey stick design is a useful option; however, in patients with a small aorta, an AR 2 may be needed. When deep seating of the catheter is required, the AL 0.75, 1 or 2 curves are useful.

**Left Coronary.** Amplatz shapes AL 0.75 through AL 3 are excellent, especially when engaging a left main coronary with a superior takeoff or when approaching a left anterior descending coronary with superior angulation. Other useful curves include the JCL or Q, Voda, XB, or EBU (3.5, 3.75, 4.0) and Kimny (6F). From the left brachial approach, standard femoral guiding catheter shapes can be used.

**Bypass Grafts.** For left coronary vein grafts AL 1, 2, 3, and hockey stick shapes are effective. For right coronary vein graft intervention AL 1 multipurpose and JR 4.0 short-tip shapes are often successfully used.

### Repair of Vessels and Aftercare

After the completion of diagnostic studies, the left heart catheter is removed and the brachial arteriotomy is repaired. Repair may be done in many ways (purse-string, interrupted, continuous sutures). Prior to initiation arterial repair release, pressure on the proximal loop is released briefly to allow generous antegrade bleeding and flush out thrombi that may have formed around the catheter. The proximal bleeding is then controlled, and pressure on the distal umbilical tape is released to allow for retrograde (collateral-fed) bleeding to ensure patency of the distal artery. If there is brisk back-bleeding, no further maneuvers are indicated and arterial closure can commence. If no back-bleeding is present, the area overlying the radial and distal brachial artery should be manually “milked” or massaged in distal to proximal fashion to dislodge and remove any thromboemboli. If there is still no retrograde flow, a Sones or multipurpose catheter can be inserted distally through the arteriotomy, carefully advanced until resistance is met, and then slowly withdrawn while gentle suction is applied to its lumen with a syringe. If these maneuvers fail to restore back-bleeding, a Fogarty embolectomy procedure is then warranted. Dr. Grossman has traditionally favored routine use of a Fogarty arterial embolectomy catheter (Arterial embolectomy catheter; 3F, 40 cm, Shiley Laboratories, Irvine, CA) is used.

A common and very successful approach to arteriotomy repair calls for stabilization of the vessel by applying pressure with the umbilical tapes or placing a large forceps transversely beneath the artery. A stay suture is placed approximately 1 mm above the proximal end of the longitudinal arteriotomy, and a continuous lockstitch is created with sutures evenly spaced at 0.5 mm intervals (Figure 8.11). The lockstitch is closed with a second stay suture located 1 to 2 mm distal to the incision (Figure 8.12). Minor bleeding around the sutures can often be controlled with gentle manual pressure and/or temporary application of a small Gelfoam pad. Once the assistant has confirmed the presence of an adequate radial pulse, the skin and subcutaneous tissues are closed using absorbable suture material and the subcutaneous technique. Two or three 0.25 inch Steri-Strips are then applied in transverse fashion across the incision. A small Telfa pad coated with an antibacterial ointment is applied directly over the site and covered with a small stack of 4 × 4 gauze pads that are then wrapped in firm fashion with a 3 inch-wide Ace bandage.

Dr. Grossman has used administration of 10 to 15 mL of a concentrated solution of heparinized saline (3,000 IU of heparin in 30 mL normal saline) into the proximal and distal artery through the Sones catheter, locking this into the vessel by application of a vascular bulldog-type clamp (DeBakey peripheral vascular bulldog clamps with 45° to 60° angled jaws, V. Mueller, Chicago, IL) as far above and below the arteriotomy as possible (Figure 8.13). He then placed a stay suture at each end of the arteriotomy and closed it with a continuous or running stitch of fine nonwettable suture material such as 6–0 Tevdek (Tevdek, Deknatel Company, Queens Village, NY). The stay suture at one end of the incision is the start of the running stitch, and the stitch is completed by tying to the other stay suture. The advantage of a continuous suture is that it tightens as the artery expands after the clamps are removed.
After suturing the artery, he removed the distal bulldog clamp first and then massaged the forearm gently from the wrist toward the elbow to milk out any air within the lumen of the artery before releasing the proximal bulldog clamp. The proximal clamp was then removed, and any minor leaks were controlled by direct finger pressure while ensuring that the radial pulse could be palpated. If leaking did not stop within a few minutes of such finger pressure, an additional suture or two was required. In this procedure, if the radial pulse is not palpable and essentially of the same amplitude as before the arteriotomy, the artery may be reopened and a Fogarty catheter again passed proximally and distally. When unsuccessful, prompt consultation should be obtained with an experienced vascular surgeon who usually will be able to identify and correct the problem. After repairing the arteriotomy successfully, the vein used in the right heart catheterization may be tied off or repaired (a purse-string repair is usually adequate), followed by flushing the wound with copious quantities of fresh sterile saline solution followed by 10% povidone-iodine solution (Pharmadine, Sherwood Pharmaceutical, Mahwah, NJ). The skin is closed using a subcuticular stitch of an absorbable suture (4-0 Dexon Plus, Davis and Geck, Inc., Manati, Puerto Rico, on a cutting needle), thereby avoiding the need for suture removal. Antibiotic ointment is placed on the suture line and covered with a firm dressing (although not so firm that it diminishes the radial pulse).

During the postprocedure period, blood pressure measurements should not be performed on the arm for 24 hours. Distal pulses, sensation, motor function, and local bleeding should be assessed without unwrapping the Ace bandage. The Ace bandage is first released 2 hours following the procedure to reassess the surgical site and then rewrapped firmly but comfortably for 48 hours. The incision should be kept dry for at least 3 days, with the Steri-Strips removed in 1 week.
Figure 8.13 Dr. Grossman’s preferred method for vessel isolation and repair. A. The brachial artery and vein have been isolated. Both are tagged proximally and distally, the artery with moist umbilical or silicone-elastomer tape, the vein with 3-0 silk. The vein has been placed over a bridge formed by a straight forceps to enable better control. B. The vein has been incised with a small scissors, and the catheter is about to be inserted with the aid of a plastic catheter introducer. C. Passage of the right heart catheter. D. Incision of the brachial artery with a no. 11 surgical blade. The cutting edge of the blade is facing upward, and the point approaches the artery from the side and at an angle of 10° to 20° to the horizontal to avoid perforating the posterior wall. E. Passage of the left heart catheter. F. Preparation for arterial repair, concentrated heparinized saline solution is locked in the vessel by placing bulldog clamps as far above and below the arteriotomy as possible (see text). G. Closure of the arteriotomy by continuous or running stitch. Stay sutures are placed at each end of the arteriotomy (see text).

TROUBLESHOOTING

Loss of Radial Pulse

The most frequent causes of an absent or diminished radial pulse following a brachial procedure are the following: thrombosis at the arteriotomy site, embolization to the radial artery, dissection at the arteriotomy site, inappropriate suturing, and spasm. If arterial spasm was not a factor during catheter manipulation, it is unlikely to develop after arteriotomy repair and, therefore, should not be assumed to be responsible for a poor radial pulse. When the radial pulse is absent, the artery should be reisolated and secured with umbilical tapes and curved hemostats. The arteriotomy sutures are then carefully removed and antegrade and retrograde bleeding reassessed. If proximal and distal blood flows are normal, a problem with the initial arterial closure should be suspected (e.g., suturing through the posterior wall of the artery, creation of a significant cross-sectional narrowing of the arterial lumen, and so on). The arteriotomy should then be carefully resutured to avoid such problems.

If blood flow remains diminished from either direction, further massaging or milking of the artery is performed, as described previously, to dislodge and flush out any thrombi. The arteriotomy can be inspected proximally and distally to assess for a dissection flap by inserting a small forceps. If a dissection is evident, the true arterial lumen should be located with the small forceps and a soft-tipped catheter (Sones) carefully inserted a short distance to act as a stent to appose all layers of the arterial wall. While the catheter
is in place, two or three interrupted sutures are used to bind the layers of the arterial wall together, and the arteriotomy is then repaired. When dissection is not evident, the catheter aspiration maneuver described earlier should be performed before resorting to passage of a no. 3 Fogarty catheter. Following embolectomy, the arteriotomy is resutured, slightly extending the length and depth of the suture line in order to tack down any intimal disruptions (flaps). If the radial pulse is reestablished but diminished, this may be due to arterial spasm. Administration of oral nifedipine (10 mg) or intravenous papaverine (30 mg) is frequently beneficial, but prompt consultation with a vascular surgeon is imperative if a radial pulse is not reestablished, particularly if signs of neurovascular compromise are present.

Hand Numbness
Hand numbness may result from impaired circulation or median nerve compromise. If the brachial dressing is not overly tight and the radial pulse is palpable, the cause of numbness is unlikely to be circulatory. Severe median nerve injury during cutdown is usually apparent immediately as the patient experiences a striking and characteristic discomfort (electric shock sensation). The most common cause of later median nerve injury is compression induced by hematoma formation following skin closure. This usually develops gradually over the course of several hours postprocedure and should be evacuated promptly to avoid potentially irreversible damage from long-standing median nerve compression.

FEMORAL, AXILLARY, AORTIC, AND TRANSAPICAL ACCESS

The success of procedures such as transcatheter aortic valve replacement exemplifies how multidisciplinary teams comprised of interventional cardiologists, cardiac and vascular surgeons may achieve procedural excellence. Yet despite complementary skill sets, all team members should possess a fundamental technical knowledge of the exposure, cannulation, and closure of common sites of access to the central vasculature and the thorax. As such, open femoral and axillary arterial access are described, as also access to the ascending aorta and to the left ventricular apex.

Open Femoral Arterial Access
While the common femoral artery and its branches can be accessed using both general and local anesthesia, procedures of any significant duration would best be performed under general anesthesia. For simple exposure of the anterior wall of the common femoral artery, local anesthesia using 20 mL of 1% to 2% lidocaine produces sufficient analgesia. With the patient positioned supine, allowing the feet to externally rotate, the groin is sterilized and draped from the umbilicus to the mid-thigh, and laterally to the anterior superior iliac spine. A groin towel is placed medially. Intradermal lidocaine and deeper subcutaneous injections are then performed along the proposed site of incision and dissection.

Adequate access of the common femoral artery may be achieved through either a vertical or oblique skin incision. The vertical skin incision should be made using a 15 scalp directly over the palpable femoral pulse from several centimeters above the groin crease inferiorly for another 5 to 7 cm (Figure 8.14). An oblique skin incision follows the course of the inguinal ligament just inferior to that structure and ideally measures 5 to 7 cm in length, centered on the palpable femoral pulse. If no femoral pulse is palpable, the vertical incision should be centered on the pubic escutcheon or located two-thirds of the way between the anterior superior iliac spine and symphysis pubis. Here, an oblique incision provides greater medial-lateral access to the femoral vessels without lengthening the skin incision. The deep subcutaneous tissue overlying the femoral vessels is dissected sharply or using electrocautery to expose the femoral sheath. Electrocautery is preferred for this dissection to seal the numerous lymphatic vessels and superficial veins encountered during
the dissection. Sharp dissection in the periadventitial plane of Leriche using Metzenbaum scissors subsequently allows for safe exposure of the femoral artery and its branches. Self-retaining Weitlaner retractors provide excellent exposure to the depth of the common femoral artery. Superior retraction of the inguinal ligament by an assistant facilitates dissection of the external iliac artery when higher access is required. One must remain cautious not to inadvertently divide the circumflex iliac vein as it crosses the distal external iliac artery as troublesome bleeding may occur.

Depending upon the diameter of the device being inserted into the common femoral artery, the lumen may be directly accessed using either the Seldinger technique or through an arteriotomy. The Seldinger technique requires a purse-string suture of 5-0 polypropylene to be placed in the anterior wall of the vessel and drawn into a tourniquet. A needle is then advanced into the lumen through the center of the purse-string suture followed by a wire. Catheters and cannulae up to 22F can be safely inserted into the common femoral artery following proper sequential dilatation in most vessels 7 mm or larger in diameter (Estech, Vascular Dilator Kit, San Ramon, CA). To facilitate passage of larger dilators, a no. 11 blade scalpel can be used to incise the anterior superior vessel wall inside the purse-string against a dilator once the dilator is in position in the vessel. Failure to advance a catheter or cannula or significant resistance should alert the operator to abandon the approach and consider alternative sites for surgical access.

Purse-string sutures aid hemostasis when using the Seldinger technique and are tied to close the arteriotomy following the procedure. Additional interrupted 5-0 polypropylene sutures placed vertically may be necessary to achieve hemostasis. A palpable pulse in the distal superficial femoral artery suggests adequate distal perfusion, but this should then be verified through palpation of the pedal pulses. Questionable distal perfusion mandates proximal and distal control of the common femoral artery, removal of the purse-string closure, and transverse closure of the arteriotomy using running or interrupted 5-0 polypropylene sutures.

Heavily diseased or calcified femoral vessels often require circumferential mobilization and proximal and distal control for intravascular access through open arteriotomy. Once the fascia overlying the femoral artery has been divided, dissection continues in the periadventitial plane medially and laterally from below the inguinal ligament superiorly, to the bifurcation of the common femoral artery inferiorly (Figure 8.15). Small arterial branches of the common femoral artery can either be ligated with 3-0 silk suture or clipped with small titanium clips prior to sharp division. The femoral nerve and common femoral vein are nearby but protected within their own anatomic compartments. Silastic vessel loops should be passed twice around the common femoral artery superiorly and the branch vessels inferiorly for control. Prior to occlusion of the common femoral artery, heparin should be administered and anticoagulation confirmed by an ACT reading. Once the vessel loops are tightened or the vascular clamps applied, the common femoral artery may then be sharply opened transversely using a no. 11 or no. 15 scalpel and Potts scissors. Guidewires and catheters may then be passed proximally into the central circulation by controlling the proximal silastic loop or partially releasing the common femoral arterial clamp. Serial dilators (Estech, Vascular Dilator Kit, San Ramon, CA) may be helpful in creating a larger proximal vessel even through an open arteriotomy. Introduction of larger vascular devices requires that the arteriotomy be performed midway between the inferior epigastric artery and the common femoral bifurcation. Closure of the transverse arteriotomy using running 5-0 or 6-0 polypropylene is much more reliable than purse-string closure to prevent vessel narrowing.

Meticulous technique of groin closure is the key to avoid complications. The wound itself and all three layers of closure should be copiously irrigated with antibiotic-containing saline solution. The deep soft tissue or fascia lata should be closed first using absorbable 2-0 polyglactin suture, taking bites of the femoral sheath to obliterate deeper dead space against the femoral vessels. The superficial subcutaneous tissue is then approximated again with 2-0 polyglactin suture.

Figure 8.15 Silastic vessel loops placed around the inferior common femoral artery (superiorly) and the superficial femoral artery (inferiorly). The circumflex iliac vein has been divided to pass a silastic loop around the superior common femoral artery.
The skin may be closed using suture material or skin staples. A subcuticular absorbable 4-0 polyglactin suture provides a good cosmetic result and avoids the requirement to remove staples.

Common complications of femoral artery exposure include lymph fistulas and lymphocele or seroma formation. Medial dissection of the common femoral artery often involves dividing numerous lymph nodes and lymph channels. By accessing the lumen through the anterior wall of the vessel, the Seldinger technique requires little medial dissection and may decrease the frequency of these specific issues. If, however, more extensive groin dissection is required, titanium clips should be used liberally to control lymph leak, and drainage with a small-bore closed-system drain (14F) may be required. Other complications of femoral arterial access include bleeding, infection, femoral nerve injury, limb ischemia, and hematoma, pseudoaneurysm, or arteriovenous fistula formation. Secure arterial closure and vigilant assessment of distal perfusion provide the best defense here.

**Axillary/Subclavian Artery Access**

Patients with severe iliofemoral or distal aortic disease, severe femoral artery calcification, or small vessel diameter may require alternative access to the central circulation. In such cases, the axillary or subclavian artery provide sufficient arterial diameter and proximity to the aorta. In general, the left subclavian artery is preferred for access to the ascending aorta given its favorable trajectory along the curve of the aortic arch.

Access to the subclavian or axillary artery is best performed under general anesthesia. The patient is positioned supine (semi-Fowler position) with the head rotated to the opposite side and the neck slightly hyperextended. A systemic arterial monitoring catheter should be placed in the contralateral extremity. The ipsilateral neck, chest, shoulder, and the entire clavicle should be included in the operative field.

A transverse or slightly oblique 3- to 5-cm skin incision is created using a no. 15 scalpel inferior to middle and lateral third of the clavicle (Figure 8.16). Beneath the subcutaneous tissue, the fascia overlying the pectoral muscles is identified and divided. The fibers of the pectoralis major are divided along their length and held apart by placing a self-retaining Weitlaner retractor. The underlying pectoralis minor tendon may require release laterally, but often can be retracted to avoid division. In the fat pad deep to the pectoral muscles, there exist a number of venous tributaries to the subclavian vein. These veins should be divided using either clips or 3-0 silk ties to facilitate superior retraction of the subclavian vein to expose the deeper subclavian artery. The subclavian artery exists medial to the outer border of the first rib at which point it becomes the axillary artery. Regardless of this, this arterial structure has few branches at this location, having proximally given off the internal mammary artery, vertebral artery, and thyrocervical trunk.

At least 3 to 5 cm of the subclavian artery should be dissected free to obtain proximal and distal control with silastic or rubber vessel loops passed twice around the vessel (Figure 8.17). Caution should be exercised when passing vessel loops to avoid small posterior arterial branches and to recognize the thin-walled nature of this vessel and its sometimes tortuous course. With vessel loops safely in place, these can then be used for arterial control and to provide retraction of the vessel into a more superficial plane. Anticoagulation must then be administered.

A transverse arteriotomy created using a no. 11 scalpel and Potts scissors provides excellent exposure even when using the Seldinger technique for arterial access. Guidewires and dilators may be passed proximally directly through the skin incision or may require a more laterally placed access incision if the angle through the skin incision is too acute. Alternatively, anastomosis of an 8 mm Dacron graft to the subclavian artery provides a route to more easily pass guidewires and catheters remote from the vessel itself. To place this Dacron graft, a longitudinal arteriotomy is created using a no. 11 scalpel. A 4.4 mm aortic punch typically used for coronary anastomoses can then be placed through the arteriotomy and fired several times to create an oval arteriotomy. The Dacron graft is then anastomosed to the subclavian artery in an end-to-side fashion using 5-0 or 6-0 polypropylene suture. To close the Dacron graft, place a small vascular clamp across the graft close to the subclavian vessel, divide, and oversew the graft end with 6-0 polypropylene. Closure of the incision requires 2-0 polyglactin for deeper tissues and 4-0 polyle­caprone or staples for skin closure. Although no drain is required, note that pneumothorax may complicate this access route given the adherence of the pleura to the deep wall of
the subclavian artery. As always, the access procedure is not complete until distal perfusion has been assessed as adequate. Complications associated with axillary or subclavian access include stroke, arterial or aortic dissection, thrombus formation, and limb ischemia.

**Direct Transthoracic Aortic Access**

Upper mini-sternotomy and right anterior thoracotomy provide access to the ascending aortic and are common approaches used for open isolated aortic valve replacement by cardiac surgeons. Both approaches require general anesthesia. The patient is positioned supine and the surgical field prepared to include the chest, abdomen, and pelvis. Typical monitoring lines include a systemic arterial line and central venous access that may include a pulmonary artery catheter. Mini-sternotomy requires a 6 cm vertical skin incision centered on the angle of Louis at the sternomanubrial junction. The sternum is divided from the manubrium to the level of the third intercostal space. A transverse incision of the sternum into the third interspace bilaterally or unilaterally to the right provides visualization of the upper mediastinum including the ascending aorta. This approach generally avoids entry into either thorax, accessing the mediastinum directly. Once the thymic fat has been divided, the pericardium is divided vertically and tacked up to the skin using 2-0 silk sutures to create a “pericardial well” centered on the ascending aorta. Vascular access of the ascending aorta follows as routinely performed by cardiac surgeons to institute cardiopulmonary bypass. Two Teflon felt pledgeted purse-string 3-0 polypropylene sutures are placed in the ascending aorta through which vascular access may be obtained in either an antegrade or retrograde fashion. Alternatively, a side-biting vascular clamp can be placed on the ascending aorta to permit the creation of an aortotomy using a no. 11 scalpel. The aortotomy is then enlarged using a 4.4 mm punch tool to create a defect large enough to allow for anastomosis of an 8 mm Dacron graft in an end-to-side fashion using 5-0 or 6-0 polypropylene. Vascular access can then occur remote from the aorta through the Dacron graft. The Dacron graft can be oversewn at the completion of the procedure using 5-0 polypropylene. Chest closure requires sternal wires and closed mediastinal drainage.

Right anterior thoracotomy provides aortic access similar to that of the upper mini-sternotomy, but requires entry into the thorax. Patient positioning and preparation are identical to a mini-sternotomy. A 5 to 7 cm transverse skin incision is created over the right second intercostal space adjacent to the sternum. Dividing the pectorus major and the underlying intercostal muscle above the third rib reveals the right side of the mediastinum. The upper pericardium is then divided vertically along the right side of the ascending aorta and stay stitches (2-0 silk) are placed through the pericardium and skin to distract the upper mediastinum to the patient’s right side. The ascending aorta lies at the base of the incision for access identical to that through the mini-sternotomy. Rib approximation may not be necessary for closure of a small thoracotomy but chest tube placement is recommended.

One advantage to both mini-sternotomy and small right thoracotomy is that catastrophic complications of procedures performed through small chest incisions are more easily converted to open operations with institution of cardiopulmonary bypass if necessary.

**Left Ventricular Apical Access**

Access to the left ventricular apex is a surgical procedure that should be performed by one skilled in caring for the number of significant complications that may occur. This procedure should be performed under general anesthesia using a double-lumen endotracheal tube or bronchial blocker to provide single (right) lung ventilation during the procedure. The patient is positioned supine and the entire chest, abdomen, and pelvis should be included in the operative field. The left ventricular apex may also be palpable to guide incision location. Preoperative CT scanning is helpful in planning the location of the skin incision, as is intraoperative fluoroscopy if being used for the procedure. The left ventricular apex may also be palpable to guide incision location.

Dissection of the subcutaneous tissue and division of the fibers of the underlying pectoris major reveals the underlying bony chest wall. Electrocautery is used to
divide the intercostal muscle along the superior aspect of the chosen rib to provide entry to the thorax and to avoid the intercostal neurovascular bundle. If the apex is not apparent, either another interspace can be entered through the same skin incision or the rib can be notched with a rib shear. As a rule, it is better to be too low rather than too high when approaching the left ventricular apex because stay sutures of 2-0 polypropylene can be distracted downward into view. These stay sutures are passed through the longitudinally divided pericardium and then through the skin.

Two 2-0 polypropylene purse-string sutures with Teflon felt pledgets are placed ideally on the anterior left ventricular wall to include the apex. In this location, there is less epicardial fat and a greater likelihood that sutures have achieved significant purchase of myocardium but without entering the left ventricular cavity. These sutures are then passed through tourniquets to control bleeding as catheters or devices are placed through the apex. Care should be taken to acknowledge the location of the left anterior descending coronary artery to avoid injury (Figures 8.18 and 8.19).

Closure of the left ventricular apex requires tying the purse-string sutures following the procedure (Figure 8.20). Additional pledgeted 3-0 or 4-0 polypropylene sutures may be required to achieve hemostasis and the thin left ventricular apex represents a true surgical challenge in this regard. Cardiopulmonary bypass, preferably using femoral cannulation, may be required to decompress the left ventricle to complete complicated apical closure. The pericardium may be closed with interrupted 2-0 silk sutures or left open. A left pleural chest tube (28F or 32F) is required, although a small pericardial drain is preferred by some (19F). Pericostal sutures are required to approximate the interspace only if a rib was divided or notched (no.1 polygactin). The pectoral fibers are then closed in a running fashion (0 polyglactin) as is the subcutaneous tissue (4-0 polyglecaprone). The chest tubes are then placed to -20 cm water suction to complete the procedure. The potential complications of this vascular access route are many but primarily include bleeding, coronary artery damage, and false aneurysm formation. Respiratory complications occurring as a result of chest entry can also cause significant morbidity.
REFERENCES


As a growing population of adults reaches adulthood after being treated during infancy for congenital heart disease, a significant proportion of patients undergoing cardiac catheterization for congenital cardiac abnormalities now are older than 18 years of age; a progressive increase in the age-distribution of cardiac congenital catheterization is expected. Data from Boston Children's Hospital show that, for the period 2005–2011, approximately 20% of the catheterization laboratory case load of this tertiary referral center for treatment of congenital heart disease is composed of adult patients. Despite continuing advances in noninvasive anatomic and physiologic imaging modalities, precise catheter-based definition of anatomy and physiology remains invaluable in the primary and adjunctive management of many of these pediatric and older patients with congenital heart disease. It can elucidate the following:

1) The varying, and sometimes unique, “natural” (unoperated) and post-operated anatomicies, and the associated physiologic consequences thereof (Table 9.1).
2) The codependency between the pulmonary (ventricle/vasculature/parenchymal) and the systemic circulation.
3) The nature and precision of catheter-based anatomic-physiologic correlations.
4) Precise angiographic resolution of small (<2 to 3 mm) or tortuous structures, as well as for definition of multiple entry or exit sites or connections.
5) The increasing patient interactions with premature acquired noncardiovascular disease. In fact, increasing awareness of the neurohormonal and functional limitations in children and adults with congenital heart disease suggest an ever-increasing role for greater physiologic and anatomic understanding of such patients.

Table 9.1 Confounding Physiologic Abnormalities in Patients with Congenital Heart Disease

| Abnormalities in atrial or preventricular transport |
| Alterations in pulmonary blood flow (quantity, pulsatility, resistance) |
| Variations in pulmonary capacitance (conduit vessels) |
| Shunt-, obstruction-, or impedance-related changes in ventricular loading conditions |
| Myocardial-pericardial interaction |
| Abnormalities of electrical conduction |
In past decades, the majority of patients with congenital heart disease presented with one of several classes of “simple” anatomy or physiology, including obstructions (pulmonary/aortic stenosis [PS/AS], aortic coarctation [CoA]), or intravascular shunts (atrial/ventricular septal defects [ASD/VSD], patent ductus arteriosus [PDA]). At present, the majority of surviving patients have increasingly complex anatomy and physiology, since greater than 60% of adult congenital heart disease patients have had at least one surgery prior to their adult years (and approximately half of these patients have had a reoperation during adulthood). A complete review of every aspect of individual “natural” and prior operated history (Table 9.2) and anatomy (with particular attention to the specifics of each intervention) is required prior to embarking upon any catheter-based investigation (Table 9.3). This should be

### Table 9.2 Typical Categorization of Surgical Repairs

<table>
<thead>
<tr>
<th>Name</th>
<th>Typical Lesion Application</th>
<th>Surgical Connection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glenn (Classic)</strong></td>
<td>Single ventricle/TA</td>
<td>SVC to (right) pulmonary artery</td>
</tr>
<tr>
<td><strong>Bidirectional</strong></td>
<td>Single ventricle/TA</td>
<td>SVC to R/MPA</td>
</tr>
<tr>
<td><strong>Fontan (atriopulmonary)</strong></td>
<td>Single ventricle/TA</td>
<td>Atrial appendage to RV or PA</td>
</tr>
<tr>
<td><strong>(cavopulmonary)</strong></td>
<td></td>
<td>IVC-SVC intra-or extracardiac baffle to PAs</td>
</tr>
<tr>
<td><strong>Waterston</strong></td>
<td>TOF/DORV/pulmonary atresia</td>
<td>Ascending aorta to RPA</td>
</tr>
<tr>
<td><strong>Potts</strong></td>
<td>TOF/DORV/pulmonary atresia</td>
<td>Descending aorta to LPA</td>
</tr>
<tr>
<td><strong>Blalock-Taussig (classic)</strong></td>
<td>TOF/DORV/pulmonary atresia</td>
<td>Subclavian artery to branch PA</td>
</tr>
<tr>
<td><strong>(modified)</strong></td>
<td>TOF/DORV/pulmonary atresia</td>
<td>Conduit from subclavian artery to branch PA</td>
</tr>
<tr>
<td><strong>Mustard/Senning</strong></td>
<td>TGA</td>
<td>Baffle directing SVC-IVC flow to subpulmonary LV, pulmonary venous flow to subsystemic RV</td>
</tr>
<tr>
<td><strong>Arterial switch</strong></td>
<td>TGA</td>
<td>Translocation of more-posterior MPA to anterior supra-LV position, more-anterior aorta to posterior supra-PA position, coronary arterial reimplantation</td>
</tr>
<tr>
<td><strong>Rastelli</strong></td>
<td>TGA/TOF</td>
<td>Conduit between subpulmonary ventricle and PA</td>
</tr>
<tr>
<td><strong>Norwood</strong></td>
<td>HLHS</td>
<td>Translocation of proximal MPA to supra-LV position, end-to-side anastomosis of distal MPA to aorta, modified Blalock-Taussig shunt</td>
</tr>
<tr>
<td><strong>Double switch</strong></td>
<td>TGA</td>
<td>Atrial switch + arterial switch</td>
</tr>
</tbody>
</table>

Note: All patients have variations mandating detailed review of operative reporting.

DORV, double outlet right ventricle; HLHS, hypoplastic left heart syndrome; IVC, inferior vena cava; LPA, left pulmonary artery; LV, left ventricle; MPA, main pulmonary artery; PA, pulmonary artery; RPA, right pulmonary artery; RV, right ventricle; SVC, superior vena cava; TA, tricuspid atresia; TGA, transposition of the great arteries (L, left; D, right); TOF, tetralogy of Fallot.
### Table 9.3: Typical Indications for Diagnostic Catheterizations/Preferred Imaging Modalities/Interventions

<table>
<thead>
<tr>
<th>Typical Lesion/s</th>
<th>Diagnostic Cath Typical Indications</th>
<th>Preferred Imaging Modalities</th>
<th>Cath Indication: Interventional</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASD secundum</td>
<td>No: useful for PVR when PHT suspect → ASD test occlusion; PHT vasodilator testing; HD-based management of RV and LV dysfunction</td>
<td>TEE/ICE</td>
<td>ASD closure</td>
</tr>
<tr>
<td>PFO</td>
<td>No</td>
<td>TEE/ICE</td>
<td>PFO closure when indicated</td>
</tr>
<tr>
<td>ASD sinus venosus</td>
<td>Debated: higher incidence PHT: useful for PVR when PHT suspect; see above</td>
<td>MRI</td>
<td></td>
</tr>
<tr>
<td>ASD primum</td>
<td>No</td>
<td>TEE</td>
<td></td>
</tr>
<tr>
<td>AV canal defect</td>
<td>No: with increasing age, increased risk of PHT → check PVR; see above</td>
<td>TEE</td>
<td></td>
</tr>
<tr>
<td>TAPVR</td>
<td>Debated: PVR, PV anatomy and rule out stenoses</td>
<td>Cath/MRI</td>
<td></td>
</tr>
<tr>
<td>VSD, membranous</td>
<td>No: uncommon need to assess PVR</td>
<td>TTE/MRI</td>
<td>Investigational closure</td>
</tr>
<tr>
<td>VSD, multiple muscular</td>
<td>No: HD-based management of ventricular dysfunction, when indicated</td>
<td>TTE/MRI</td>
<td>VSD closure</td>
</tr>
<tr>
<td>Ao stenosis/ regurgitation: subvalvular/supravalvar</td>
<td>Debated: Hemodynamic changes remain the standard for intervention in children and young adults with valvar AS Supravalvar AS: Useful to define relationship to CA origins AR: demonstration of fistulous connections when indicated</td>
<td>TTE/TEE/MRI</td>
<td>AS: valve dilations</td>
</tr>
<tr>
<td>Aortic coarctation</td>
<td>No: Hemodynamic changes remain the standard for intervention in children and adults</td>
<td>MRI</td>
<td>Dilation/stent</td>
</tr>
<tr>
<td>PDA</td>
<td>No: PA pressure when PHT suspect → PDA test occlusion</td>
<td>TTE/MRI</td>
<td>PDA closure</td>
</tr>
<tr>
<td>Valvar PS</td>
<td>No: HD-based management of RV failure when appropriate</td>
<td>TTE/MRI</td>
<td>Valve dilation</td>
</tr>
<tr>
<td>Peripheral PS</td>
<td>No: HD-based management of RV failure or PHT when appropriate</td>
<td>Nuclear scintigraphy/MRI</td>
<td>PA dilation/stent</td>
</tr>
</tbody>
</table>
Table 9.3

<table>
<thead>
<tr>
<th>Typical Lesion/s</th>
<th>Diagnostic Cath Typical Indications</th>
<th>Preferred Imaging Modalities</th>
<th>Cath Indication: Interventional</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOF, preoperative</td>
<td>No: Anatomy when CA's, VSD's, Ao-PA collaterals cannot be otherwise sufficiently imaged</td>
<td>TTE/MRI</td>
<td>Close muscular VSD's</td>
</tr>
<tr>
<td>TOF, postoperative</td>
<td>Assess for residual shunts; HD-based management of RV or LV dysfunction; PHT therapy</td>
<td>TTE / MRI</td>
<td>Close residual shunts/VSD's; PA or conduit dilation/stent</td>
</tr>
<tr>
<td>TOF, pulmonary atresia</td>
<td>Yes: define PA anatomy and hemodynamics</td>
<td>MRI</td>
<td>Close Ao-PA connections; dilate/stent stenoses</td>
</tr>
<tr>
<td>Pulmonary atresia/ intact septum</td>
<td>In children, define coronary anatomy; in adults, define CA anatomy or HD-based management of ventricular dysfunction, as indicated</td>
<td>MRI</td>
<td></td>
</tr>
<tr>
<td>TGA-D, preoperative</td>
<td>No</td>
<td>TTE</td>
<td>Atrial septostomy</td>
</tr>
<tr>
<td>TGA-D, postoperative atrial switch</td>
<td>Assessment of residual shunting; HD-based management of systemic ventricular dysfunction or PHT</td>
<td>MRI</td>
<td>Shunt closure</td>
</tr>
<tr>
<td>TGA-D VSD/PS; Truncus; DORV postoperative</td>
<td>No; HD-based management of systemic ventricular dysfunction or PHT</td>
<td>MRI</td>
<td>Shunt closure; conduit dilation/stent</td>
</tr>
<tr>
<td>TGA-D, postoperative arterial switch</td>
<td>Assessment of PA stenoses, coronary arterial stenoses</td>
<td>MRI; IVUS</td>
<td>CA dilation/stent</td>
</tr>
<tr>
<td>TGA-L</td>
<td>HD-based management of systemic ventricular dysfunction</td>
<td>MRI</td>
<td></td>
</tr>
<tr>
<td>Single ventricle, preoperative</td>
<td>Yes: hemodynamics/PVR</td>
<td>TTE/MRI</td>
<td>Close collaterals, PA dilatation/stent</td>
</tr>
<tr>
<td>Single ventricle, post-Fontan</td>
<td>Yes: HD-based management of load and ventricular function</td>
<td>MRI</td>
<td>Conduit and PA dilatation/stent; close collaterals</td>
</tr>
</tbody>
</table>

Ao, aorta; AR, aortic regurgitation; AS, aortic stenosis; ASD, atrial septal defect; AV, atioventricular; CA, coronary artery; DORV, double outlet right ventricle; HD, hemodynamics; ICE, intracardiac echocardiography; IVUS, intravascular ultrasonography; LV, left ventricle; MRI, magnetic resonance imaging; PA, pulmonary artery; PFO, patent foramen ovale; PHT, pulmonary hypertension; PS, pulmonary stenosis; PV, pulmonary valve; PVR, pulmonary vascular resistance; RV, right ventricle; TAPVR, total anomalous pulmonary venous return; TEE, transesophageal echocardiography; TGA, transposition of the great arteries (L, left; D, right); TOF, tetralogy of Fallot; TTE, transthoracic echocardiography; VSD, ventricular septal defect.

coupled with a full understanding of potential anatomic and physiologic variations and sequelae, as well as awareness and potential to perform intervention, as needed. As with investigation of patients with acquired heart disease, a detailed preprocedural investigational plan—with attention to adequately trained support staff, available tools, and preprocedural and postprocedural monitoring—is required.
Vascular Access/Vessel and Chamber Entry

Although usual femoral or jugular arterial and venous access can be used in larger children and adults (see Chapter 6), special access routes are usually required in neonates and infants. Options for vascular access vary depending on body habitus, vessel patency, and area to be accessed. Patient size, chamber dilation, and vessel distortion present additional technical challenges that can usually be overcome with experience.

Umbilical Vessels

Umbilical vessels have decreasing patency over the first 72 postnatal hours, but their use allows sparing of other vessels. Vascular access via the umbilical vein (5F umbilical catheter entry) directs catheter position posteriorly in the right atrium, which assists balloon atrial septostomy but adds considerable difficulty to achieving stable right ventricle (RV) and pulmonary artery (PA) access. Given the nearly 180° turns involved in catheter passage (umbilical vein [UV] → portal vein → ductus venosus → inferior vena cava [IVC] → right atrium), concomitant angiographic delineation of course during entry is suggested. Hand-administered contrast injection to demonstrate ductus patency, combined with either use of a tip-deflecting or torque-controlled wire, permits posterior advancement of the catheter, avoidance of intubation of the liver, and successful passage of the UV catheter to the IVC, where it is exchanged for an access sheath after angiographic corroboration. Likewise, the additional curve required to pass a catheter from the umbilical artery (patent for up to 7–10 days post-natally) through the iliac artery may decrease success of retrograde catheter passage to the systemic ventricle, although this maneuver is frequently successful.

Direct Hepatic Vein

Direct hepatic vein entry can be considered when the femoral veins are impassable. A Chiba needle is passed between the mid and anterior axillary line, near the costal margin between the diaphragm and the inferior liver edge. The needle is typically advanced using ultrasound guidance, passing posteriorly and cephalad toward the infrahepatic IVC or just caudal to the IVC-right atrial (RA) junction, to within a few centimeters of the right border of the spine. Contrast injection confirms entry into a large central hepatic vein, where a sheath and dilator are advanced over a guidewire to the RA. Large sheath entry and transseptal passage can be performed without complication via this route. At end of procedure, a catheter IF size smaller than the entry catheter is exchanged, and this sheath is withdrawn, with hand injection of contrast until the sheath is out of the vessel and within the liver parenchymal tract. This tract is then filled with either coils or gelfoam, with subsequent pain at the entry site expected for an ensuing 24 hours, due to peritoneal irritation.

Intracardiac Catheter Manipulation

Even after vessel access, catheter passage into the desired chambers may require particular knowledge and experience. Appropriate catheter positioning may be facilitated by use of torque-controllable, extendible, tip deflecting, stiff, extra-stiff, 0.035 inch and 0.038 inch guide wires, as well as by increased use of shaped catheters designed for peripheral or coronary use.

Entry to the superior vena cava (SVC) is easiest via advancement of a straight wire or catheter from the IVC (soft catheters tend to advance anteriorly toward the atrial appendage, away from the SVC). A straight catheter may be gently advanced with a soft counterclockwise rolling to ensure freedom of the catheter tip. Foreshortening of the catheter tip in the anteroposterior (AP) projection typically marks successful posterior angulation, permitting advancement of the free catheter tip to the SVC, avoiding the more anterior right atrial appendage. Particular caution in catheter manipulation is required in those patients with history of atrial arrhythmias or in those patients where a rapid atrial tachycardia could lead to acute hemodynamic decompensation (such as severe pulmonary hypertension, severe left ventricular outflow tract obstruction, mitral valve stenosis, and others).

On occasion, interruption of the IVC, with azygos continuation, may complicate catheter passage, markedly elongating the catheter course. Multiple curves along the catheter course may make further posterior or transseptal passage extremely difficult from this access.

Passage to the RV may be complicated when (1) the RA is excessively large; (2) the tricuspid valve (TV) or RV is diminutive; (3) marked TV regurgitation is present; (4) pulmonary atresia is present. Entry can be facilitated by either advancement of a preformed catheter with curvature aimed toward the TV, or with a soft-tipped catheter into which may be introduced the preformed bend on the stiff end of a wire or a tip-deflecting wire, always leaving the wire within the catheter rather than allowing it to protrude into the vasculature. The guidewire–soft-catheter technique allows for adjustment of entry angle and length of curvature by balancing the distance of the guidewire tip from the catheter end, prior to catheter advancement over the guidewire. Particular care must be taken with this approach to ensure that the catheter tip is moving freely, prior to further manipulation or balloon tip inflation.

Intubation of a normally positioned RV outflow/main pulmonary artery (MPA) may be difficult when (1) the RV is particularly dilated, or (2) the TV is regurgitant. Passage via an internal jugular or subclavian vein approach may increase
stability and aid in anterior angulation to and through the RV outflow tract. A multipurpose or similarly precurved soft-tipped catheter can be turned gently in clockwise fashion, with either concomitant contrast injection or use of a torque-controlled wire. Similarly, a soft balloon end-hole catheter can be stiffened at its distal end either with a sharp S-shaped bend to the stiff end of a 0.035 inch guidewire wire, or with a tip-deflecting wire, to facilitate passage to the RV outflow tract. An alternative approach requires the creation of a controlled loop in the RA to enhance catheter stability to engage the RV outflow and MPA.

Passage of a catheter from the femoral vein through the RV outflow typically is directed toward a normally positioned, posteriorly directed left pulmonary artery (LPA). When the PAs are in altered positions, or are dilated, shaping the stiff end of a guidewire with a compound clockwise or counterclockwise loop, and advancing it to the end of a soft catheter may help direct the catheter to the right or to the left PA, respectively. Such compound curves may prove extremely useful in individual circumstances, transforming basic shaped catheters into individualized, “custom-fitted” entry devices. For example, use of a similar, tight, S-shaped compound guidewire curve can assist in directing a catheter from the proximal branch right pulmonary artery (RPA) to the upper lobe vessel. Similarly, a preshaped catheter can be used with contrast injection or a torque-controlled guidewire to assist branch PA entry. Intubation of a dilated or angulated branch RPA may be particularly difficult from a femoral approach, and we have found that retraction of a left Judkins coronary catheter from the LPA into the MPA and angled toward the right often facilitates RPA entry.

When the PAs are posteriorly directed (TGA), entry via the subpulmonary left ventricle (LV) is generally performed with a soft-tipped, balloon end-hole catheter placed in the LV apex. After ensuring that the catheter tip is free, a tip-deflecting wire is placed within the catheter, proximal to its tip, and is deflected with sufficient traction to guide the catheter tip in a posterior direction, away from the ventricular apex, and toward the base of the heart. A slight retraction of both catheter and guidewire, as a unit, is typically performed, allowing alignment with the LV outflow. The guidewire is held firmly, acting as a fulcrum from which the catheter is extruded, away from the ventricular apex and into the LV outflow.

Left atrial entry via a transseptal approach can be accomplished on retraction from the SVC with gentle counterclockwise rotation of a leftward-facing catheter, or with clockwise advancement from a similarly leftward-facing catheter positioned near the TV. Biplane fluoroscopic assessment facilitates safe transseptal passage, though some centers note increasing use of intracardiac echocardiographic guidance. Typical AP location of the atrial septum is frequently just rightward of the center of the spine. Posterior, clockwise catheter rotation from this position will facilitate passage into the pulmonary veins, which may be probed with use of a torque-controlled guidewire. The position of the wire/catheter should be checked using a lateral projection to ensure that the wire/catheter takes a posterior course and is not located within the left atrial appendage, or anteriorly toward the aorta. In addition, particular caution in intracardiac manipulation is required for those patients with history of atrial fibrillation or increased risk for this arrhythmia (such as severe left atrial enlargement, mitral stenosis, hypertensive cardiomyopathy). Lower pulmonary vein entry is frequently facilitated by use of a tight, near 180° C-shaped compound curve to the stiff end of a guidewire placed within the entry catheter, directing it to the vessel orifice. Left pulmonary venous entry is typically routine on crossing the atrial septum, though it may be complicated by entry into the atrial appendage. Considerable catheter retraction and further posterior redirection outside of the appendage typically facilitates prompt left pulmonary venous entry. The right-sided pulmonary veins typically require further posterior, clockwise rotation until the catheter tip appears on AP projection to be to the right of the spine, and then subsequent catheter advancement.

Shunt entry is typically facilitated by precise preentry knowledge (reviewing before the procedure three-dimensional imaging modalities such as cardiac magnetic resonance or CT scans) of the location of the shunt origin. High-volume shunts (Waterston/Pott’s/alternative central aorta to PA) may be entered via transiently inflated, balloon-tipped flotation catheters, or with preformed individually adjusted catheters (e.g., Judkins right coronary catheter modified by cutting its distal tip) directed manually or via tip-deflecting or torque-controlled wires. A preformed Cobra catheter, or a modified pigtail (individually cut to approximately 180°) may facilitate torque-controlled wire passage from the subclavian artery through a Blalock-Taussig shunt.

The ductus arteriosus was one of the original congenital defects intubated during early catheterization attempts, although this is rarely present in adult congenital cardiac cases. The ductus, when present, can be intubated relatively easily from either an anterograde venous or retrograde arterial approach. From the descending aorta, a preshaped catheter (Cobra, right Judkins, or multipurpose in children; left Judkins in adults) directs a soft-tipped torque-controlled guidewire across the ductus. From a venous approach, stationing of a multipurpose catheter within the MPA angled slightly leftward to the MPA-LPA junction, allows similar passage of a soft-tipped straight or torque-controlled guidewire across the ductus.

Pressure Measurements and Oximetry

Pressure and systolic or diastolic gradient measurements require stability of loading conditions and contractility, as well as precise localization of the catheter tip. Improved atrioventricular compliance in youth contributes to lower “normal” values of filling pressures in children (RA ≤ 3 to 5 mm, PCW/LA ≤ 5 to 8 mm). Localization of pressure gradients can be facilitated by pressure transduction through manufactured, or modified (“cut”) side-hole pigtail catheters equipped with a Touhy-Borst Y-arm adaptor and retracted...
over a stable guidewire. Alternatively, a double-lumen end-hole catheter may accomplish this goal of near-simultaneous pressure measurements.

Oximetry remains the gold standard for shunt detection. Error range of modern high-fidelity oximeters remains approximately ± 3%. This, combined with flow-sampling and venous mixing errors, leads to a required oximetric saturation difference of between 4% and 9% to be assured of the presence of left to right shunting. These errors must be taken into account when assessing the accuracy of shunt and resistance calculations (Table 9.4, Figure 9.1). Common correctable errors in assessing oximetric values include the following:

1) Use of IVC sampling as measure of “mixed venous” saturation. Especially in the fetus, but likewise for all aged persons, hepatic, renal (and ductus venosus) flow may not fully mix within the IVC, giving inaccurate reflection of flow due to streaming effects.

2) Use of “wedged” samples that do not reflect the sampled chamber or vessel, but, rather, are partially contaminated by values from proximal or distal chambers.

3) Mistaking elevated SVC saturation as normal, rather than recognizing either shunt directly into the SVC from anomalous pulmonary veins, or regurgitation from the RA in the presence of atrial level shunting.

4) Focusing on a particular degree of shunting, without noting overall flows. For example, in a patient with a secundum ASD, SVC oxygen (O₂) saturation 50%, PA O₂ saturation 80%, aortic O₂ saturation of 100%, hemoglobin (Hgb) 14, and pulmonary flow/systemic flow (Qp/Qs) ratio of 2.6, correction of atrial shunting

| Qp | VO₂ | (PV sat – PA sat) (Hgb)(1.36)(10) |
| Qs | VO₂ | (Ao sat – SVC sat)(Hgb)(1.36)(10) |
| Qp/Qs | | (Ao sat – SVC sat)/(PV sat – PA sat) |
| Qp effective (Qs effective) | VO₂ | (PV sat – SVC sat)(Hgb)(1.36)(10) |
| Q Left → Right | | (Qp – Qp effective) |
| Q Right → Left | | (Qs – Qs effective) |
| % Left → Right = 1 – (Qp effective/Qp) | | (PA sat – SVC sat) |
| % Right → Left = 1 –(Qs effective/Qs) | | (PV sat – Ao sat) |
| PVR | | (mean PA pressure – LA pressure) |
| PVR of multiple lung segments | | 1/R₁ = 1/R₁ + 1/R₂ + ... |
| | | 1/R₁ = [Flow₁/Pressure (PA1 – PV₁)] + [Flow₂/Pressure (PA1 – PV₂)] ... |

Q, flow; p, pulmonary; s, systemic; PVR, pulmonary vascular resistance; VO₂, oxygen consumption; R, resistance; PV, pulmonary vein; PA, pulmonary artery; Hgb, hemoglobin (gm/dl); Ao, aorta; SVC, superior vena cava.
Figure 9.1  A. Commonly used box diagram for displaying hemodynamic and oximetric data. *Open circles* surround oximetric percent at a given location, whereas pressures are recorded directly where they were measured. Anatomic variants are drawn in *yellow circles*, with shunt or blood flow direction demonstrated by *arrow and color*. **B and table.** Hemodynamic and oximetric (including shunt) calculations and measures noted for a patient with atrial level bidirectional shunting.
related oximetry and measure of vascular flow and resistance. Certain additional truisms regarding congenital heart disease:

4) Averaging pulmonary vein saturations in the presence of pulmonary venous desaturation. Segmental pulmonary blood flow is never uniform or sufficiently predictable as to allow for estimation without direct measure. Hence, in the setting of nonuniform pulmonary venous saturations (all pulmonary veins should be sampled for maximal accuracy), relative contribution of each pulmonary segment to total pulmonary blood flow must be known to calculate pulmonary vascular resistance. If supplemental oxygen corrects desaturation and reestablishes uniformity of venous sampling, improved estimation of pulmonary vascular resistance (PVR) can be made. However, disparities in dissolved oxygen (at PO2 > 100) and hence total blood oxygen content in each pulmonary vein contributes to inaccuracy even with this technique.

Certain additional truisms regarding congenital heart disease-related oximetry and measure of vascular flow and resistance should be recognized:

1) Shunt detection is enhanced in the presence of low systemic venous saturation.

2) Total PVR is lowered by recruitment of any additional conduit for flow, regardless of resistance of that vessel (PVR is calculated in series).

3) PVR is typically flow dependent. Typical recruitment of additional zones of pulmonary blood flow at greater amounts of pulmonary blood flow allow for decrease in overall resistance. Hence, surgical elimination of shunt flow to the lungs may not, in fact, lead to decrease in pulmonary pressures (as would be estimated if pulmonary blood flow decreased with a constant PVR), but rather, may allow for persistently elevated pulmonary pressures due to reduction in Qp and elevation in PVR.

4) When multiple sources of pulmonary blood flow with differing oxygen saturations (e.g., Qp effective from a systemic venous shunt along with ineffective systemic arterial flow from an aortopulmonary shunt) exist in given lung segments or to the entire lung, segmental or total Qp cannot be directly measured. However, isolation of each source of flow, temporary occlusion of all but one source, and measure of pulmonary blood flow (mean PA and PV pressures, PA and PV saturations) from that single source to the lung segment/s in question can allow calculation of PVR, albeit at a typically lower flow (“worst case scenario” of PVR).

5) Hemodynamic assessment of patients with single ventricular palliation (Fontan circulation) tests our recognized extrapolations from physiologic principles involved in understanding relationships between flow, pressure, and resistance, and applying those to measures performed at a particular moment in time in the absence of a fully pulsatile circulation. This palliative physiology is particularly sensitive to increases of PVR or decreases in pulmonary vascular capacitance, and, as such, challenges the ability of hemodynamic-driven parameters to accurately reflect the real burden of vascular impedance. In addition, Fontan circulation relies on very low hydraulic energy dissipation profile, as no ventricle supports the pulmonary circulation. Sophisticated approaches using computational fluid dynamic investigations and in vitro hydraulic measurements of hydraulic power loss have demonstrated that energy dissipation in Fontan is influenced by branch point configuration of the Fontan pathway, minimal lumen area, and flow distribution between LPA and RPA. The ability of catheter-based measurements to collect such important information is limited, thus affecting the role of diagnostic catheterization to detect subtle changes contributing to hemodynamic compromise and functional well-being in persons with Fontan circulation.

6) Measurement of vascular pressures and resistance may be affected by recent trauma (vascular intervention) or inflammation/infection, localized compression (e.g., by adjacent structures, surrounding effusion, or atelectasis), by contrast administration, or by changes in systemic adrenergic state, local pH, pCO2, or PO2. Optimally, key aspects of hemodynamic assessment are performed prior to significant contrast exposure, perturbation of resting stable state, or intervention. Likewise, hemodynamics obtained after such exposure may be “worst case” and may improve with time.

Angiography

Few human structures are perfectly symmetrical, so viewing vessels, chambers, and their connections requires multiple (typically orthogonal) views that minimize overlap and foreshortening of critical areas (Table 9.5). Optimally, biplane or multiplane imagery is utilized to decrease radiation and contrast exposure. Recording of individualized angiographic angles and views utilized enhances accuracy of later comparisons.

Contrast administration is typically limited to a dose per injection that is tolerated by the involved ventricle (e.g., segmental or subsegmental PA injections are preferable to larger branch or MPA injections in patients with elevated PVR or RV contractile dysfunction), as long as they are sufficient for maximal anatomic documentation. Past fluoroscopic limitations required contrast administration of approximately 1 cc/kg over 1 second for complete chamber delineation in infants and young children with normal volume flow, and ≥1.5 cc/kg over 1 second, when excessive shunt flow is present. Estimates of contrast need within modern angiographic laboratories with enhanced fluoroscopic fidelity have not been sufficiently calculated, but appear to be less.

Given that total contrast administration is designed to optimally be ≤5 cc/kg catheterization, complete angiographic planning should be performed before the procedure, with ability to shift in “mid-stream” to optimize obtaining of required data with greatest patient safety.
Table 9.5  **Typical Angiographic Projections and Lesions Best Imaged**

<table>
<thead>
<tr>
<th>Projection</th>
<th>Degrees</th>
<th>Vessel/Chamber Imaged</th>
<th>Lesion/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long axial oblique</td>
<td>70° LAO, 30° cranial</td>
<td>LV</td>
<td>Membranous VSD, conotruncal VSD, LVOT obstruction</td>
</tr>
<tr>
<td>Hepatoclavicular</td>
<td>45° LAO, 45° cranial</td>
<td>LV</td>
<td>AV canal defect, mid-muscular VSD</td>
</tr>
<tr>
<td>Lateral</td>
<td>90°</td>
<td>RV/branch PA's</td>
<td>LV-RA connections</td>
</tr>
<tr>
<td>LAO</td>
<td>60°–70° LAO</td>
<td>Aorta</td>
<td>Coarctation/PDA</td>
</tr>
<tr>
<td>LAO-cranial</td>
<td>15° LAO, 30° cranial</td>
<td>MPA-branch origins</td>
<td>TOF/PA stenoses</td>
</tr>
<tr>
<td>Steep LAO-cranial</td>
<td>60° LAO, 15° cranial</td>
<td>Atrial septum origins</td>
<td>ASD, PFO</td>
</tr>
<tr>
<td>AP-cranial</td>
<td>0° LAO, 30° cranial</td>
<td>RV/conduits</td>
<td>TOF/PS/DORV</td>
</tr>
<tr>
<td>AP-caudal</td>
<td>0° LAO, 45° caudal</td>
<td>Ascending aorta/coronary artery origins</td>
<td>TGA/DORV/anomalous CA origins</td>
</tr>
<tr>
<td>AP</td>
<td>0°</td>
<td>RV, peripheral PA's</td>
<td>TGA/DORV/peripheral PS</td>
</tr>
<tr>
<td>RAO</td>
<td>30° RAO, with or without caudal angulation</td>
<td>LV, RVOT</td>
<td>Anterior VSD, mitral valve disease, failing RVOT</td>
</tr>
</tbody>
</table>

Ao, aorta; ASD, atrial septal defect; AV, atrioventricular; CA, coronary artery; DORV, double outlet right ventricle; LAO, left anterior oblique; LV, left ventricle; LVOT, left ventricular outflow tract; PA, pulmonary artery; PDA, patent ductus arteriosus; PFO, patent foramen ovale; (P) PS, (peripheral) pulmonary stenosis; RAO, right anterior oblique; RV, right ventricle; RVOT, right ventricular outflow tract; TGA, transposition of the great arteries (L, left; D, right); TOF, tetralogy of Fallot; VSD, ventricular septal defect.

1. Certain angiographic views serve as reasonable starting points for imaging specific sites or lesions, with individualized adjustment (Table 9.5).  
2. The best angiography may be performed with greatest fidelity and least contrast exposure when angiography is performed in local fashion, typically via a side-hole angiographic catheter placed over a wire or via injection through a large bore, “guiding” sheath. When using the side-hole angiographic approach, the catheter is adjusted to allow the side holes to be at the site of, upstream, or downstream of flow through the region of question in order to maximize anatomic imaging. Contrast administration in this fashion may be markedly reduced, and is dependent on flow through the passage in question, rate of contrast administration, and volume of the specific region to be imaged.  
3. Retrograde imaging via wedge angiography may assist in delineation of otherwise unreachable vessels or chambers. Some patients, as a result of a congenital defect or prior cardiac surgery, have complete occlusion of a proximal PA (typically the left). Due to bronchial arterial collateralization of the more distal portion of the occluded branch PA, this vessel may remain patent even decades later. Aortic and collateral vessel angiography or MRI may not be able to adequately assess vessel patentcy or size, due to restricted baseline flow and vessel underfilling. A balloon-tipped end-hole catheter can be placed into the draining vessel (typically the corresponding PV) from which the image is desired (typically the occluded PA). With the balloon inflated, ≤0.3 mL/kg of nonionic contrast agent (which causes less coughing than high-osmolar ionic agents) is injected, and followed immediately by an equal volume of saline. The parenchymal vessels are usually well outlined by this method, with back-filling, if present, of the mediastinal segment. On occasion, the main and contralateral PA may also fill in, if they are in continuity. It is important to use biplane cineangiography for these injections, to accurately identify the degree of
proximal extension of the vessel relative to landmarks, such as the bronchus, on that side. Similar technique may be utilized for angiography of particular pulmonary venous pathways when vessel access is restricted or difficult. Catheter placement within the feeding PA may be followed by biplane balloon-inflation angiography.

SPECIAL CIRCUMSTANCES

Certain circumstances lead to specific diagnostic considerations for individuals affected by congenital heart disease:

**Pregnancy**

Increased preload, heart rate, and cardiac output, coupled with varying ventricular contractile function, may exacerbate preexisting hemodynamic compromise. Catheterization is safe to mother and fetus when limited to those circumstances (usually mitral or ventricular outflow obstruction) where a combined cardiology and high-risk obstetrics team determines that catheter-based diagnostics or interventions are required despite adequate volume and heart rate control. Choice in timing of catheterization may not be feasible, but should be timed to optimize maternal safety while minimizing fetal teratogenicity or mortality risk. In the past, regardless of food intake, the pregnant woman was typically considered to have a “full stomach,” and hence to be at increased risk of reflux and aspiration; this concept has recently been challenged and in most centers caring for such patients, pregnant mothers are now felt not to carry this excessive risk. Overall uterine radiation exposure should be minimized (direct shielding with lead aprons may intensify rather than reduce exposure, and should be avoided). In such circumstances, the unknown long-term teratogenic risks of low-dose radiation exposure to fetus in modern laboratories is often outweighed by fetal benefit by improving understanding of ramifications of further management strategies or by direct change in hemodynamics. Availability of fetal monitoring and urgent access to the delivery room should be determined by the obstetrical staff prior to catheterization. Typical scenarios leading to catheterization during pregnancy might include maternal suspected or known pulmonary vascular disease, suspected coronary arterial abnormalities, pulmonary venous or functional left atrial outflow obstruction, ventricular outflow obstruction, or subpulmonary or subaortic ventricular failure, unresponsive to standard therapy.

**Down Syndrome**

The adult patient with Down syndrome frequently has increasing medical comorbidity (thyroid disease, upper and lower airway disease, gastrointestinal reflux, aspiration, limited communication skills, and dementia). Despite restricted all-

Pulmonary Ventricular Failure and Pulmonary Vascular Disease

Elevation of subpulmonary ventricular systolic pressure is often seen in adult patients with repaired congenital heart disease. This may be related to fixed obstruction at the level of right ventricular outflow tract (such as in patients with dysfunctional right ventricle-to-PA conduit or reconstructed outflow tract) or at the level of peripheral PA branches (such as in patients with complex cases of tetralogy of Fallot with or without pulmonary atresia or in patients who underwent unifocalization of aorta-to-PA collaterals). In a significant proportion of cases, the increase in subpulmonary ventricular afterload is due to progressive remodeling of pulmonary vascular bed, leading to elevation of PVR (pulmonary arterial hypertension, PAH). PAH is usually related to long-term effects of left-to-right intravascular shunting (such as in tricuspid septal defect, PDA, or less likely ASD), but in some clinical scenarios the risk of developing PAH seems to be out of proportion to the initial hemodynamic insult (such as in patients with Down syndrome or in patients with transposition of the great arteries). In other circumstances the leading mechanism is represented by the increase of pulmonary venous or LA pressure which activates a complex interplay of molecular, cellular, and matrix factors resulting in intimal hyperplasia, medial thickening, and adventitial fibrosis (such as repaired atroventricular canal, congenital mitral stenosis, congenital pulmonary vein stenosis or other left-sided intracardiac or intravascular lesions); in this latter scenario the term PAH should not be used, since in these patients with very high pulmonary capillary wedge pressure the transpulmonary gradient is preserved or only minimally increased (pulmonary hypertension, PH).

The accepted definition of PAH requires a mean pulmonary arterial pressure above 25 mmHg (at rest) with relatively preserved wedge pressure (<15 mmHg) and elevated PVR above 3 indexed Wood Units. In some patients with open left-to-right shunt lesions (such as ASD), the pulmonary arterial pressure and transpulmonary gradient can be elevated in the setting of high-flow circulation (given the very high Qp/Qs); in these cases the measured PVR can fall within normal limits, though select patients may remain at risk over time for development of further changes in PVR.

In the adult, the failing “right” pulmonary ventricle appears to be less “forgiving” when acutely compromised, and rapid uncorrectable hemodynamic collapse may ensue. Avoidance of large shifts in preload (rapid volume infusion) and afterload (large contrast bolus, embolization) are
important. Therapeutic advances for patients with acquired or congenital pulmonary vascular disease have markedly improved potential for increased quantity and improved quality of life. Historically, the assessment of pulmonary vascular reactivity as a marker for further surgical or medical therapy began in the congenital catheterization laboratories, and it has taken on an increasingly meaningful role in guiding care. Extreme care should be taken to avoid acute confounding in-laboratory worsening of PVR by excessive sedation-induced hypoventilation, anesthetic-induced negative inotropy, pain, hemorrhage, acidemia, or severe alterations of loading conditions. Potential for in-laboratory support with intravenous (prostacyclin) or inhaled (nitric oxide, prostacyclin) pulmonary vasodilators or mechanical assist may be requisites for even basic hemodynamic assessments in such patients. An intensive monitoring environment outside of the catheterization laboratory is needed for optimization and “tailoring” of longer-term management strategies. Acute vasoreactivity to vasodilatory agents (inhaled nitric oxide, inhaled prostacyclin, intravenous prostacyclin, intravenous adenosine, intravenous endothelin antagonists), utilized to estimate PVR for assistance in planning modern medical or surgical strategies, typically increases Qp, and hence lowers PVR as compared to that encountered in real-world environments, free of such vasodilator therapy. PVR measured in such fashion may be sufficiently low as to permit acute convalescence from cardiopulmonary surgery. However, longer-term postoperative well-being of such patients may require additional, longer-term pulmonary vasomodulatory therapy.\(^\text{14,15}\)

Acute vasodilator testing is recommended in every patient with PAH because it will improve risk stratification (responders have usually a better prognosis) and it will guide therapeutic decision (responders usually can be treated with calcium channel blockers) (see Chapter 42). Table 9.6 summarizes indication, route of administration, and dose titration of the most common recommended regimens to perform acute vasodilator testing. The definition of a positive response may vary subtly between testing centers. The most recent and widely accepted definition includes reduction of mean pulmonary arterial pressure of at least 10 mmHg to an actual value below 40 mmHg, with preserved cardiac output.\(^\text{16}\) We usually perform vasodilator testing challenge using inhaled NO due to its associated low rate of major hemodynamic compromise. Caution should be advised for those patients who present with very high capillary wedge pressure at rest (>25 to 30 mmHg) who may experience worsening pulmonary edema in the setting of acute vasodilator testing using inhaled NO.

A complete and patient-specific understanding of the PVR profile is required to guide a number of transcatheter interventions in those patients with left-to-right shunt lesions that may be suitable for percutaneous closure. Improvement in device manufacture, safety testing, and operator experience has led to extension of transcatheter device septal closure to populations with increased risk and less well-defined criteria for intervention, such as the patient with ASD, RV dysfunction, and/or cyanosis (see below). The concept of transcatheter temporary balloon occlusion to mimic the acute physiologic change of defect closure was pioneered by pediatric cardiologists for the management of surgically placed fenestrations in Fontan baffles, establishing criteria to best estimate the long-term cardiopulmonary tolerance of a removal of a pop-off between circulatory systems.\(^\text{17}\) Extrapolation of these criteria to the older adult with RV dysfunction and cyanosis is unsubstantiated, but serves as a guide for at least acute testing of physiologic tolerance. Performance of temporary balloon defect occlusion with compliant large balloon catheters and subsequent measure of change in cardiac output and right atrial pressures is recommended in highest risk patients contemplating catheter-based or surgical ASD closure.\(^\text{18}\) Care must be taken to avoid obstruction of associated flow (e.g., pulmonary veins, mitral valve) that could alter hemodynamics.

### Right Ventricular Outflow Failure

Use of transannular patch repair, persistence or recurrence of right ventricular outflow obstruction, or elevation of distal PA pressure in patients with tetralogy of Fallot may contribute to increased incidence of right ventricular outflow and pulmonary arterial aneurysmal dilation. Criteria for timing of right

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**Table 9.6** Agents for Acute Vasodilator Testing

<table>
<thead>
<tr>
<th>Route of administration</th>
<th>Epoprostenol</th>
<th>Adenosine</th>
<th>Nitric Oxide</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intravenous infusion</td>
<td>Intravenous infusion</td>
<td>Inhaled</td>
</tr>
<tr>
<td>Dose titration</td>
<td>2 ng/Kg/min every 10–15 min</td>
<td>50 μg/Kg every 2 min</td>
<td>None</td>
</tr>
<tr>
<td>Dose range</td>
<td>2–10 ng/Kg/min</td>
<td>50–250 μg/Kg/min</td>
<td>10–80 ppm</td>
</tr>
<tr>
<td>Side effects</td>
<td>Headache, nausea, lightheadedness</td>
<td>Dyspnea, chest pain, atrioventricular block</td>
<td>Increased left heart filling</td>
</tr>
</tbody>
</table>
ventricular outflow reconstruction in this setting remain unknown. In addition right ventricular to PA conduit placement is used to treat a variety of conotruncal malformations including (but not limited to) truncus arteriosus, double outlet right ventricle, transposition of the great arteries with pulmonary stenosis, and pulmonary atresia with intact ventricular septum; in addition the use of pulmonary homograft to restore right ventricle to PA continuity is used in the Ross procedure to treat the spectrum of congenital left ventricular outflow tract obstruction in addition to native pulmonary autograft translocation.

Catheterization of such patients may be indicated to define hemodynamics in the setting of changing exercise capacity or worsening arrhythmia, or to define anatomy in the setting of chest pain or cyanosis with either suspected encroachment of pulmonary venous drainage or pulmonary arterial dissection.

Stent implantation as well as recently introduced percutaneous transcatheater valve implantation offers a reliable and minimally invasive modality to restore right ventricular outflow tract function. Suitability for such interventions requires careful analysis of conduit or reconstructed outflow diameter and length, wall distensibility, and relation with surrounding structures. One key aspect of preimplantation angiographic study visualizes the relationship between coronary arteries and native or reconstructed right ventricular outflow tract. A variety of abnormal course and origin of coronary arteries is described in this group of diseases. In addition, some surgical approaches (such as the Ross procedure) imply coronary artery reimplantation in a nonanatomical position. To avoid coronary artery compression during percutaneous valve implantation, in selected cases, selective coronary angiography is simultaneously performed with balloon dilation of right ventricular outflow tract to assess for dynamic compression of origin or proximal segment of coronary arteries (Figure 9.2) (see Chapter 35).

**Cyanosis**

Long-standing effects of hypoxia-mediated secondary erythrocytosis lessen glomerular filtration rate and increase viscosity, raising risk for contrast-induced acute tubular necrosis and vascular thrombosis. Catheterization should be planned appropriately in such patients, and may be accompanied by preprocedural organized reduction in red blood cell mass. The congenital patient has an increased risk of developing pulmonary parenchymal and ventilatory cyanosis, but congenital or acquired vascular causes of decreased systemic arterial saturation should be sought vigorously in an effort to avoid the long-term ravages of chronic cyanosis and erythrocytosis. Presence of right to left shunting at the level of systemic veins to pulmonary veins, atrial baffle leaks, patent foramen ovale, and PA to pulmonary veins should be explored and potentially treated in the catheterization laboratory. Similarly, pulmonary venous desaturation in the setting of pulmonary venous hypertension due to (a) systolic or diastolic subaortic ventricular failure, (b) AV valve regurgitation, (c) intravascular obstruction or extravascular compression by an enlarging RA or PA should be explored for potential medical, surgical, or transcatheter intervention.

**Systemic Ventricular “Heart Failure”**

The inability of the heart and lungs to meet the metabolic demands imposed by the patient with congenital heart disease may have unique anatomic and physiologic etiologies,
and widely differing therapies than those utilized for children or adults with acquired heart disease (Table 9.7). Use of tailored, hemodynamic-based changes in medical therapy, to date, has not been studied in patients with congenital heart disease.

## Coronary Artery Disease

Patients may have abnormalities of coronary artery origin (e.g., anomalous coronary sinus origin of either the RCA or LCA, or origin of LCA/RCA from the PA, i.e., ALCAPA), passage (intramural or between the great arteries), and vessel characteristics (such as those seen in ALCAPA, Kawasaki disease, or coronary reimplantation during arterial switch for TGA) (see Chapter 16). Definition of such abnormalities combines knowledge of congenital cardiology with expertise in the use of tools of the adult cardiologist (including intravascular ultrasound, TIMI framecount, provocative endothelial function testing), and may ultimately lead to improved understanding of the etiology of and therapy for such diseases.

## Vascular Anatomy Before Cardiac Surgery

Reoperation to treat residual defect, sequelae, or original repair failure is frequently performed in adults and adolescents living with congenital heart disease. In this patient population, repeat sternotomy and initiation of cardiopulmonary bypass can be challenging due to multiple adhesions and unusual structural anatomy. Major bleeding and need for emergent bypass is relatively frequent and some centers pursue routine peripheral vascular access preparation (femoral
or subclavian vessels) to establish emergent cardiopulmonary bypass if needed. Given the relatively frequent compromise of vascular anatomy (with occlusion of femoral, iliac, or subclavian vessels or severe stenosis) due to multiple previous catheterizations and cardiac surgeries, we perform routine IVC and abdominal aorta angiograms in adult patients who undergo presurgical catheterization to document suitability of those vessels for emergent bypass cannulation.

CONCLUSION

Accurate planned and coordinated multidisciplinary care is required for the hemodynamic evaluation of young and older patients with congenital heart disease. Few other circumstances necessitate such an intricate understanding and assessment of
1. interactions between circulations (systemic $\leftrightarrow$ pulmonary)
2. coupling between chambers and circulation (subpulmonary ventricle $\leftrightarrow$ pulmonary arteries, subaortic ventricle $\leftrightarrow$ systemic arteries)
3. coupling between chambers (right $\leftrightarrow$ left ventricles, atroventricular transport post atrial switch repair)
4. unusual and lesion-specific substrate for catheter-based procedures.

Increasing survival and complexity of children with congenital heart disease and the common survival of such children with congenital heart disease into adulthood mandates preparedness on the part of the congenital heart disease physician to provide ready and expert provision of hemodynamic assessment and potential medical, catheter-based (see Chapter 35), and surgical interventions, as appropriate. Future incorporation of physiologic imaging (primary MRI-based imaging for catheter manipulations, intracardiac echocardiography, intravascular ultrasonography, high-fidelity tonometry) with catheter-based diagnostics for this population is anticipated, but the cardiac catheter itself remains an important tool in making these decisions.

REFERENCES

The measurement of dynamic blood pressure has been of interest to physiologists and physicians since 1732, when Reverend Stephen Hales measured the blood pressure of a horse by using a vertical glass tube connected to a brass rod inserted in the femoral artery of the horse (see Chapter 1).\(^1\) Methodology has advanced impressively since then, but with increased technical capability has come greater complexity of instrumentation, such that few physicians today have a firm understanding of the instruments on which they rely.

**THE INPUT SIGNAL: WHAT IS A PRESSURE WAVE?**

Force is transmitted through a fluid medium as a pressure wave, and an important objective of the cardiac catheterization procedure is to assess accurately the forces and therefore the pressure waves generated by various cardiac chambers. A ventricular pressure wave may be considered a complex periodic fluctuation in force per unit area, with one cycle consisting of the time interval from the onset of one systole to the onset of the subsequent systole. The number of times the cycle occurs in 1 second is termed the fundamental frequency of cardiac pressure generation. Thus, a fundamental frequency of two corresponds to a heart rate of 120 beats per minute (bpm). Definitions of terms relevant to the theory and practice of pressure measurement are listed in Table 10.1.

As a complex periodic waveform, the pressure wave may be subjected to a type of analysis developed by the French physicist Fourier, whereby any complex wave form may be considered the mathematical summation of a series of simple sine waves of differing amplitude and frequency (Figure 10.1). Even the most complex waveform can be represented by its own Fourier series, in which the sine wave frequencies are usually expressed as harmonics, or multiples of the fundamental frequency. For example, at a heart rate of 120 bpm, the fundamental frequency is 2 cycles per second (Hz) and the first five harmonics are sine waves whose frequencies are 2, 4, 6, 8, and 10 Hz. The practical consequence of this analysis is that, to record pressure accurately, a system must respond with equal amplitude for a given input throughout the range of frequencies contained within the pressure wave. If components in a particular frequency range are either suppressed or exaggerated by the transducer system, the recorded signal will be a grossly distorted version of the original physiologic waveform. For example, the dicrotic notch of the aortic pressure wave contains frequencies above
Table 10.1  Definitions of Terms Relevant to the Theory and Practice of Pressure Measurement

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pressure wave</td>
<td>Complex periodic fluctuation in force per unit area</td>
</tr>
<tr>
<td></td>
<td>Units: dynes/cm²; 1 dyne/cm² = 1 microbar = $10^{-1}$ N/m² = $7.5 \times 10^{-4}$ mmHg</td>
</tr>
<tr>
<td></td>
<td>mmHg: 1 mmHg = 1 Torr = 1/760 atmospheric pressure</td>
</tr>
<tr>
<td>Fundamental frequency</td>
<td>Number of times the pressure wave cycles in 1 s</td>
</tr>
<tr>
<td>Harmonic</td>
<td>Multiple of the fundamental frequency</td>
</tr>
<tr>
<td>Fourier analysis</td>
<td>Resolution of any complex periodic wave into a series of single sine waves of differing frequency and amplitude</td>
</tr>
<tr>
<td>Sensitivity of pressure measurement system</td>
<td>Ratio of the amplitude of the recorded signal to the amplitude of the input signal</td>
</tr>
<tr>
<td>Linearity</td>
<td>Relationship between input and output of the first order</td>
</tr>
<tr>
<td>Frequency response of pressure measurement system</td>
<td>Ratio of output amplitude to input amplitude over a range of frequencies of the input pressure wave</td>
</tr>
<tr>
<td>Natural frequency</td>
<td>Frequency at which the pressure measurement system oscillates or responds when shock-excited; also, the frequency of an input pressure wave at which the ratio of output/input amplitude of an undamaged system is maximal. Units: cycles/sec, Hz</td>
</tr>
<tr>
<td>Damping</td>
<td>Dissipation of the energy of oscillation of a pressure measurement system owing to friction. Units: damping coefficient, D (see text)</td>
</tr>
<tr>
<td>Optimal damping</td>
<td>Damping that progressively blunts the increase in output/input ratio that occurs with increasing frequency of pressure wave input. Optimal damping can maintain frequency response flat (output/input ratio = 1) to 88% of the natural frequency of the system</td>
</tr>
<tr>
<td>Strain gauge</td>
<td>Variable-resistance transducer in which the strain ($\Delta L/L$) on a series of wires is determined by the pressure on the transducer’s diaphragm. Over a wide range, electrical resistance ($R$) of the wire is directly proportional to $\Delta L/L$</td>
</tr>
<tr>
<td>Wheatstone bridge</td>
<td>Arrangement of electrical connections in a strain gauge such that pressure-induced changes in resistance result in proportional changes in voltage across the bridge</td>
</tr>
<tr>
<td>Balancing a transducer</td>
<td>Interpolating a variable resistance across the output of a Wheatstone bridge/strain gauge transducer so that atmospheric pressure at the zero level (e.g., midchest) induces an arbitrary voltage output on the monitor/recording device (i.e., a voltage that positions the transducer output on the oscilloscopic pressure baseline)</td>
</tr>
</tbody>
</table>
10 Hz. If the pressure measurement system were unable to respond to frequencies greater than 10 Hz, the notch would be slurred or absent.

**PRESSURE MEASURING DEVICES**

The manometer used by Starling, Wiggers, and others was a modification of that devised by Húrlhe in 1898 and illustrated in Figure 10.2. A rubber tambour was coupled with a writing lever that recorded change in pressure on a rotating smoked drum. The system had a high inertia and a low elasticity, giving it a narrow range of usefulness. However, consideration of the mechanics of this primitive system helps give a tangible meaning to key concepts applicable to modern pressure measurement devices.

**Sensitivity**

The sensitivity of such a measurement system is the ability to detect small changes in the input signal. It may be defined as the ratio of the amplitude of the recorded signal to the amplitude of the input signal. With the Húrlhe manometer illustrated in Figure 10.2, the more rigid the sensing membrane, the lower the sensitivity; conversely, the more flaccid the membrane, the higher the sensitivity. This general principle applies to manometers currently in use, where the instrument must be sensitive enough to respond to a small input signal with an adequate output.

**Frequency Response**

A second crucial property of any pressure measurement system is its frequency response. The frequency response of a pressure measurement system may be defined as the ratio of output amplitude to input amplitude over a range of...
frequencies of the input pressure wave. To measure pressure accurately, the frequency response (amplitude ratio) must be constant over a broad range of frequency variation. Otherwise, the amplitude of major frequency components of the pressure waveform may be attenuated while minor components are amplified, so that the recorded waveform becomes a distorted caricature of the physiologic event. Referring again to the Hurthle manometer in Figure 10.2, the range of good frequency response is improved by stiffening the membrane, and it is narrowed by making the membrane more flaccid, because the flaccid membrane cannot respond well to higher frequencies. Thus, frequency response and sensitivity are related reciprocally, and one can be obtained only by sacrificing the other.

Natural Frequency and Damping

A third important concept is the natural frequency of a sensing membrane and how it determines the degree of damping required for optimal recording. If the sensing membrane were to be shock-excited (like a gong) in the absence of friction, it would oscillate for an indefinite period in simple harmonic motion. The frequency of this motion would be the natural frequency of the system. Any means of dissipating the energy of this oscillation, such as friction, is called damping. The dynamic response characteristics of such a system are determined largely by the natural frequency and the degree of damping that the system possesses. The significance of the natural frequency and the importance of proper damping are illustrated in Figure 10.3. The amplitude of an output signal tends to be augmented as the frequency of the input signal approaches the natural frequency of the sensing membrane. The physical counterpart of this augmentation is that the sensing membrane of the pressure transducer vibrates with increasing energy and violence. The same mechanism underlies the fracture of a crystal glass when an opera singer vocalizes the appropriate input frequency. Damping dissipates the energy of the oscillating sensing membrane, and optimal damping dissipates the energy gradually, thereby maintaining the frequency response curve nearly flat (constant output/input ratio) as it approaches the region of the pressure measurement system's natural frequency.

As an analogy to further help the reader understand the significance of damping, consider the simple case of a weight suspended from a spring. If the weight is displaced and then released, the stretched spring recoils so that the weight moves past its original position and then oscillates up and down. In the absence of frictional forces (damping), the oscillation would continue indefinitely at a frequency determined by the stiffness of the spring and an amplitude determined by the mass of the weight. In practice there is always some damping, and this has two effects: the amplitude of the oscillations gradually diminishes, and the frequency of oscillation is reduced. This second important consequence of damping—reduction of the natural frequency of a system—is not widely appreciated. If we continue with our analogy, imagine that the spring and its weight are suspended in a jar of syrup or honey; the spring will clearly vibrate with lesser amplitude of vibration and lesser frequency than before. The effect of the viscous medium is to further damp the oscillations. If the medium's viscosity is high enough, it prevents any overshoot or oscillation: the weight returns to its original position regardless of its initial displacement. Further damping at this point simply slows the return of the weight to its equilibrium position, thereby depressing the frequency response characteristics of the system. Therefore, damping helps to prevent overshoot artifacts resulting from resonance of the system, but at the cost of diminished frequency response.

Linearity

Linearity is an additional critical component of recording systems, and it exists when the relationship between the input signal and the output signal is of the first order. Linearity

![Figure 10.3](image-url) Frequency-response curves of a pressure measurement system, illustrating the importance of optimal damping. The amplitude of an input signal tends to be augmented as the frequency of that signal approaches the natural frequency of the sensing membrane. Optimal damping dissipates the energy of the oscillating sensing membrane gradually and thereby maintains a nearly flat natural frequency curve (constant output/input ratio) as it approaches the region of the pressure measurement system's natural frequency (see text). D, damping coefficient.
allows the use of a single calibration factor for different amplitudes of the input signal.

**WHAT FREQUENCY RESPONSE IS DESIRABLE?**

Wiggers\(^3\) suggested that the shortest significant vibrations contained within physiologic pressure waves have one-tenth the period of the entire pressure curve—that is, the essential physiologic information is contained within the first 10 harmonics of the pressure wave’s Fourier series. At a heart rate of 120 bpm, the fundamental frequency is 2 Hz and the tenth harmonic is 20 Hz. Therefore, a pressure measurement system with a frequency response range that is flat to 20 Hz should be adequate in such a circumstance, and support for this hypothesis has come from experimental work comparing high frequency-response systems with conventional catheter systems.\(^5\)

The useful frequency-response range of commonly used pressure measurement systems is usually <20 Hz unless special care is taken. Wood and colleagues\(^6\) and Gleason and Braunwald\(^7\) found that frequency response was flat to <10 Hz with small-bore (6F) catheters attached to standard strain gauge manometers.

To ensure a high frequency-response range, the pressure measurement system must be set up in such a way that it has the highest possible natural frequency as well as optimal damping. The natural frequency is directly proportional to the lumen radius of the catheter system. It is inversely proportional to the length of the catheter and associated tubing and to the square root of the catheter and tubing compliance and the density of fluid filling the system. The highest natural frequency is obtained by using a short, wide-bore, stiff catheter connected to its transducer without intervening tubing or stopcocks and filled with a low-density liquid from which small air bubbles, which increase compliance, have been excluded (e.g., boiled saline solution). Such a system is impractical for routine use, but deviation from it occurs only at a significant sacrifice.

If such a system is constructed, it will be found to be grossly underdamped (Figure 10.3). Accordingly, it is important to introduce damping into the system to keep the frequency response flat as the frequency of the input signal approaches the natural frequency of the pressure measurement system. With optimal damping, the frequency response can be maintained flat (±5%) to within 88% of the natural frequency, according to Fry,\(^4\) although it is unusual to achieve >50% in most laboratories. Damping may be introduced by interposing a damping needle between the catheter and manometer\(^8\) and gradually shortening it until optimal damping is obtained, by filling the manometer or tubing with a viscous medium such as Renografin (a radiographic contrast agent), or by any of several other methods.

**EVALUATION OF FREQUENCY RESPONSE CHARACTERISTICS**

Ideally, the frequency-response characteristics of a pressure measurement system should be evaluated using a sine wave pressure generator to construct curves similar to those seen in Figure 10.3. By altering the characteristics of the system discussed in the previous section, a reasonable compromise between frequency response, damping, and practicality can be achieved for each laboratory. An example of the use of this device in estimating frequency response of a pressure measurement system is provided in Figure 10.4.

Another method, which does not require the use of such a pressure waveform generator, is described here. This technique may be used for measuring the dynamic response characteristics of a pressure measurement system.

The catheter to be studied is connected by means of a three-way stopcock with or without intervening tubing to one arm of a strain gauge transducer (Figure 10.5). The transducer used should be of the low-volume-displacement type (small chamber capacity) to enhance frequency response. The tip of the catheter is snugly projected through a hole in a no. 6 rubber stopper, which is tightly inserted into the cutoff barrel of a 60 mL plastic syringe. The syringe plunger is removed, and the barrel is fixed in a vertical position, pointing downward, so that the catheter enters from below. The manometer and catheter are filled with saline solution, care being taken to avoid even small air bubbles, and the catheter is flushed until the catheter tip and holes are submerged in approximately 30 mL of saline solution. The plunger is slowly inserted into the syringe, producing an upward deflection of the pressure trace on the oscilloscope. When the trace comes to rest at the top of the oscilloscope, the recorder is turned on at rapid paper speed and the plunger is suddenly withdrawn. This method, modified from Hansen,\(^8\) produces shock-excitation vibrations of the type seen in Figure 10.6. The mathematical foundation for analysis of such a shock excitation has been described by Wiggers\(^3\) and Fry\(^4\) and may be summarized as follows:

The frequency of the after-vibrations produced by shock excitation is the damped natural frequency of the system. This is obtained by measuring the time, \(t\), between two successive vibrations and obtaining the damped natural frequency, \(N_0\), as \(1/t\). In the example in Figure 10.6, \(N_0 = 1/0.04 = 25\) Hz. Next, the damping coefficient, \(D\), is calculated as a function of the ratio by which successive single vibrations decrease. In Figure 10.6, this may be calculated from the ratio of \(x_2\) to \(x_1\), the percent overshoot

\[
D = \sqrt{\ln(\frac{x_2}{x_1})/\left[\pi^2 + \ln(\frac{x_2}{x_1})\right]} \quad (10.1)
\]

where \(\ln(x_2/x_1)\) is the natural logarithm of the percent overshoot. In our example, \(x_2/x_1 = 0.093, \ln(x_2/x_1) = -2.379, and\)
Figure 10.4

Left ventricular pressure (center) measured with a fluid-filled standard catheter and micromanometer (catheter-tip pressure manometer) in a patient undergoing cardiac catheterization. **Left and right.** In vitro frequency response for micromanometer (upper) and fluid-filled (lower) systems. The left panel recordings were obtained by continuously increasing the input frequency of a sine wave pressure waveform from 2 to 200 Hz. The fluid-filled system resonated (natural frequency) at 37 Hz but was flat (±5%) only to 12 Hz. Therefore its useful range is only to approximately 12 Hz. The right panel shows the response of each system to a square wave pressure input signal. (From Nichols WW, Pepine CJ, Millar HD, et al. Percutaneous left ventricular catheterization with an ultraminiature catheter-tip pressure transducer. *Cardiovasc Res* 1978;12:566; with permission.)

Figure 10.5

Practical evaluation of dynamic response characteristics of a catheter–transducer system. The catheter hub is connected by means of a three-way stopcock to one arm of a low-volume-displacement pressure transducer. The tip of the catheter is snugly projected through a hole in a no. 6 rubber stopper, which is tightly inserted into the cutoff barrel of a 60 mL plastic syringe. The manometer and catheter are filled with saline solution, care being taken to avoid even small air bubbles, and the catheter is flushed until the catheter tip and holes are submerged in approximately 30 mL of saline solution. Next, the plunger is slowly inserted into the syringe, producing an upward deflection of the pressure trace on the oscilloscope of the recording apparatus. When the pressure trace comes to rest at the top of the oscilloscope screen, the recorder is turned on and the plunger is suddenly withdrawn from the syringe barrel. Dynamic response characteristics are then calculated as shown in Figure 10.6.
In example B, \( t = 40 \text{ msec}, N_0 = 1/t = 25 \text{ cycles/second} \)
\[ D = \sqrt{\ln^2(x_2/x_1) / \left[ \left( \frac{x^2}{x_1} \right)^2 + \ln^2 \left( \frac{x_2}{x_1} \right) \right]} = 0.603 \]
\[ N = N_0 / \sqrt{1 - D^2} = 31.3 \text{ cycles/second} \]

**Figure 10.6** Records of dynamic frequency-response characteristics obtained from the system illustrated in Figure 10.5. A, B, and C. Progressive increases in damping produced by introducing increasing amounts of a viscous radiographic contrast agent (Renografin-76) into the catheter–transducer system. The catheter was 80 cm long, and its diameter was 8F. A. Underdamped. B. Almost optimally damped. C. Overdamped. The percent overshoot \((x/x_1)\) is used in the calculation of the damping coefficient, D. The undamped natural frequency, \(N\), is calculated from D and the damped natural frequency, \(N_0\). Time lines are 20 milliseconds. Using the curves shown in Figure 10.3 for various values of D, the frequency response of the system in B can probably be considered flat (±5%) to 0.88 \(N\), or 27.5 Hz.

D = 0.603. From the damping coefficient D and the damped natural frequency \(N_0\), we may determine the undamped natural frequency \(N\) as
\[ N = N_0 / \sqrt{1 - D^2} \quad (10.2) \]

A simple practical goal is to try to regulate the damping of an actual pressure measurement system so that its damping coefficient is as close to 0.64 (so-called optimal damping) as possible. At this value, the pressure measurement system shows uniform frequency response (±5%) to about 88% of its natural frequency, according to Fry. If such optimal damping is achieved for the system illustrated in Figure 10.6, its frequency response could be considered flat to 0.88 \(N\), or 27.5 Hz. Improperly damped systems with low natural frequencies (because of small air bubbles or excessively compliant tubing) may achieve uniform frequency response to <10 Hz.

**TRANSFORMING PRESSURE WAVES INTO ELECTRICAL SIGNALS: THE ELECTRICAL STRAIN GAUGE**

Pressure measurement systems today generally use electrical strain gauges based on the principle of the Wheatstone bridge. In its simplest form, the strain gauge is a variable-resistance transducer whose operation depends on the fact that when an electrical wire is stretched, its resistance to the flow of current increases. As long as the strain remains well below the elastic limit of the wire, there is a wide range within which the increase in resistance is accurately proportional to the increase in length.

Figure 10.7 illustrates how the Wheatstone bridge uses this principle in converting a pressure signal to an electrical signal. In this schematic representation of a pressure transducer, pressure is transmitted through port P and acts on diaphragm D, which is vented to atmospheric pressure on its opposite side. In the illustration, the diaphragm is attached on its undersurface to a plunger, which in turn is attached to four wires, \(G_1\) through \(G_4\), as illustrated. The manner of attachment is such that increased pressure on the diaphragm stretches and therefore increases the electrical resistance of \(G_1\) and \(G_2\) and has the opposite effect on \(G_3\) and \(G_4\). In the Wheatstone bridge, \(G_1\), \(G_2\), \(G_3\), and \(G_4\) are connected electrically as in Figure 10.8 and are attached to a voltage source, B. If all four resistances are equal, then exactly half the voltage of battery B exists at the junction of \(G_1\) and \(G_2\) and half at the junction of \(G_3\) and \(G_4\), therefore, no current flows between the output terminals. However, when pressure is applied to the diaphragm (Figure 10.7), the resistances are unbalanced, so that the junction of \(G_1\) and \(G_2\) becomes negative, and a current flows across the output terminals.

Because movement of the diaphragm (D) in Figure 10.7 is necessary to produce current flow in the Wheatstone bridge, a certain volume of fluid must actually move through the catheter and connecting tubing to produce a recorded pressure. Therefore, the use of a low-volume-displacement
Strain gauge connection of the Wheatstone bridge. In this arrangement, if all resistances are equal, then exactly half the voltage of battery B exists at the junction of G₁ and G₂, and half at the junction of G₃ and G₄; therefore, no current will flow between the output terminals. However, when pressure is applied to the diaphragm (see Figure 10.7), the resistances are unbalanced, so that the junction of G₁ and G₄ becomes negative and a current flows across the output terminals.

transducer with a small chamber volume improves the frequency-response characteristics of the system.

Balancing a transducer is simply a process whereby a variable resistance (the R balance of most amplifiers) is interpolated into the circuit (Figure 10.8) so that at an arbitrary baseline pressure, the voltage across the output terminal can be reduced to zero. Some amplifiers use an alternating current signal in place of the DC current source shown in Figure 10.8. When these carrier current amplifiers are used, a variable capacitor (the C balance) must be used in addition to the variable resistor to balance the bridge.

**Figure 10.7** Schematic representation of a strain gauge pressure transducer. Pressure is transmitted through port P and acts on diaphragm D, which is vented to atmospheric pressure on its opposite side. Pressure causes the diaphragm to stretch, in turn stretching and therefore increasing the resistance of wires G₁ and G₄, while having the opposite effect on wires G₂ and G₃. The wires are electrically connected as shown in Figure 10.8.

**Figure 10.8** Strain gauge connection of the Wheatstone bridge. In this arrangement, if all resistances are equal, then exactly half the voltage of battery B exists at the junction of G₁ and G₂, and half at the junction of G₃ and G₄; therefore, no current will flow between the output terminals. However, when pressure is applied to the diaphragm (see Figure 10.7), the resistances are unbalanced, so that the junction of G₁ and G₄ becomes negative and a current flows across the output terminals.

Incorporating all the principles discussed so far in this chapter, many laboratories have settled on a practical system in which a fluid-filled catheter is attached by means of a manifold to a small-volume-displacement strain gauge type pressure transducer (Figures 10.9 and 10.10).

The system illustrated is used for pressure measurement from the right side of the heart and for arterial monitor lines. The system used for left-sided heart pressure measurement is more complex because it also incorporates ports for radiographic contrast administration and blood discard, as well as a syringe for coronary angiography (see also Chapters 6 and 15). Virtually all catheterization laboratories use relatively inexpensive, sterile, disposable pressure transducers in which a tiny integrated circuit on a thin silicon diaphragm serves as the sensing element. Fluid pressure is transmitted to this element through a gel medium, bending the circuit and altering the resistance of resistors in the silicon diaphragm. The circuit delivers an electrical output proportional to the pressure being applied, as discussed previously.

To the first side arm of the manifold (Figure 10.9), a fluid-filled connecting tube is attached, the distal end of which is connected to the transducer through a stopcock (see above). The second side arm is connected by a fluid-filled tube to a pressurized flush bag containing heparinized saline solution. The cardiac catheter is connected directly to the front of the manifold through a built-in rotating adapter. By turning the stopcock attached to the flush solution, the operator can flush the catheter intermittently (e.g., every 3 minutes) to clear blood, or flush directly the transducer with the transducer stopcock turned in the opposite way. Turning this stopcock the other way permits filling a syringe connected to the manifold. With this system, a frequency response that is flat (±5%) up to 20 Hz can be achieved routinely. Figure 10.11 illustrates an alternative set up of the manifold, which includes a separate zero line and which allows keeping the transducer on the table and connected directly to the manifold. With this set up, the exit port of the zero line must be positioned at the appropriate height. The establishment of a zero reference is an important practical undertaking that must be accomplished as a part of each catheterization procedure. Midchest level is used widely as zero reference, because fluoroscopic visualization in a lateral projection confirms that the left ventricle and aorta are generally
located midway between the sternum and the table top when the patient is supine. However, the validity of choosing the midchest level for zero reference has been challenged in an excellent study by Courtois et al. They carefully examined the influence of hydrostatic forces (caused by the effects of gravity) and concluded that intracardiac pressures should be referenced to an external fluid-filled transducer aligned with the uppermost blood level in the chamber where pressure is being measured. In practical terms, for measurement of left ventricular and aortic pressure, the zero level should...
Figure 10.11  Alternative set up for a pressure manifold for pressure measurement. The catheter is connected by a stopcock to a manifold, which is connected at its other end to a small-volume fluid-filled pressure transducer. The manifold’s two side arms are connected by fluid-filled tubing to a zero-pressure reference level and to a pressurized flush solution. Thus, this set up includes a separate zero line, which should be positioned at the appropriate height as shown in Figure 10.14.

be positioned approximately 5 cm below the left sternal border at the fourth left intercostal space (LICS) (Figure 10.12). This eliminates the gravitational/hydrostatic effect of a column of blood above the catheter tip and within the ventricular chamber (Figure 10.13). Although the right ventricle and left atrium are at different levels in the chest than the left ventricle, Courtois et al. calculated that the error introduced by use of a point 5 cm below the fourth LICS, at the left sternal border, is approximately ±0.8 mmHg for chambers other than the left ventricle.

If a decision has been made to use the midchest level for zero reference, each case should begin with measurement of the patient’s anteroposterior (AP) thoracic diameter at the level of the angle of Louis. This is can be done with the use of a large square x-ray caliper as illustrated in Figure 10.14, or with an “outside” chest caliper. The patient then lies supine on the catheterization table and is draped and otherwise prepared for catheterization (a 12-lead electrocardiogram is recorded, skin sites are shaved and cleansed), and the zero level is established on an adjustable pole attached to the side of the table. This is accomplished with the use of a yardstick to which a carpenter’s level has been taped. One end of the yardstick is placed on the patient’s sternum at the angle of Louis and the other end against the adjustable metal pole. As illustrated in Figure 10.15, the transducers are mounted on the metal pole and their height can be adjusted as needed once the appropriate midchest level (one half of the patient’s AP diameter below the angle of Louis), or the 5 cm level below the left sternal border at the fourth LICS has been identified. An alternative method includes connecting all the transducers to a Morse manifold (NAMIC, Medical Products Division, Hudson Falls, NY) or similar device that can be moved up and down the metal; one end of the zero line (clear polyethylene tubing) is connected to the manifold, and the other end is connected to the pressure measurement manifold (Figure 10.14). The zero line, manifold, and pressure transducer are next filled with saline from the flush line so that the pressure transducer can be connected directly with the zero line by the turn of a stopcock on the pressure manifold. It is critical to remove any air bubble, as air bubbles result in an underdamped pressure waveform. In the past, pressure transducers were calibrated by means of a mercury manometer attached to a free port on the Morse manifold. The manometer would be inflated to a 100 mmHg pressure transmitted through the fluid-filled zero line to all pressure transducers to be used in a particular case (e.g., left heart.

Figure 10.12  Schematic representation of measured heights for an external fluid-filled transducer reference position relative to the anterior chest wall at a midchest level and at the uppermost blood level (H) in the left ventricle in seven patients. (Reproduced with permission from: Courtois M, Fattal PG, Kovacs SJ Jr, Tiefenbrunn AJ, Ludbrook PA. Anatomically and physiologically based reference level for measurement of intracardiac pressures. Circulation 1995;92:1994–2000.)
right heart, arterial monitor). Modern pressure transducers are precalibrated and many manufactures provide electronic devices to validate calibration. Otherwise, the free port of the Morse manifold is left open to air, in communication with the individual zero lines of the various left and right heart manifold systems by way of the series of stopcocks that constitute the Morse manifold, thus referencing all the transducer systems to a common zero level.

### PHYSIOLOGIC CHARACTERISTICS OF PRESSURE WAVEFORMS

**Reflected Waves**

Recognizing the appearance of normal pressure waveforms is a prerequisite to identifying abnormalities that characterize certain cardiovascular disorders. As shown in Figure 10.16 forward pressure and flow waves, as seen in the central aorta, are intrinsically identical in shape and timing. The pressure wave is modified by summation with a reflected pressure wave \( (P_{\text{backward}}) \), and the resultant measured central aortic pressure wave shows a steady increase throughout ejection\(^{10,11} \) (Figure 10.17). The flow wave is also modified by summation with a reflected flow wave \( (F_{\text{backward}}) \), but because flow is directional, \( F_{\text{backward}} \) reduces the magnitude of flow in late ejection, giving the characteristic \( F_{\text{measured}} \) as is seen with aortic flowmeters or Doppler signals.

The reflections for pressure occur from many sites within the arterial tree, but the major effective reflection site in humans appears to be the region of the terminal abdominal aorta.\(^{10} \) As seen in Figure 10.18, ascending aortic pressure is increased substantially within one beat after bilateral occlusion of the femoral arteries by external manual compression. High-speed recordings (Figure 10.18, right) show that the major part of the increase in pressure occurs late in systole, consistent with an increase in the magnitude of the reflected pressure.

Various factors influence the magnitude of reflected waves (Table 10.2). Pressure reflections are diminished during the strain phase of the Valsalva maneuver,\(^{11} \) with the result that pressure and flow waveforms become similar in appearance (Figure 10.19). After release of the Valsalva strain, reflected waves return and are exaggerated. Therefore, the commonly noted late-peaking appearance of central aortic and left ventricular pressure tracings in humans (Figure 10.20), referred to as the type A waveform pattern,\(^{11} \) is a result of strong pressure reflections in late systole. In addition to the Valsalva maneuver, pressure reflections are diminished during hypovolemia, hypotension, and in response to a variety of vasodilator agents (Table 10.2). In these circumstances, the left ventricular and central aortic pressure waves exhibit a type C pattern (Figure 10.20). However, vasoconstriction and hypertension may be expected to accentuate the normal type A waveform. Because the contribution of reflections to the arterial
A pressure waveform should move earlier in systole the closer one gets to the source of the reflections, it is not surprising that the pressure peaks earlier as the catheter is withdrawn from the central aorta to the periphery (Figure 10.21).

Reflected waves can be of substantial magnitude (Figure 10.17) and are increased in the patient with heart failure. Laskey and Kussmaul showed that reflected pressure waves were increased in amplitude in 17 patients with heart failure secondary to idiopathic dilated cardiomyopathy, often producing an exaggerated dicrotic wave. The magnitude of these reflections did not decrease consistently during exercise, as is characteristic of the normal circulation. Infusion of sodium nitroprusside intravenously markedly reduced the magnitude of the reflected pressure waves and delayed their timing; both these changes were deemed beneficial with regard to left ventricular systolic load.

Wedge Pressures

A physiologic aspect of pressure measurement that has been of interest for many years is the concept of the “wedge pressure.” Broadly stated, a wedge pressure is obtained when an end-hole catheter is positioned in a designated blood vessel with its open end-hole facing a capillary bed, with no connecting vessels conducting flow into or away from the designated blood vessel between the catheter tip and the capillary bed. A true wedge pressure can be measured only in the absence of flow. In the absence of flow, pressure equilibrates across the capillary bed so that the catheter-tip pressure is equal to that on the other side of the capillary bed. If minimal damping occurs between the catheter tip and the opposite side of the capillary bed—that is, if there is a large, relatively dilated capillary bed, if the precapillary arterioles and postcapillary venules are not constricted, and if there is no other source of obstruction, such as the presence of microthrombi—phasic as well as mean pressure may be transmitted to the wedged catheter. Thus, an end-hole catheter wedged in a hepatic vein may be used to measure portal venous pressure; a catheter wedged in a distal pulmonary artery measures pulmonary venous pressure; and if it is wedged in a pulmonary vein, it measures pulmonary artery pressure. The details involved in measurement of pulmonary artery wedge pressure, commonly termed pulmonary capillary wedge pressure, are discussed in Chapter 6. Properly performed, this determination accurately measures pulmonary venous pressure. In the absence of cor triatratium or obstruction to pulmonary venous outflow, the pulmonary venous and left atrial pressures are equal, so that pulmonary artery wedge pressure may be used as a substitute for left atrial pressure. Issues of damping and time delay need to be considered when using this pressure to assess a transmitral gradient in a patient with mitral stenosis or prosthetic valve obstruction. These issues have been addressed by Lange et al.

NORMAL CONTOURS OF PRESSURE WAVEFORMS

Atrial Pressure

The atrial pressure waveform includes three positive waves, the a, c, and v waves, and three negative waves or descents, the x, x1, and y descent (Figure 10.22). The a wave corresponds to atrial contraction and it occurs within the PR interval. It is followed by the x descent, which corresponds to atrial relaxation, and which is absent in patients with atrial fibrillation. The x descent is followed by the positive c wave, due to a slight increase in atrial pressure following closure of the atrioventricular valve at the beginning of ventricular systole and its bulging into the atrium. During ventricular
systole, continuous atrial relaxation and the descent of the atrioventricular valve annulus result in further reduction of atrial pressure and the corresponding $x_1$ descent. Venous return to the atrium while the atrioventricular valve is closed leads to a progressive increase in atrial pressure ($v$ wave) which is then followed by the $y$ descent after opening of the atrioventricular valve and rapid emptying of the atrium (Figure 10.22). The left and right atrial pressure contours are similar, with the left atrial pressure being generally higher than the right atrial pressure and with a more prominent $V$ wave in the left atrial pressure contour. As described in Chapter 23, hemodynamic changes secondary to the development of constrictive or tamponade physiology result in characteristic changes in the atrial pressure contour.

**Ventricular Pressure**

The ventricular pressure waveform is characterized by a systolic and a diastolic phase. As ventricular systole begins, pressure rises and the atrioventricular valve closes. The end diastolic point corresponds to the beginning of ventricular systole, and it is timed to the peak or nadir of the QRS complex.

![Graph showing ventricular pressure](image1)

**Figure 10.16** Central aortic pressure ($P$) and flow ($F$) measured in a patient during cardiac catheterization. Computer-derived forward and backward pressure and flow components are shown individually: their sum results in the measured waves. (See text for discussion.) (From Murgio JP, Westerhof N, Giolma JP, et al. Manipulation of ascending aortic pressure and flow wave reflections with Valsalva maneuver: relationship to input impedance. *Circulation* 1981;63:122, with permission.)
complex. Closing of the atroventricular valves is followed by the isovolumic contraction phase, characterized by a raise in intraventricular pressure without a change in volume until the opening of the semilunar valve (Figure 10.23). The ejection phase then ensues following opening of the semilunar valve and it ends with the closing of the valve. This phase is followed by isovolumic relaxation, which ends with opening of the atroventricular valve and the beginning of diastolic ventricular filling. The ventricular pressure continues to fall at the beginning of rapid filling, reaching a minimum after which the pressure starts raising and ends with a positive wave corresponding to the contribution of atrial systole to ventricular filling. The diastasis corresponds to the phase of diastole characterized by a gradual increase in left ventricular diastolic pressure without a significant increase in volume.

Aortic Pressure

The contour of the aortic pressure is the result of the forward wave and reflected waves. It should be noted that the arterial pressure might rise slightly during isovolumic contraction of the left ventricle. The mechanism is similar to the mechanism behind the c wave in the atrial pressure waveform, and is due to bulging of the semilunar valve in the aorta. At the end of the isovolumic ventricular contraction phase, with opening of the aortic valve, the ejections phase begins and the aortic pressure starts rising. The initial steep increase is followed by a peak and then by a decline to the dicrotic notch, which corresponds to closure of the aortic valve and end of ejection.

Sources of Error and Artifact

Even when every effort has been made to design a pressure measurement system with high sensitivity, uniform frequency response, and optimal damping, distortions and inaccuracies in the pressure waveform may occur. Some common sources of error and artifact in clinical
pressure measurement include deterioration in frequency response, catheter whip artifact, end pressure artifact, catheter impact artifact, systolic pressure amplification in the periphery, and errors in zero level, balancing, and calibration.

### Deterioration in Frequency Response

Although frequency response may be high and damping optimal during setup of the transducers, substantial deterioration in the characteristics can develop during the course of a

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**Figure 10.18** Ascending aortic (ASC Ao) pressure waveform in a patient before and after bilateral occlusion of the femoral arteries by external manual compression (left arrow). On the right, high-speed recordings show that the major portion of the increase in pressure results from augmentation of the late (reflected) wave. ECG, electrocardiogram. (From Murgo JP, Westerhof N, Giolma JP, et al. Aortic input impedance in normal man: relationship to pressure wave forms. *Circulation* 1980;62:105, with permission.)

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**Table 10.2** Factors that Influence the Magnitude of Reflected Waves

<table>
<thead>
<tr>
<th>Factors that augment pressure wave reflections</th>
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<tbody>
<tr>
<td>Vasoconstriction</td>
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<td>Heart failure</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Aortic or iliofemoral obstruction</td>
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<tr>
<td>Valsalva maneuver—after release</td>
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<table>
<thead>
<tr>
<th>Factors that diminish pressure wave reflections</th>
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<tbody>
<tr>
<td>Vasodilation</td>
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<tr>
<td>Physiologic (e.g., fever)</td>
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<tr>
<td>Pharmacologic (e.g., nitroglycerin, nitroprusside)</td>
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<tr>
<td>Hypovolemia</td>
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<tr>
<td>Hypotension</td>
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<tr>
<td>Valsalva maneuver—strain phase</td>
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</tbody>
</table>
Figure 10.19 Measurements of central aortic pressure ($P_m$) and flow ($F_m$) in a patient performing Valsalva maneuver during cardiac catheterization. Control, Valsalva strain, and post-Valsalva release tracings are shown. $P_m$ is the sum of forward ($P_f$) and backward or reflected ($P_b$) pressure waves; $F_m$ is the sum of $F_f$ and $F_b$. (See text for discussion.) (From Murgu JP, Westerhof N, Giolma JP, et al. Manipulation of ascending aortic pressure and flow wave reflections with Valsalva maneuver: relationship to input impedance. *Circulation* 1981;63:122, with permission.)

catheterization study. Air bubbles may be introduced into the catheters, stopcocks, or tubing, or dissolved air may come out of the saline solution used to fill the transducer (just as dissolved air may come out of solution in a glass of water allowed to stand unperturbed for a few hours). Even the smallest air bubbles have a drastic effect on pressure measurement because they cause excessive damping and lower the natural frequency (by serving as an added compliance). When the natural frequency of the pressure measurement system falls, high-frequency components of the pressure waveform (such as those that occur with intraventricular pressure rise and fall) may set the system in oscillation, producing the ventricular pressure overshoot commonly seen in early systole and diastole (Figures 10.4 and 10.24). Flushing out the catheter, manifold, and transducer dispels these small air bubbles and restores the frequency response of the pressure measurement system (Figure 10.25).

**Catheter Whip Artifact**

Motion of the tip of the catheter within the heart and great vessels accelerates the fluid contained within the catheter. Such catheter whip artifacts may produce superimposed waves of ±10 mmHg. Catheter whip artifacts are particularly common in tracings from the pulmonary arteries and are difficult to avoid.

**End Pressure Artifact**

Flowing blood has a kinetic energy by virtue of its motion, and when this flow suddenly comes to a halt, the kinetic energy is converted into part into pressure. Therefore, an end-hole catheter pointing upstream (e.g., radial or femoral arterial pressure monitoring line) records a pressure that is artifically elevated by the converted kinetic energy. This added pressure may range from 2 to 10 mmHg.

**Catheter Impact Artifact**

Catheter impact artifact is similar but not identical to catheter whip artifact. When a fluid-filled catheter is hit (e.g., by valves in the act of opening or closing or by the walls of the ventricular chambers), a pressure transient is created. Any frequency component of this transient that coincides with the natural frequency of the catheter–manometer system causes a superimposed oscillation on the recorded pressure wave.
Catheter impact artifacts are common with pigtail catheters in the left ventricular chamber, where the terminal pigtail may be hit by the mitral valve leaflets as they open in early diastole.

**Systolic Pressure Amplification in the Periphery**

When radial, brachial, or femoral arterial pressures are measured and used to represent aortic pressure, it must be remembered that peak systolic pressure in these arteries may be considerably higher (e.g., by 20 to 50 mmHg) than peak systolic pressure in the central aorta (Figures 10.17 and 10.18), although mean arterial pressure will be the same or slightly lower. There has been debate concerning the mechanism of this amplification of systolic pressure. McDonald and Murgo presented convincing evidence that the change in waveform of arterial pressure as it travels away from the heart is largely a consequence of reflected waves. These waves, presumably reflected from the aortic bifurcation, arterial branch points, and small peripheral vessels, reinforce the peak and trough of the antegrade pressure waveform, causing amplification of the peak systolic and pulse pressures (Figure 10.26). The peripheral arterial systolic pressure may appear to be 20 mmHg higher than the left ventricular systolic pressure as a result of this phenomenon. This pressure amplification in the periphery is particularly marked in the radial artery (Figures 10.26 and 10.27), especially if there is also some end pressure artifact, and may mask and distort pressure gradients across the aortic valve or left ventricular outflow tract. Use of a double-lumen catheter (e.g., double-lumen pigtail) allows measurement of left ventricular and central aortic pressures simultaneously, thus avoiding this problem. Another method is the transeptal technique with a second catheter in the central aorta (see Chapter 6) and a third method is to use another pigtail catheter inserted from the contralateral femoral artery. Finally, special attention to performing careful pullback tracings may also help the operator to avoid this particular error.

The operator should record central aortic pressure together with peripheral arterial pressure routinely, immediately before entering the left ventricle during retrograde left heart catheterization. If this tracing shows a reverse gradient (peak systolic pressure in periphery higher than in central aorta), the amount of this pressure difference must be considered when subsequent comparisons of left ventricular and systemic arterial pressure are made for the detection of aortic or subaortic stenosis. If any doubt exists concerning the presence of a true pressure gradient, either a double-lumen left heart catheter or a second central aortic catheter should be introduced to measure accurately the gradient across the aortic valve.
Figure 10.21 Pressure waveforms in a patient undergoing cardiac catheterization, as a function of distance from the aortic valve (Ao V). Ao, aorta; ASC, ascending; Hi D, high descending; MID T, midthoracic; DIAP, diaphragmatic; ABD, abdominal; TERM, just above aortic bifurcation; ECG, electrocardiogram. First vertical line marks onset of primary (forward) pressure wave, which occurs progressively later after the QRS complex with increasing distance from the aortic valve. Second vertical line marks onset of secondary pressure rise associated with the backward or reflected pressure wave. See text for discussion. (From Murgo JP, Westerhof N, Giolma JP, et al. Aortic input impedance in normal man: relationship to pressure wave forms. *Circulation* 1980;62:105, with permission.)

Figure 10.22 Simultaneous left atrial and ventricular pressure recording in a patient with mitral stenosis. See text for the description of the components of the atrial pressure waveform.
Errors in Zero Level, Balancing, or Calibration

Error in the quantitation of pressures because of improper zero reference is common. As mentioned earlier, in many laboratories the zero-reference point is taken at the midchest with the patient supine, although some laboratories use a point 10 cm vertically up from the back or 5 cm vertically down from the sternal angle. All manometers must be zeroed at the same point (Figures 10.10 and 10.14), and the zero-reference point should be changed if the patient’s position is changed during the course of the study (e.g., if pillows are placed to prop up the patient). Transducers requiring calibration should be calibrated before each period of use. Electrical calibration signals and calibration factors can usually be relied on as a substitute for mercury calibration, but they should be confirmed against a standard mercury reference. Linearity of response should be checked by using mercury inputs of 25, 50, and 100 mmHg. If possible, all transducers should be exposed to the calibrating system simultaneously to avoid false gradients caused by unequal amplification of the same pressure signal. In the system described here (Figure 10.10), a bubble in the zero-reference line can result in a false zero level; therefore, in tracking down an unexpected pressure gradient, flushing of the zero line is an important initial step, followed by rebalancing all the transducers. If the unexpected gradient persists, catheter attachments should be switched between the two involved manifolds. An artifactual gradient reverses direction, whereas a true gradient persists after this maneuver.

MICROMANOMETERS

To reduce the mass and inertia of the pressure measurement system, improve the frequency-response characteristics, and decrease artifacts associated with underdamping, overdamping, and catheter whip, miniaturized transducers...
Figure 10.25 Pitfalls in measurements of the left ventricular diastolic pressure. All measurements were obtained in the same patient. **Left Panel:** The left ventricular end diastolic pressure is markedly elevated, and there is an abnormal contour of the pressure waveform. The abnormal contour and elevation of left ventricular diastolic pressure is due to inappropriate position of the left ventricular pigtail catheter, with a side hole in the ascending aorta. **Middle Panel:** There is an early diastolic overshoot, which is due to an air bubble in the system. **Right Panel:** Normal tracing after repositioning and flushing the catheter.

have been developed that fit on the distal tip of standard catheters and therefore may be used as intracardiac manometers (Figures 10.4 and 10.24). Measuring pressure directly within the vessel or cardiac chamber with the transducer on the tip of the catheter prevents the distortions associated with fluid-filled systems. In addition, these micromanometers have a flat frequency response up to 1,000 Hz, thus allowing accurate recording at high heart rates. Particularly reliable catheter-tip manometers are made by Millar Instruments. Variations of these catheters include a pigtail tip, as well as one or two pressure sensors and as many as 12 electrodes for simultaneous high-fidelity pressure and volume measurements (see Chapter 21). The catheter may be subjected to gas sterilization (ethylene oxide) along with other catheters and instruments. Some laboratories have used disposable high-fidelity transducer catheters and have shown that the pressures measured with these catheters are superior in waveform and accuracy to those measured with standard techniques. A disposable version of Millar catheters is available for clinical use.

For accurate measurement of the rate of ventricular pressure rise (dP/dt) and other parameters of myocardial performance occurring during the first 40 to 50 ms of ventricular systole, high frequency-response characteristics are necessary. Although there is some debate on this subject, micromanometer-tipped catheters are generally required in patient studies when myocardial mechanics are being examined (see Chapter 22). Gersh et al. published a careful study on the physical criteria for measurement of left ventricular pressure and its first derivative. They showed that pressure measurement flat to ±5% of the first 20 harmonics of the left ventricular pressure curve is required for accurate reproduction of the amplitude of maximal dP/dt. In their study, accuracy to six harmonics led to a 20% underestimation of peak dP/dt. At a heart rate of 80 bpm, the fundamental frequency is 80/60, or 1.33 Hz, and the 20th harmonic is 26.7 Hz. As seen in Figure 10.6, this may be possible to achieve with a short, wide-bore catheter attached directly to the pressure transducer, with optimal damping. If the heart rate increases to 100 bpm,
Figure 10.26 Transformation of arterial pressure waveform with transmission to the periphery in a healthy 30-year-old man. Onsets of pressures are aligned for comparison. As the pulse wave moves peripherally, the upstroke steepens and increases in magnitude, giving the pressure a spiky appearance. The horizontal line intersecting onset of each pulse contour is a calibration reference of 90 mmHg. (From Marshall HW, et al. Physiologic consequences of congenital heart disease. In: Hamilton WF, Dow P, eds. Handbook of Physiology: Section 2. Circulation, Vol. 1. Washington, DC: American Physiologic Society; 1962:417.)

Figure 10.27 Simultaneous recording of aortic and radial artery pressure waves during rest (A), 28.2 (B), 47.2 (C), and 70% (D) of maximal oxygen uptake in a subject. Tracings were taken at the peaks of slow pressure oscillation and show the relationship of these extreme peripheral values to the severity of exercise. (Reproduced with permission from: Rowell LB, Brengelmann GL, Blackmon JR, Bruce RA, Murray JA. Disparities between aortic and peripheral pulse pressures induced by upright exercise and vasomotor changes in man. Circulation 1968;37:954–964.)
however, the 20th harmonic becomes \(100/60 \times 20\), or \(33.3\) Hz, which exceeds the capacity for even this optimal fluid-filled system. Therefore, to minimize the chance of error, micromanometer catheters should be used exclusively when \(dP/dt\) is being measured. Examples of pressure recordings taken with and without micromanometer-tipped catheters may be seen in Figures 10.4 and 10.24.

**CONCLUSION**

Pressure measurement is a fundamental component of cardiac catheterization. As described in other chapters of this textbook, the correct diagnosis of valvular and structural cardiovascular pathology relies on accurate measurements of complex hemodynamic changes and alterations of the pressure waveforms. Familiarity with the recording chain, with normal pressure waveforms, and with sources of errors and artifacts can help in avoiding erroneous conclusions that could lead to the wrong diagnosis.

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The maintenance of blood flow commensurate with the metabolic needs of the body is a fundamental requirement of human life. In the absence of major disease of the vascular tree (e.g., arterial obstruction), the maintenance of appropriate blood flow to the body depends largely on the heart's ability to pump blood in the forward direction. The quantity of blood delivered to the systemic circulation per unit time is termed the cardiac output, generally expressed in liters per minute.

**Extraction Reserve and Cardiac Output**

The extraction of nutrients by metabolizing tissues is a function not only of the rate of delivery of those nutrients (the cardiac output) but also of the ability of each tissue to extract those nutrients from the circulation. Therefore, tissue viability can be maintained despite a fall in cardiac output as long as there is increased extraction of required nutrients. The extraction of a given nutrient (or of any substance) from the circulation by a particular tissue is expressed as the arteriovenous difference across that tissue, and the factor by which the arteriovenous difference can increase at constant flow (owing to changes in metabolic demand) may be termed the extraction reserve. For example, arterial blood in humans is normally 95% saturated with oxygen; that is, if 1 L of blood has the capacity to carry approximately 200 mL of oxygen when fully saturated, arterial blood will usually be found to contain 190 mL of oxygen per liter (190/200 = 95%). Venous blood returning from the body normally has an average oxygen saturation of 75%; that is, mixed venous blood generally contains 150 mL of oxygen per liter of blood (150/200 = 75%). Thus the normal arteriovenous difference for oxygen is 40 mL/L (190 – 150 mL/L).

The normal extraction reserve for oxygen is 3, which means that under extreme metabolic demand, the body's tissues can extract up to 120 mL of oxygen (3 × 40 mL) from each liter of blood delivered. Thus if arterial saturation remains constant at 95%, full use of the extraction reserve will result in a mixed venous oxygen content of 70 mL/L (190 – 120 mL/L) or a mixed venous oxygen saturation of 35% (70/200 = 35%). This is essentially the value found for mixed venous (i.e., pulmonary artery) oxygen saturation in normal men studied at maximal exercise. The relation between cardiac output and arteriovenous O₂ difference is illustrated in Figure 11.1.

**Lower Limit of Cardiac Output**

The value of 3 for the oxygen extraction reserve predicts that in progressive cardiac decompensation, meeting the basal oxygen requirements of the body demands that oxygen extraction increase as cardiac output falls until the arteriovenous oxygen difference has tripled and cardiac output has fallen to one-third of its normal value (Figure 11.1). Because the extraction reserve has now been used fully, any further reduction of cardiac output will result in tissue hypoxia, anaerobic metabolism, acidosis, and eventually, circulatory collapse. This prediction appears to be quite accurate; clinical investigators have observed for many years that a fall in resting cardiac output to below one-third of normal (i.e., a cardiac index of ≤1.0 L/minute per m²) is incompatible with life.

**Upper Limit of Cardiac Output**

Several studies have indicated that the largest increase in cardiac output that can be achieved by a trained athlete at maximal exercise is 600% of the resting output. If a normal 70 kg man has a cardiac output of 5 L/minute or 3.0 L/minute...
per m², his maximal cardiac output might be as high as 30 L/minute (18 L/minute per m²). Because cardiac output increases by approximately 600 mL for each 100 mL increase in oxygen requirements of the body, an increase in cardiac output of 25 L/minute with maximal exercise would suggest an increase in total-body oxygen requirements of 4,167 mL/minute, which is approximately an 18-fold increase over the normal resting value of 250 mL/minute. The 18-fold increase in total-body oxygen requirements is met by the combined sixfold increase in oxygen delivery (i.e., cardiac output) and threefold increase in oxygen extraction (extraction reserve). These relations are illustrated in Figure 11.1.

Factors Influencing Cardiac Output in Normal Subjects

The range of the “normal” cardiac output is difficult to define with precision because it is influenced by several variables. Obviously, body size is important, and the ranges of normal values of cardiac output for 2-year-old children, 10-year-old children, and 50-year-old men are so different that they show only minimal overlap. For this reason, normalization of the cardiac output for differing body size is considered fundamental by all students of this subject, although there is disagreement about the best way to accomplish this normalization. Because cardiac output seems to be predominantly a function of the body's oxygen consumption or metabolic rate¹,² and because metabolic rate is thought to correlate best with body surface area,³,⁴ it has become customary to express cardiac output in terms of the cardiac index ([liters/minute]/[body surface area, m²]). Body surface area is not measured directly, but is instead calculated from one of the experimentally developed formulas, such as that of Dubois.⁴

\[
\text{Body surface area (m}^2) = 0.007184 \times \text{weight}^{0.425} \times \text{height}^{0.725} \ (\text{cm})
\]

(11.1)

Despite the shortcomings and weaknesses of this approach to normalization of the cardiac output,¹,⁵ the method has gained nearly universal acceptance by clinicians over the past 40 years and will be used throughout this book. The availability of automatic calculators, which are now incorporated in modern hemodynamic equipment, has facilitated accurate calculation of normalized data and incorporation of these data in standard reporting.

Although expression of cardiac output as the cardiac index narrows to a great extent the range of normal values among our groups of 2-year-old children, 10-year-old children, and 50-year-old men, it does not completely abolish the differences in these ranges. In fact, the normal cardiac output appears to vary with age, steadily decreasing from approximately 4.5 L/minute per m² at age 7 years to 2.5 L/minute per m² at age 70 years.¹,⁶ This is not surprising, because it is well known that the body's metabolic rate is affected to a great extent by age, being the highest in childhood and progressively diminishing with age.
In addition to age, cardiac output is affected by posture, decreasing by approximately 10% when a person rises from a lying to a sitting position and by approximately 20% when a person rises (or is tilted) from a lying to a standing position. Also, body temperature, anxiety, environmental heat and humidity, and a host of other factors influence the normal resting cardiac output, and these must be considered in interpreting any value of cardiac output measured in the clinical setting.

TECHNIQUES FOR DETERMINATION OF CARDIAC OUTPUT

Of the numerous techniques devised over the years to measure cardiac output, two have won general acceptance in cardiac catheterization laboratories: the Fick oxygen technique and the indicator dilution technique. Both techniques are similar in that they are based on the theoretical principle enunciated by Adolph Fick in 1870. The principle, which was never actually applied by Fick and was first used by O’Klein in Prague to measure cardiac output in men, states that the total uptake or release of any substance by an organ is the product of blood flow to the organ and the arteriovenous concentration difference of the substance. For the lungs, the substance released to the blood is oxygen, and the pulmonary blood flow can be determined by knowing the arteriovenous difference of oxygen across the lungs and the oxygen consumption per minute.

Fick’s principle is illustrated in Figure 11.2. In this figure, a train is passing by a hopper that is delivering marbles to the boxcars at a rate of 20 marbles per minute. If the boxcars each contain 16 marbles before passing under the hopper, the train is moving at a speed sufficient to deliver 5 boxcars per minute to any point down the line. This could have been calculated as

\[
\text{Train’s speed (boxcars/minute)} = \frac{\text{marble delivery rate (marbles/minute) “AV”}}{\text{marble difference (marbles/boxcar)}} \\
= \frac{20 \text{ marbles/minute}}{4 \text{ marbles/boxcar}} \\
= 5 \text{ boxcars/minute}
\]

If one boxcar is 1 L of blood and each marble is 10 mL of oxygen, then we have an arteriovenous oxygen difference of 40 mL/L, an \(O_2\) consumption of 200 mL/minute, and a cardiac output of 5 L/minute.

(Illustration kindly provided by Jennifer Grossman, age 11 years.)
systemic arterial blood is sampled and assumed to have an arteriovenous oxygen difference. Pulmonary venous blood is not sampled. Instead, left ventricular or pulmonary venous drainage, the oxygen content of systemic arterial blood is common 2 to 5 mL/L of blood lower than that of pulmonary venous blood as it leaves the alveoli.

**Fick Oxygen Method**

In the Fick oxygen method, pulmonary blood flow should be determined ideally by measuring the arteriovenous difference of oxygen across the lungs and the rate of oxygen uptake by blood from the lungs. If there is no intracardiac shunt and pulmonary blood flow is equal to systemic blood flow, the Fick oxygen method also measures systemic blood flow. Thus, cardiac output equals oxygen consumption divided by arteriovenous oxygen difference.

In actual practice, the rate at which oxygen is taken up from the lungs by blood is not measured, but rather the uptake of oxygen from room air by the lungs is measured, because at steady state these two measurements are equal. Furthermore, arteriovenous oxygen difference across the lungs is not measured directly. Generally, pulmonary arterial blood (true mixed venous blood) is sampled, but pulmonary venous blood is not sampled. Instead, left ventricular or systemic arterial blood is sampled and assumed to have an oxygen content representative of mixed pulmonary venous blood. Actually, because of bronchial venous and thebesian venous drainage, the oxygen content of systemic arterial blood is commonly 2 to 5 mL/L of blood lower than that of pulmonary venous blood as it leaves the alveoli.

**Oxygen Consumption**

Methods for measurement of oxygen consumption have included the Douglas bag method, the polarographic method, and the paramagnetic method. The instruments described in previous editions of this book are no longer available, and today, direct measurements of oxygen consumption are rarely obtained in the cardiac catheterization lab. However, a description of each method and older instruments is still useful for understanding the challenges in obtaining accurate measurements and how the systems have evolved. The older Douglas bag method required the standard procedure of collecting expired air for 3 minutes in a Douglas bag and measuring its volume (Tissot spirometer) and oxygen content. Interested readers are referred to earlier editions of this book for further details.

The metabolic rate meter (MRM) polarographic instrument (formerly manufactured by Waters Instruments, Rochester, MN) includes a polarographic oxygen sensor cell (gold and silver/silver chloride electrodes), a hood or face mask, and a blower of variable speed connected to a servo control loop with the oxygen sensor (Figure 11.3). The principle of operation involves using a variable-speed blower to maintain a unidirectional flow of air from the room through the hood and via a connecting hose to the polarographic oxygen-sensing cell. As illustrated in Figure 11.3, room air enters the hood at a rate $V_{in}$ (mL/minute), which is determined by the blower’s discharge rate $V_{blower}$ (mL/minute) and the patient’s ventilatory rate ($V_{vent}$, inhaled air in mL/minute; $V_{ex}$, exhaled air). The blower speed $V_{blower}$ is controlled by a servo loop designed to maintain the oxygen content of the air flowing past the polarographic cell constant at a predetermined value. In a steady state, the average value of $V_{blower}$ together with the oxygen content of room air and of the air flowing past the polarographic cell can be used to calculate the patient’s oxygen consumption, as follows:

The patient’s oxygen consumption $\dot{V}_{O_2}$ is given by

\[
\dot{V}_{O_2} = (F_R O_2 \cdot \dot{V}_R) - (F_M O_2 \cdot \dot{V}_M) \tag{11.2}
\]

where $F_R O_2$ and $F_M O_2$ are the fractional contents of oxygen in room air and in the air flowing past the polarographic cell, respectively.

As can be seen from Figure 11.3,

\[
\dot{V}_R = \dot{V}_R - \dot{V}_i + \dot{V}_E \tag{11.3}
\]

which can be rewritten as

\[
\dot{V}_E = \dot{V}_M + \dot{V}_i - \dot{V}_E \tag{11.4}
\]

Substituting this in Eq. (11.2) gives

\[
\dot{V}_O_2 = F_R O_2 (\dot{V}_M + \dot{V}_i - \dot{V}_E) - F_M O_2 \cdot \dot{V}_M \tag{11.5}
\]

\[
= F_R O_2 (\dot{V}_M) - F_M O_2 (\dot{V}_M) + F_M O_2 (\dot{V}_i) - F_R O_2 (\dot{V}_E)
\]

Because the fractional content of oxygen in room air ($F_R O_2$) is 0.209, oxygen consumption is given by

\[
\dot{V}_{O_2} = \dot{V}_M (0.209 - F_M O_2) + 0.209(\dot{V}_i - \dot{V}_E) \tag{11.6}
\]

Thus in a steady state (where $\dot{V}_i - \dot{V}_E$ is constant), oxygen consumption can be determined by measuring the volume rate of air moved by the blower motor ($\dot{V}_M$) and the fractional oxygen content of air moving past the polarographic sensor. In the MRM, a servo-controlled system adjusts $\dot{V}_M$ to keep
Figure 11.3  Measurement of O₂ consumption by a polarographic cell technique using the Waters Instruments metabolic rate meter (MRM). A transparent hood fits snugly over the patient’s head, resting on a pillow. Air enters the hood through holes in a plastic sheet at a flow rate of \( V_R \). The patient’s inspiratory flow rate (\( V_i \)) subtracts from and expiratory flow rate (\( V_e \)) adds to \( V_R \) to yield \( V_M \), the flow rate leaving the hood and entering the servo unit. A blower motor in the servo unit adjusts \( V_M \) to keep the O₂ sensed by a polarographic cell constant. (See text for details.)

\[
\dot{V}_{\text{M}} = \dot{V}_M(0.209 - 0.199) + 0.209(\dot{V}_i - \dot{V}_e) \quad (11.7)
\]

For practical purposes, the respiratory quotient (RQ) is assumed to be 1.0; accordingly, \( \dot{V}_i = \dot{V}_e \) and \( \dot{V}_{O_2} = 0.01 \dot{V}_M \). If the RQ is actually 0.9 (e.g., the patient releases 0.9 L of CO₂ for each liter of O₂ consumed), the error in \( \dot{V}_O_2 \) resulting from the assumption of an RQ of 1.0 is 1.6%, and if RQ is 0.8, the error is 3.2%.

This device was a significant advance over the Douglas bag method. A study by Lange et al. however, found that values of oxygen consumption measured by metabolic rate meter (MRM-2, Waters Instruments, Rochester, MN) were significantly lower than those measured using the standard Douglas bag technique, mentioned previously.

The SensorMedics Deltatrac II (also no longer available) differed from the Waters Instruments MRM device in several aspects. First, it was more sophisticated than the MRM and directly measured the fractional content of oxygen as well as the concentration of carbon dioxide in expired flow, and thus calculated the RQ of each patient. The SensorMedics device was calibrated prior to each period of use with a cylinder containing a test gas of 95% oxygen and 5% carbon dioxide. It used a constant flow rate \( \dot{V}_M \) leaving the canopy or hood and entering the metabolic monitor unit. The sensors in this unit measured oxygen (paramagnetic sensor) and carbon dioxide (infrared sensor) content, and the unit adjusted for temperature and the partial pressure of water vapor, expressing O₂ consumption and CO₂ production at standard temperature and pressure, and dry (STPD; dry gas at 0°C and 760 mmHg). There are several newer systems currently available for metabolic testing and \( \dot{V}_O_2 \) measurements. They are generally portable; they tend to be easier to use; and they can be employed in the cardiac catheterization suite for measuring \( \dot{V}_O_2 \) at rest and during exercise. A description of each system and brand is beyond the scope of this chapter.

**Arteriovenous Oxygen Difference**

The arteriovenous oxygen difference across the lungs must be measured to calculate cardiac output by Fick’s principle, and this can be accomplished by the following method. From appropriately positioned catheters, systemic arterial and mixed venous (pulmonary arterial) blood samples are obtained during the period when O₂ consumption is being measured. The samples are drawn into heparinized syringes and capped quickly. If the patient has received heparin systemically, the syringes used for collection of these blood samples need not be heparinized. Also, if the samples will be analyzed immediately by oximetry, plastic syringes may be used. It should be noted that O₂ may diffuse through the walls of plastic syringes. However, in a laboratory test (William Grossman’s laboratory), no appreciable increase in O₂ saturation of venous blood could be detected over 2 hours (a capped plastic 15 mL syringe filled with venous blood sitting at room temperature was sampled every 15 minutes for oximetry). The samples should be drawn...
Section III Hemodynamic Principles

Oxygen content (in milliliters of oxygen per liter of blood) can be determined by a variety of methods, the most classic of which (and the one that serves as a standard for all others) being the manometric technique of Van Slyke and Neill. The major drawback of the Van Slyke and Neill technique is that 15 to 30 minutes are required to run a single blood sample. The different devices for oximetry measurement have been studied and compared by Shepherd and McMahan. The older Van Slyke methodology is rarely used today, and the Lex-O2 Con fuel cell technique is no longer available. Devices in widespread use today are of the co-oximeter class and either hemolyze the blood sample (by ultrasonic or chemical techniques) or use whole blood; both types of co-oximeter depend on spectrophotometric measurement of the percent oxygen saturation of hemoglobin. Using these devices, oximetry of heparinized blood samples is simple and quick, and measures the percentage of hemoglobin present as oxyhemoglobin. This percentage, multiplied by the theoretical oxygen-carrying capacity of the patient’s blood, yields the calculated oxygen content of that sample (Figure 11.4).

A formula for approximating the theoretical oxygen-carrying capacity in humans is

\[
\text{Hemoglobin (g/dL)} \times 1.36 \text{ (mL O}_2/\text{g of hemoglobin)} \times 10 = \text{theoretical O}_2\text{-carrying capacity (mL O}_2/\text{liter of blood)}
\]

In several textbooks the constant is given as 1.34, but studies on crystalline human hemoglobin suggest that the correct number may be 1.36. Whatever is its correct value, the formula is only an approximation. The steps of Figure 11.4 may be used to calculate oxygen content of blood samples and arteriovenous oxygen difference when the spectrophotometric oximeter method is used. Oxygen contents of arterial and mixed venous blood samples are calculated as the percentage of oxyhemoglobin saturation of these samples multiplied by the oxygen-carrying capacity (steps 2 to 5, Figure 11.4). Oxygen consumption (determined as described earlier) may then be divided by the arteriovenous oxygen difference (step 3 minus step 5, Figure 11.4) to yield the cardiac output. Current oximeters, such as the AVOXimeter 1000 or 4000 (A-VOX Systems, Inc. San Antonio, Texas USA), illuminate a very small sample of heparinized blood (volume, 50 μL) with light of multiple wavelengths and record the optical density of each transmitted wavelength. This approach allows estimation of total hemoglobin concentration as well as the concentrations of its various components: oxyhemoglobin, methemoglobin, and carboxyhemoglobin. This permits instantaneous calculation of oxygen content, which is displayed on the oximeter’s liquid crystal display screen. This value can then be entered directly in steps 3, 5, and 6 of Figure 11.4. The complete formula for calculation of cardiac output using the Fick’s method is shown in Figure 11.5.

Arterial blood may be taken from a systemic artery, the left ventricle, the left atrium, or the pulmonary veins. Theoretically, pulmonary venous blood is preferable to peripheral arterial blood for the arteriovenous oxygen difference calculations. However, except in the presence of a right-to-left intracardiac shunt, pulmonary venous oxygen content may be approximated by systemic arterial oxygen content, ignoring the small amount of venous admixture resulting from bronchial and thebesian venous drainage. If arterial desaturation (e.g., arterial blood oxygen saturation <95%) is present, a central right-to-left shunt should be excluded before accepting systemic arterial oxygen content as representative.

**Figure 11.4**
Calculation of oxygen content and AV oxygen difference when using the reflectance oximetry method.
of pulmonary venous blood. Techniques for detecting and quantifying such shunts are described in Chapter 12.

The most reliable site for obtaining mixed venous blood is the pulmonary artery. Because of streaming and incomplete mixing, using the blood from more proximal sites such as the right atrium or vena cavae as representative of mixed venous blood is much less accurate. Right ventricular blood is closer to true mixed venous blood and may be substituted for pulmonary arterial blood if necessary.

**Sources of Error**

The techniques described for cardiac output measurement by application of Fick's principle assume that a steady state exists (i.e., that the cardiac output and oxygen consumption are constant during the period of measurement). Therefore strict quiet, calm, and decorum must be maintained in the cardiac catheterization laboratory during this time to encourage the achievement of a steady state condition. Potential errors in the determination of cardiac output by the Fick oxygen technique may come from a number of sources.

The spectrophotometric determination of blood oxygen saturation may introduce inaccuracies related to carboxyhemoglobin or other abnormal hemoglobins, as discussed previously. This method also may be inaccurate if indocyanine green dye is present in the circulation, although the newer oximeters are not affected by this problem. Reflectance oximetry, as performed on whole blood, is accurate in the range of blood oxygen saturations from 45% to 98%, but may not be reliable when blood \( \text{O}_2 \) saturation is <40%, as is the case with pulmonary artery blood from patients with very low cardiac output or during strenuous exercise.

Improper collection of the mixed venous blood sample (e.g., air bubbles) is a common source of error. Partial contamination of pulmonary arterial blood with pulmonary capillary wedge blood may result in a falsely high mixed venous blood oxygen content. If the mixed venous blood sample is taken from the right atrium, inferior vena cava, coronary sinus, or similar sites, a falsely low or high value for arteriovenous difference may result. Also, care must be taken not to dilute the blood sample with an excessive quantity of heparinized saline solution.

The average error in determining oxygen consumption has been estimated to be approximately 6%. The error for arteriovenous oxygen difference has been estimated at 5%. Narrow arteriovenous oxygen differences are more prone to introduce error than are wide arteriovenous oxygen differences. Thus the Fick oxygen method is most accurate in patients with low cardiac output, in whom the arteriovenous oxygen difference is wide. The total error in determination of the cardiac output by the Fick oxygen method has been established to be about 10%.

Does oxygen consumption actually need to be measured? To avoid the technical difficulties and expense associated with measurement of oxygen consumption, some laboratories assume that \( \text{O}_2 \) consumption can be predicted from the body surface area, with or without a correction for age and sex. Thus, some laboratories assume that resting \( \text{O}_2 \) consumption is 125 mL/m², or 110 mL/m² for elderly patients. The validity of such an assumption has been addressed in a study from the University of Texas at Dallas. Cardiac output was determined by the indicator dilution technique, and \( \text{O}_2 \) consumption was calculated by dividing cardiac output by arteriovenous oxygen difference, which was measured directly. In the 108 patients studied, the \( \text{O}_2 \) consumption index averaged 126 ± 26 mL/minute per m² (mean ± standard deviation), but there was wide variability as indicated by the standard deviation, and the authors concluded that \( \text{O}_2 \) consumption varies widely among adults at the time of cardiac catheterization. In another study from Bristol Royal Infirmary in the United Kingdom, direct measurement of \( \text{O}_2 \) consumption was compared with assumed values in 80 patients (aged 38 to 78 years). Large discrepancies were evident, with more than half the values differing by more than ±10% and several by ±25% or more. Thus, assumed values for \( \text{O}_2 \) consumption are likely to introduce considerable error.

**Indicator Dilution Methods**

The indicator dilution method is merely a specific application of Fick's general principle. In the Fick oxygen method, the indicator is oxygen, the site of injection is the lungs, and the injection procedure is that of continuous infusion. Stewart was the first to use the so-called indicator dilution method for
measuring cardiac output; he used the continuous-infusion technique and reported his first studies in 1897.

There are two general types of the indicator dilution method: the continuous-infusion method and the single-injection method. The single-injection method is the most widely used and is discussed here in detail. The fundamental requirements for this method include the following:

A bolus of nontoxic indicator substance is injected; the substance mixes completely with blood, and its concentration can be measured accurately.

The indicator substance is neither added to nor subtracted from blood during its passage between the injection and the sampling site.

Most of the indicator substance must pass the site of sampling before recirculation begins.

The indicator substance must go through a portion of the central circulation where all the blood of the body becomes mixed.

The theoretical considerations for the single-injection method may be summarized as follows: An injection of a specified amount of an indicator, \( I \), into a proximal vessel or chamber (e.g., the vena cava or right atrium for the thermodilution method and the pulmonary artery for the indocyanine green dye method) is followed by continuous measurement of the indicator concentration \( C \) in blood as a function of time, \( t \), at a point downstream from the injection (e.g., pulmonary artery for thermodilution technique and radial or femoral artery for the indocyanine green dye method). Because all of the injected indicator, \( I \), must pass the downstream measurement site,

\[
I = \dot{Q} \int_0^\infty C(t) \, dt \quad (11.9)
\]

where \( \dot{Q} \) is the volume flow (in milliliters per minute) between the site of injection and the site of measurement. Thus \( \dot{Q} \) (which is the cardiac output in the methods to be described) may be calculated as

\[
\dot{Q} = \frac{I}{\int_0^\infty C(t) \, dt} \quad (11.10)
\]

Numerous indicators have been used successfully, and the history of this subject is reviewed thoroughly by Guyton et al. Indocyanine green previously had enjoyed long-standing acceptance in clinical practice but is no longer used today for routine measurement of cardiac output. Accordingly, it will not be discussed here and the interested reader is referred to previous editions of this textbook. We will only discuss thermodilution (in which “cold” is the indicator), which is now the dominant technique.

### Thermodilution Method

A thermal indicator method for measuring cardiac output was first introduced by Fegler in 1954 but was not applied to the clinical situation until the works of Branthwaithe and Bradley and Ganz et al. were published. In the initial study by Ganz et al., two thermistors were used (Figure 11.6): one in the superior vena cava at the site at which the cold dextrose solution was injected into the bloodstream and a second downstream thermistor in the pulmonary artery. These two thermistors allowed accurate measurement of the temperature of the injectate, \( T_i \), as well as the temperature of blood, \( T_b \), downstream from the injection site. Using the basic indicator dilution equation, the cardiac output by thermodilution \( CO_{10} \) in milliliters is given as

\[
CO_{10} = \frac{V_i (T_i - T_b) (S_i \cdot C_i / S_b \cdot C_b) \cdot 60}{\int_0^\infty \Delta T_b(t) \, dt} \quad (11.11)
\]

where \( V_i \) is the volume of injectate (mL) and \( S_i, S_b, C_b, C_i \) are the specific gravity and specific heat of blood and injectate, respectively. When 5% dextrose is used as the indicator, \( S_i \cdot C_i / S_b \cdot C_b = 1.08 \). Most of the commercially available thermodilution systems use a single thermistor only, placed at the downstream site, and assume that the temperature of the injectate (measured in a bowl before injection) increases by a predictable amount (catheter warming) during injection. The cardiac output calculated by the thermodilution equation is multiplied by an empirical correction factor (0.825) to correct for the catheter warming. However, a recent report has demonstrated that improved accuracy and precision can be obtained with the thermodilution technique when cardiac output is measured using a dual-thermistor catheter system. These investigators used a specialized dual-thermistor right heart catheter, constructed with a second thermistor positioned to measure temperature at the point where the injectate exits the catheter in the right atrium. This takes into account any warming of the injectate that may take place as it travels from the injectate syringe to the point of exit from the catheter in the right atrium. This technique provided substantially less measurement variability, and the result was in better agreement with simultaneously measured Fick cardiac output (the latter determined using a 5-minute Douglas bag collection of expired air and paired blood samples from pulmonary and femoral arteries).

The thermodilution method for measuring cardiac output has several advantages over the indocyanine green dye method, including the following:

1. It does not require withdrawal of blood.
2. It does not require arterial puncture.
3. An inert and inexpensive indicator is used.
4. There is virtually no recirculation, making computer analysis of the primary curve simple.

### Sources of Error

1. The method is unreliable in the presence of significant tricuspid regurgitation.
2. The baseline temperature of blood in the pulmonary artery usually shows distinct fluctuations associated with respiratory and cardiac cycles. If these fluctuations are
large, they may approach the magnitude of the temperature change produced by the cold-indicator injection.

3. Loss of injected indicator (cold) between the injection and the measuring site (vena cava and pulmonary artery) is not usually a problem, but in low-flow, low-output states, loss of indicator may occur because of warming of blood by the walls of the cardiac chambers and surrounding tissues. This concern is supported by the study of van Grondelle et al.\textsuperscript{15} who found that thermodilution cardiac output measurements overestimated cardiac output consistently in patients with low output (<3.5 L/minute), and this overestimation was the highest, averaging 35%, in patients whose cardiac output was <2.5 L/minute. This is what might be expected from the equation for calculation of cardiac output by thermodilution, since the change in pulmonary artery blood temperature ($\Delta T_p$) will be reduced if cold is lost owing to warming of the injectate during its slow passage through the vena cava, right atrium, and right ventricle. Because $\Delta T_p$ is the denominator in the equation for cardiac output calculation, reduction in $\Delta T_p$ will result in a rise in calculated cardiac output.

4. The empirical correction factor of 0.825 may be inadequate to correct for deviations of true injectate temperature from the temperature of the injectate in the bowl or reservoir, owing to warming in the syringe by the hand of the individual injecting the dextrose solution from the syringe or by catheter warming.

5. Most laboratories today use room temperature, rather than ice-cold, D5W or saline. The use of room temperature solutions rather than ice-cold solutions reduces the signal-to-noise ratio, and it can introduce additional variability from sample to sample.

In general, indicator dilution cardiac output determinations involve an error of 5% to 10% when performed carefully. The values obtained correlate well with those calculated by the Fick oxygen method. Table 11.1 summarizes pitfalls of cardiac output determination with the Fick method and with the thermodilution indicator method.

Continuous Cardiac Output Monitoring

The evolution of ICU care and invasive hemodynamic monitoring has spearheaded the development of right heart catheters and technology for continuous cardiac output monitoring.
Table 11.1  Pitfalls in the Determination of Cardiac Output with the Fick Method and the Thermodilution Method

<table>
<thead>
<tr>
<th>The Fick Method</th>
<th>Thermodilution Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inadequate mixing of blood in the right atrium</td>
<td>Low-output states (incomplete mixing of the indicator)</td>
</tr>
<tr>
<td>Inappropriate sampling (high right atrium, low right atrium, distal PA in partial wedge position)</td>
<td>Atrial fibrillation (incomplete mixing of the indicator)</td>
</tr>
<tr>
<td>Contamination of blood sample with air or heparinized saline</td>
<td>Tricuspid regurgitation (indicator abnormally recirculated)</td>
</tr>
<tr>
<td>( \dot{V}_0 ), usually not measured. There might be significant variation in ( \dot{V}_0 ), particularly in critically ill patients.</td>
<td>Intracardiac shunts (indicator abnormally recirculated)</td>
</tr>
<tr>
<td>Improper measurement of ( \dot{V}_0 )</td>
<td>Simultaneous administration of intravenous fluids</td>
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</tbody>
</table>

(Edwards Lifesciences, Irvine, CA). These catheters are based on the thermodilution method, with the difference that they use a warm indicator rather than a cold indicator. The catheter includes a proximal thermal filament, located in the right atrium, and a distal thermistor or sensor, located in the pulmonary artery at 4 cm from the tip of the catheter. The thermal filament generates an input signal, which results in warming of the blood. Thus, a “warm” bolus rather than a “cold” bolus is generated. The input signal is detected by the distal sensor in the pulmonary artery and processed by a computer, which creates a washout curve and determines the cardiac output. These catheters are occasionally used for continuous monitoring of critically ill patients in the ICU setting, trauma patients, and cardiac surgery patients in the perioperative period. Several studies have shown that when compared with the standard intermittent bolus thermodilution technique, continuous cardiac output monitoring with the “warm” bolus provides more accurate and reproducible measurements.26-28

CLINICAL MEASUREMENT OF VASCULAR RESISTANCE

Poiseuille’s Law

The French physician Jean Léonard Marie Poiseuille (1799–1869) made many important contributions to the study of hemodynamics. At the age of 18 years, he introduced the mercury manometer for the measurement of blood pressure, a technical innovation that continues to be in use to this day. In 1846, he formulated a series of equations describing the flow of fluids through cylindrical tubes. Although Poiseuille was interested in blood flow, he substituted simpler liquids in his measurements of flow through rigid glass tubes. His discoveries, later modified by others, are expressed in what is regarded as Poiseuille’s law,29 which may be stated as follows:

\[
Q = \frac{\pi (P_i - P_o) r^4}{8\eta l} \quad (11.12)
\]

where \( Q \) is the volume flow; \( P_i - P_o \) is inflow pressure – outflow pressure; \( r \) is the radius of the tube; \( l \) is the length of the tube; and \( \eta \) is the viscosity of the fluid.

This relationship applies in the specific circumstance of steady state laminar flow of a homogeneous fluid through a rigid tube. Under these conditions, flow, \( Q \), varies directly as the pressure difference, \( P_i - P_o \), and the fourth power of the tube’s radius, \( r \). It varies inversely as the length, \( l \), of the tube and the viscosity, \( \eta \), of the fluid.

Hydraulic resistance, \( R \), is defined by analogy to Ohm’s law as the ratio of mean pressure drop, \( \Delta P \), to flow, \( Q \), across the vascular circuit. The various factors contributing to vascular resistance can be illustrated by rearranging Poiseuille’s law as follows:

\[
R = \frac{P_i - P_o}{Q} = \frac{8\eta l}{\pi r^4} \quad (11.13)
\]

It is apparent from this equation that, in the condition of steady laminar flow of a homogeneous fluid through a rigid cylindrical tube, resistance to flow depends only on the dimensions of the tube and the viscosity of the fluid. In particular, the resistance is remarkably sensitive to changes in the radius of the tube, the former varying inversely with the fourth power of the latter.
Vascular Resistance and Pressure–Flow Relationships

The applicability of laws derived from steady state fluid mechanics in assessing vascular resistance is somewhat ambiguous because blood flow is pulsatile, blood is a non-homogeneous fluid, and the vascular bed is a nonlinear, elastic, frequency-dependent system. In such a system, resistance varies continuously with pressure and flow, and is influenced by many factors, such as inertia, reflected waves, and the phase angle between pulse and flow wave velocities.29·31

To assess both vessel caliber and vessel elasticity, the resistive and compliant characteristics of the vascular system, the concept of vascular impedance has been used.30 Vascular impedance has been defined as the instantaneous ratio of pulsatile pressure to pulsatile flow.31·32 Because impedance may not be the same for all frequencies, its calculation requires resolution of the harmonic components of both pressure and flow pulsations. The impedance modulus so calculated is then expressed as a spectrum of impedance versus frequency. Although measurement of impedance is important in research studies, it is rarely included in routine diagnostic cardiac catheterization, and the reader is referred elsewhere29 for a full discussion.

As a consequence of the foregoing considerations and the many active and passive factors that influence pressure and flow in blood vessels, the concept of vascular resistance in its pure physical sense is limited in application. In the context of the clinical and physiologic setting, however, pulmonary and systemic vascular resistances calculated from hemodynamic measurements made during cardiac catheterization have acquired empiric pathophysiologic meaning and often become important factors in clinical decision making.

Estimation of Vascular Resistance in the Clinical Situation

Calculations of vascular resistance are usually applied to both the pulmonary and the systemic circulations. Although many authors refer to systemic or pulmonary arteriolar resistance, we prefer the term vascular resistance because it is less committal concerning the anatomic site of the resistance. As has been mentioned, arteriolar tone is only one of the determinants of vascular resistance to blood flow. To estimate pulmonary and systemic vascular resistances quantitatively, knowledge of both the driving pressure across the pulmonary and systemic vascular beds and the respective blood flow through them is required.

The formulas generally used are the following:

A. Systemic vascular resistance

\[ R_s = \frac{A_o - RA}{Q_s} \]

B. Total pulmonary resistance

\[ R_p = \frac{PA}{Q_p} \]

C. Pulmonary vascular resistance

\[ R_p = \frac{PA - LA}{Q_p} \]

where \( A_o \) is mean systemic arterial pressure, \( RA \) is mean right atrial pressure, \( PA \) is mean pulmonary arterial pressure, \( LA \) is mean left atrial pressure, \( Q_s \) is systemic blood flow, and \( Q_p \) is pulmonary blood flow.

In many laboratories, the mean pulmonary capillary wedge pressure is used as an approximation of mean left atrial pressure. This should cause no problem because there is ample evidence that pulmonary capillary wedge pressure, properly obtained, closely approximates the level of left atrial pressure.33·35 The flows are volume flows (as opposed to velocity flows) and are expressed in liters per minute, and the pressures are expressed in millimeters of mercury (mmHg). These equations yield resistance in arbitrary resistance units (R units) expressed in mmHg per liter per minute, also called hybrid resistance units (HRUs). These HRUs are sometimes referred to as Wood units because they were first introduced by Dr. Paul Wood. They may be converted to metric resistance units expressed in dynes-sec-cm⁻³ by use of a conversion factor of 80. In this system, resistance is expressed as

\[ \text{Resistance} = \frac{\Delta P(\text{mm Hg}) \times 1,332 \text{dynes/cm}^2/\text{mm Hg}}{Q_s \text{ or } Q_p \times 1,000 \text{mL/L} \times 60 \text{sec/min}} \]

\[ = \frac{\Delta P}{Q_s \text{ or } Q_p} \times 80 \text{ dynes-sec-cm}^{-3} \]  

Equation (11.15)

There is no particular advantage to either system, since both express precisely the same ratio. Most pediatric cardiologists use HRUs, whereas cardiologists with adult practices generally use metric units.

In pediatric practice, it is conventional to normalize vascular resistances for body surface area (BSA), thus giving a resistance index. Although this is not commonly done in adult cardiac catheterization laboratories, the practice makes sense because normal cardiac output and therefore vascular resistance may be substantially different in a 260 lb man and a 110 lb woman. The normalized resistance, however, is not obtained by dividing resistance (as calculated in Eq. 11.14) by body surface area. Rather, normalized resistance is calculated by substituting the blood flow index for blood flow in the resistance formula. Thus systemic vascular resistance index (SVRI) is calculated as

\[ \text{SVRI} = \frac{(A_o - RA) \times 80}{CI} \]  

Equation (11.16)

where CI is the cardiac (or systemic blood flow) index. Therefore, SVRI equals SVR multiplied by BSA.

Cardiac output, usually measured by either the Fick or the thermodilution method, is used as mean blood flow. It is important to realize that in conditions of intracardiac shunts or shunts between the pulmonary and systemic circulations, pulmonary blood flow and systemic flow may not be equal, and the respective flow through each circuit must be measured and used in the appropriate resistance calculation. Normal values for vascular resistance in adults are given in Table 11.2.
interpreted by McDonald to suggest that the decline in systemic vascular resistance with increase in venous pressure results from dilation of small venous channels, whereas systemic arterioles do not distend passively with increased pressure. Therefore, measurement of vascular resistance is not a precise tool for assessing the dynamics of individual sections of the vascular bed, and the term vascular resistance should not be used as synonymous with arteriolar resistance.

### Systemic Vascular Resistance

The minute-to-minute control of vascular resistance, at least in the systemic bed, is an amalgam of autonomic nervous system influences and local metabolic factors. Hypotension or reduced cardiac output generally triggers increased systemic resistance by means of the baroreceptors, α-adrenergic neural pathways, and release of humoral vasoconstrictor hormones, but these influences may be opposed by metabolic factors if the hypotension or low cardiac output results in decreased tissue perfusion with local hypoxia and acidosis. This latter circumstance is commonly seen in congestive heart failure or shock.

Knowledge of changes in systemic vascular resistance is also important in evaluating the hemodynamic response to stress tests, such as dynamic or isometric exercise. In this regard, there is ample evidence suggesting that normally systemic vascular resistance falls in response to dynamic exercise, but pulmonary vascular resistance remains unchanged (at least with supine bicycle exercise). Transient elevations in systemic vascular resistance have been provoked by infusions of vasopressor drugs to evaluate the left ventricular response to a sudden increase in afterload.

Low systemic vascular resistance may be seen in conditions in which blood flow is abnormally high, such as may occur in patients with arteriovenous fistula, severe anemia, and other high-output states or conditions associated with peripheral vasodilation and high output, such as septic shock. It is important to realize that in these circumstances there may well be regional differences in vascular resistance (e.g., very low in the arteriovenous fistula but normal or increased in other vascular beds), and calculations based on mean pressure and flow in the entire systemic circulation must be interpreted with caution.

### Total Pulmonary Resistance

Calculated as the ratio of mean pulmonary arterial pressure to pulmonary blood flow, total pulmonary resistance expresses the resistance to flow in transporting a volume of blood from the pulmonary artery to the left ventricle in diastole, neglecting left ventricular diastolic pressure. This relationship is obviously influenced by alterations in left atrial pressure and will not consistently provide useful information about the condition of the pulmonary vasculature. Although widely used 25 years ago, this parameter is less commonly used.

### Clinical Use of Vascular Resistance

As can be deduced from the Poiseuille equation, changes in systemic or pulmonary vascular resistance may result theoretically from one of three mechanisms. Because changes in length of the vascular beds are uncommon after growth has been completed, changes in vascular resistance reflect either altered viscosity of blood or a change in cross-sectional area (radius) of the vascular bed.

There is ample evidence that changes in blood viscosity alter measured vascular resistances. Nihill has shown that an approximate doubling of pulmonary vascular resistance occurs with increases in hematocrit from 43% to 64%. Similarly, low values for measured vascular resistance are commonly seen in patients with severe chronic anemia, although the low vascular resistance in such cases probably represents more than a viscosity effect alone.

With regard to changes in cross-sectional area of the pulmonary or systemic vascular bed, such changes do not invariably imply altered arteriolar tone. In the normal systemic circulation, mean aortic pressure may be 100 mmHg, whereas right atrial pressure is only 5 mmHg. Although the largest part of this pressure drop occurs at the arteriolar level (approximately 60%), about 15% occurs in the capillaries, 15% in small veins, and 10% in the arterial system proximal to the arterioles. Thus although systemic vascular resistance is dominated by the caliber of the arterioles, the influence of other characteristics of the systemic vascular bed is by no means negligible. For example, Read and coworkers studied systemic vascular resistance in dogs with constant (pump-controlled) cardiac output and found that a rise in venous pressure consistently caused a fall in resistance. The magnitude of the fall was proportional to the increment in venous pressure rise and was about 20% for an increase in venous pressure of 20 mmHg. Other studies showed no change in resistance when arterial pressure is so manipulated (in the absence of baroreceptor control). These findings have been

### Table 11.2 Normal Values of Vascular Resistance

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic vascular resistance</td>
<td>$1,170 \pm 270$ dynes-sec-cm$^{-5}$</td>
</tr>
<tr>
<td>Systemic vascular resistance index</td>
<td>$2,130 \pm 450$ dynes-sec-cm$^{-5} \cdot M^2$</td>
</tr>
<tr>
<td>Pulmonary vascular resistance</td>
<td>$67 \pm 30$ dynes-sec-cm$^{-5}$</td>
</tr>
<tr>
<td>Pulmonary vascular resistance index</td>
<td>$123 \pm 54$ dynes-sec-cm$^{-5} \cdot M^2$</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± standard deviation and were derived from 37 subjects without demonstrable cardiovascular disease (17 males, 20 females, age 47 ± 9 years) who underwent diagnostic cardiac catheterization at the Peter Bent Brigham Hospital between July 1, 1975, and June 30, 1978.
today and in general should be used primarily in the patient in whom measurement of left atrial or pulmonary capillary wedge pressure is not possible.

Pulmonary Vascular Resistance

Sometimes (inappropriately) called pulmonary arteriolar resistance, pulmonary vascular resistance expresses the pressure drop across the major pulmonary vessels, the precapillary arterioles, and the pulmonary capillary bed and is more precise in assessing the presence and degree of pulmonary vascular disease than is total pulmonary resistance. Simple calculation of pulmonary vascular resistance provides general information about the pulmonary circulation, but this must be interpreted in the context of the clinical situation and other hemodynamic data obtained during cardiac catheterization. The pulmonary vasculature is a dynamic system and is subject to many mechanical, neural, and biochemical influences.

Measured pulmonary vascular resistance may be elevated by hypoxia, hypercapnia, increased sympathetic tone, polycythemia, local release of serotonin, mechanical obstruction by multiple pulmonary emboli, precapillary pulmonary edema, or lung compression (pleural effusion, increased intrathoracic pressure via respirator). On the other hand, pulmonary vascular resistance may be reduced by oxygen, adenosine, isoproterenol, α-antagonists such as phentolamine or tolazoline, inhaled nitric oxide, prostacyclin infusions, nitroprusside and high doses of calcium channel blockers. These vasodilators may be used to test for fixed, irreversible pulmonary hypertension. For a detailed description of the protocols and agents used in assessing reversibility of pulmonary hypertension and/or optimization of pharmacological therapy in patients with primary or secondary pulmonary hypertension, the reader is referred to Chapters 9, 42, and 43.

Patients with high pulmonary vascular resistance (e.g., ≥600 dynes-sec-cm⁻²) in association with a central shunt (e.g., ventricular septal defect) should be given 100% oxygen via face mask before concluding that the changes are fixed. Elderly patients with a combination of left heart failure and chronic obstructive lung disease may have considerable pulmonary vasoconstriction owing to alveolar hypoventilation and its resultant hypoxia. Inhalation of 100% oxygen in such cases may result in a dramatic fall in pulmonary arterial pressure and vascular resistance.

PULMONARY VASCULAR DISEASE IN PATIENTS WITH CONGENITAL CENTRAL SHUNTS

The decision as to whether a patient with congenital heart disease would benefit from corrective surgery often hinges on the calculated pulmonary vascular resistance. Although each case must be evaluated based on its own characteristics, many criteria for operability have been proposed. It has been suggested that the ratio between pulmonary vascular resistance and systemic vascular resistance (resistance ratio, PVR/SVR) be used as a criterion for operability in dealing with congenital heart disease. Normally, this ratio is ≤0.25. Values of 0.25 to 0.50 indicate moderate pulmonary vascular disease, and values higher than 0.75 indicate severe pulmonary vascular disease. When the PVR/SVR resistance ratio is ≥1.0, surgical correction of the congenital defect is considered contraindicated because of the severity of the pulmonary vascular disease.

The resistance ratio offers the advantage of factoring in miscellaneous neural, hormonal, and blood viscosity influences that may be affecting both pulmonary and systemic vascular beds and that may be primarily related more to the patient’s immediate clinical status than to intrinsic pulmonary vascular changes. Many patients with left ventricular failure and low systemic output (from any cause) have associated high systemic and pulmonary vascular resistance, but their resistance ratio will be normal in the absence of intrinsic vascular pathology.

We have reported three patients with congenital heart disease (two with atrial septal defect and one with patent ductus arteriosis) having cyanosis and pulmonary arterial hypertension at nearly systemic levels. Each of our patients had PVR/SVR ratio of <0.50 and net left-to-right shunts, despite severe pulmonary hypertension (e.g., pulmonary artery pressure was 110/55 mmHg). Each patient had progressive improvement in pulmonary vascular resistance toward normal following operative closure of the shunts. These cases illustrate the importance of increased blood viscosity associated with polycythemia secondary to cyanosis (hematocrits in the 56% to 66% range), which may contribute substantially to the increase in the measured values of pulmonary and systemic vascular resistances. As mentioned earlier, studies in dogs have shown that calculated pulmonary vascular resistance doubled when hematocrit was raised from 43% to 64%. Accordingly, elimination of severe cyanosis with return of hematocrit level to normal may lead to a 50% reduction in pulmonary vascular resistance. This influence of viscosity, as well as the generalized vasoconstriction often seen in patients with advanced cardiac disease, will be factored out by the ratio of PVR/SVR.

In his classic description of the Eisenmenger syndrome, Wood pointed out that attempted surgical repair of the shunt defect was a major cause of death in these patients. He stated that in patients with a pulmonary blood flow of <1.75 times the systemic flow or with a total pulmonary vascular resistance of >12 Wood or hybrid units (960 dynes-sec-cm⁻²), ordinary surgical repair of the defect should not be attempted. Others have suggested similar criteria for special instances or conditions. In our opinion, surgical repair should be limited to patients in whom the net shunt is left-to-right and the pulmonary vascular resistance is less than systemic vascular resistance, preferably with a resistance ratio of <0.50.
Marked elevations in pulmonary vascular resistance may also be seen in acquired heart disease, notably in mitral stenosis. The effect of mitral valve replacement in patients with mitral stenosis and/or regurgitation associated with pulmonary hypertension has been evaluated.\(^\text{42,43}\) Most patients experience significant reduction in pulmonary vascular resistance following successful repair of the mitral valve lesion. Although some degree of pulmonary hypertension may persist postoperatively, significant palliative benefit usually occurs, and the decision regarding surgery must be made in light of information regarding left and right ventricular function as well as the degree of pulmonary hypertension.

Currently, percutaneous balloon mitral valvuloplasty is widely used as an alternative to surgery for treating patients with advanced mitral stenosis. The procedure brings about an immediate improvement in mitral valve area and in pulmonary hypertension. Its effects on pulmonary vascular resistance have been studied in a cohort of 14 patients with advanced mitral stenosis. The procedure brings about a significant reduction in pulmonary vascular resistance following successful repair of the mitral valve lesion. Although some degree of pulmonary hypertension may persist postoperatively, significant palliative benefit usually occurs, and the decision regarding surgery must be made in light of information regarding left and right ventricular function as well as the degree of pulmonary hypertension.

Cardiac catheterization provides an ideal opportunity for assessing the potential response of a patient to a change in medical regimen, particularly with regard to vasodilator drugs. In recent years, vasodilator drugs have assumed a major role in the treatment of patients with congestive heart failure. There is, however, wide variability among currently used vasodilator agents, and the relative effects of a particular drug on resistance and capacitance vessels is of major importance in predicting its hemodynamic effects.\(^\text{45}\) This problem may become complex when a particular drug may have different effects, depending on the level of resting tone in resistance and capacitance beds. For example, nitrate preparations are well known to influence venous capacitance; this influence is presumably responsible (at least in part) for the fact that ventricular filling pressures and pulmonary congestion consistently improve when nitrate therapy is given to patients with congestive heart failure. Despite this consistent effect on preload, the effect of nitrates on forward cardiac output has been variable,\(^\text{46-48}\) and studies have reported decreases, increases, or mixed effects on cardiac output in normal subjects and in patients with heart failure.

Goldberg and colleagues\(^\text{49}\) studied 15 patients with chronic congestive heart failure who were given an oral nitrate (erythritol tetranitrate) at the time of cardiac catheterization to identify the predictors of nitrate effect on cardiac output. There were significant reductions in right atrial, pulmonary capillary wedge, and mean arterial pressure in nearly all patients. Augmentation in cardiac output by ≥10% occurred in eight patients (thereby defined as responders), but no change or decline occurred in seven patients (nonresponders). The level of peripheral vasoconstriction, as reflected by resting systemic vascular resistance, was significantly higher for the responders than for the nonresponders (2,602 ± 251 versus 1,744 ± 193 dynes-sec-cm\(^{-5}\), \(P < 0.02\)). Furthermore, a significant reduction in systemic vascular resistance occurred only in the responders, and the decline was a linear function of resting resistance (Figure 11.7).

Thus, although reductions in arterial pressure and left and right ventricular filling pressures are consistent results of nitrate therapy, significant augmentation in forward cardiac output is likely only in patients with most intense resting peripheral vasoconstriction. The design of a catheterization protocol for a patient with congestive heart failure can include assessment of vasodilator therapy based on these principles. For example, if resting cardiac output is low and if right and left ventricular filling pressures as well as systemic vascular resistance are high, a long-acting nitrate or a balanced agent (e.g., sodium nitroprusside or an angiotensin-converting enzyme inhibitor) might be expected to be particularly beneficial and can be tested while the catheters are still in place. On the other hand, if the output is low and resistance is high but filling pressures are near normal, a nitrate might not help because the lowered resistance may be offset by the fall of the already normal preload, the result being no increase in output. In such a patient, a selective lowering of resistance would be desirable, and hydralazine could be tested before removing the catheters. If the cardiac output is low but resistance is normal, neither a nitrate nor an angiotensin-converting enzyme inhibitor is likely to increase output and should be tested only if filling pressures are high and symptoms of congestion form a prominent part of the clinical picture. In such patients, the combination of an inotropic agent and a nitrate
may be particularly helpful and could be tested at the time of catheterization. Finally, if the output is low but filling pressures and systemic vascular resistance are normal, vasodilator drugs will probably do more harm than good, and a therapeutic trial of preload elevation (administration of colloid) with or without an inotropic agent could be tested during catheterization.

These examples are presented merely to illustrate the principle of using cardiac catheterization parameters (i.e., resistances, flows, and filling pressures) to design a therapeutic regimen and then, while the catheters are still in place, putting it to test. We have found this most useful with regard to the patient with heart failure, and cardiac catheterization in such patients should include full right and left heart catheterization with measurement of cardiac output, left and right heart pressures, and systemic and pulmonary vascular resistances (see also Chapter 43).

REFERENCES

Detection, localization, and quantification of intracardiac shunts are an integral part of the hemodynamic evaluation of patients with congenital heart disease. In most cases, an intracardiac shunt is suspected on the basis of the clinical evaluation of the patient before catheterization. There are several circumstances, however, in which data obtained at catheterization should alert the cardiologist to look for a shunt that had not been suspected previously:

1. Unexplained arterial desaturation should immediately raise the suspicion of a right-to-left intracardiac shunt, which may then be assessed by the methods to be discussed. Most commonly, arterial desaturation (i.e., arterial blood oxygen saturation <95%) detected at the time of cardiac catheterization represents alveolar hypoventilation. The causes for this alveolar hypoventilation and its associated physiologic right-to-left shunt include (a) excessive sedation from the premedication, (b) chronic obstructive lung disease or other pulmonary parenchymal disease, and (c) pulmonary congestion/edema secondary to the patient's cardiac disease. Alveolar hypoventilation associated with each of these problems is exacerbated by the supine position of the patient during the catheterization procedure. Helping the patient to assume a more upright posture (head-up tilt or propping the patient up with a large wedge if tilt mechanism is not available) and encouraging the patient to take deep breaths and to cough will correct or substantially ameliorate arterial hypoxemia in most cases. If arterial desaturation persists, oxygen should be administered by face mask for both therapeutic and diagnostic purposes. If full arterial blood oxygen saturation cannot be achieved by face-mask administration of oxygen (it is best in this regard to use a rebreathing mask that fits snugly), a right-to-left shunt is presumed to be present, and its anatomic site and magnitude should be determined using the methods described later in this chapter.

2. Conversely, when the oxygen content of blood in the pulmonary artery is unexpectedly high (i.e., if the pulmonary artery [PA] blood oxygen saturation is >80%), the possibility of a left-to-right intracardiac shunt should be considered. It is for these two reasons that arterial and pulmonary artery saturation should be measured routinely during cardiac catheterization.

3. When the data obtained at cardiac catheterization do not confirm the presence of a suspected lesion, one should consider the presence of an intracardiac shunt. For example, if left ventricular cineangiography fails to reveal mitral regurgitation in a patient in whom this was judged to be the cause of a systolic murmur, it is prudent to look for evidence of a ventricular septal defect (VSD) with left-to-right shunting.

### DETECTION OF LEFT-TO-RIGHT INTRACARDIAC SHUNTS

Many techniques are available for the detection, localization, and quantification of left-to-right intracardiac shunts. The techniques vary in their sensitivity, the type of indicator they use, and the equipment needed to sense and read out the presence of the indicator.

#### Measurement of Blood Oxygen Saturation and Content in the Right Heart (Oximetry Run)

In the oximetry run, a basic technique for detecting and quantifying left-to-right shunts, the oxygen content or percentage saturation is measured in blood samples drawn sequentially...
shunts who were undergoing diagnostic cardiac catheterization for evaluation of coronary artery disease, valvular heart disease, cardiomyopathy, or possible pulmonary embolism. Each patient had a complete right heart oximetry run (see later discussion) with sampling of multiple sites in each chamber. Oxygen content was measured directly by an electrochemical fuel cell method (Lex-O₂-Con, Lexington Instruments, Lexington, MA), a method that had been previously validated against the Van Slyke method. Oxygen saturation was calculated as blood oxygen content divided by oxygen-carrying capacity. The relationship between oxygen content and oxygen saturation obviously depends on the hemoglobin concentration in the patient’s blood (e.g., 75% oxygen saturation of pulmonary artery blood will be associated with a substantially lower oxygen content in an anemic patient than in one with normal hemoglobin concentration). Also, systemic blood flow may be an important determinant of oxygen variability in the right heart chambers because high systemic flow tends to equalize the differences across various tissue beds.

In the context of these considerations, listed in Table 12.1 are the criteria for a significant step-up in right heart oxygen content and percentage oxygen saturation associated with various types of left-to-right shunt, based on the study of Antman and coworkers\(^2\) and other investigators.\(^3\) As can be seen from the bottom line (“Any level”) of Table 12.1, the simplest way to screen for a left-to-right shunt is to sample SVC and PA blood and measure the difference, if any, in percentage O\(_2\) saturation. It is recommended that blood samples from SVC and PA be routinely obtained at the time of right heart catheterization and their O\(_2\) saturation determined by reflectance oximetry. If the ΔO\(_2\) saturation between these samples is ≥8%, a left-to-right shunt may be present at atrial, ventricular, or great vessel level, and a full oximetry run should be done.

**Oximetry Run**

The blood samples needed to localize a step-up in the right heart are obtained by performing what is called an oximetry run. The samples needed and the recommended order in which they should be obtained follow.

Obtain a 2 mL sample from each of the following locations:

1. Left and/or right pulmonary artery
2. Main pulmonary artery\(^b\)
3. Right ventricle, outflow tract\(^b\)
4. Right ventricle, mid\(^a\)
5. Right ventricle, tricuspid valve or apex\(^a,c\)
6. Right atrium, low or near tricuspid valve
7. Right atrium, mid
8. Right atrium, high

\(^a\)Confirm location by pressure measurement.
\(^b\)If frequent extrasystoles occur, do not persist. Obtain samples from three different locations in right ventricle and right atrium.
### Table 12.1
Detection of Left-to-Right Shunt by Oximetry

<table>
<thead>
<tr>
<th>Level of Shunt</th>
<th>Mean of Distal Chamber Samples</th>
<th>Mean of Proximal Chamber Samples</th>
<th>Highest Value in Proximal Chamber</th>
<th>Highest Value in Distal Chamber</th>
<th>Approximate Minimal $Q_s/Q_r$ Required for Detection (Assuming SBFI = 3 L/min/M²)</th>
<th>Possible Causes of Step-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial (SVC/IVC to RA)</td>
<td>$O_2 %_{sat}$: $\geq 7$</td>
<td>$O_2 %_{vol}$: $\geq 1.3$</td>
<td>$O_2 %_{sat}$: $\geq 11$</td>
<td>$O_2 %_{vol}$: $\geq 2.0$</td>
<td>1.5–1.9</td>
<td>Atrial septal defect; partial anomalous pulmonary venous drainage; ruptured sinus of Valsalva; VSD with TR; coronary fistula to RA</td>
</tr>
<tr>
<td>Ventricular (RA to RV)</td>
<td>$O_2 %_{sat}$: $\geq 5$</td>
<td>$O_2 %_{vol}$: $\geq 1.0$</td>
<td>$O_2 %_{sat}$: $\geq 10$</td>
<td>$O_2 %_{vol}$: $\geq 1.7$</td>
<td>1.3–1.5</td>
<td>VSD; PDA with PR; primum ASD; coronary fistula to RV</td>
</tr>
<tr>
<td>Great Vessel (RV to PA)</td>
<td>$O_2 %_{sat}$: $\geq 5$</td>
<td>$O_2 %_{vol}$: $\geq 1.0$</td>
<td>$O_2 %_{sat}$: $\geq 5$</td>
<td>$O_2 %_{vol}$: $\geq 1.0$</td>
<td>$\geq 1.3$</td>
<td>PDA; aortopulmonic window; aberrant coronary artery origin</td>
</tr>
<tr>
<td>Any level (SVC to PA)</td>
<td>$O_2 %_{sat}$: $\geq 7$</td>
<td>$O_2 %_{vol}$: $\geq 1.3$</td>
<td>$O_2 %_{sat}$: $\geq 8$</td>
<td>$O_2 %_{vol}$: $\geq 1.5$</td>
<td>$\geq 1.5$</td>
<td>All of the above</td>
</tr>
</tbody>
</table>

SVC and IVC, superior and inferior vena cavae; RA, right atrium; RV, right ventricle; PA, pulmonary artery; VSD, ventricular septal defect; TR, tricuspid regurgitation; PDA, patent ductus arteriosus; PR, pulmonic regurgitation; ASD, atrial septal defect; SBFI, systemic blood flow index; $Q_s/Q_r$, pulmonary to systemic flow ratio.

9. Superior vena cava, low (near junction with right atrium)
10. Superior vena cava, high (near junction with innominate vein)
11. Inferior vena cava, high (just at or below diaphragm)
12. Inferior vena cava, low (at L4–L5)
13. Left ventricle
14. Aorta (distal to insertion of ductus)

In performing the oximetry run, an end-hole catheter (e.g., Swan-Ganz balloon flotation catheter) or one with side holes close to its tip (e.g., a Goodale-Lubin catheter) is positioned in the right or left pulmonary artery. Cardiac output is measured by the Fick method. As soon as the determination of oxygen consumption is completed, the operator begins to obtain 2 mL blood samples from each of the locations indicated. This is done under fluoroscopic control, with catheter tip position further confirmed by pressure measurement at the sites noted. The entire procedure should take less than 7 minutes. If a sample cannot be obtained from a specific site because of ventricular premature beats, that site should be skipped until the rest of the run has been completed.

Oxygen saturation and/or content in each of the samples is determined as discussed previously, and the presence and localization of a significant step-up are determined by applying the criteria listed in Table 12.1.

An alternative method for performing the oximetry run is to withdraw a fiberoptic catheter from the pulmonary artery through the right heart chambers and the inferior and superior venae cavae. This permits a continuous readout of oxygen saturation that allows detection of a step-up in oxygen content.
If the oximetry run reveals that a significant step-up is present, the pulmonary blood flow, systemic blood flow, and magnitude of left-to-right and right-to-left shunts may be calculated according to the following formulas.

**Calculation of Pulmonary Blood Flow (Qp)**

Pulmonary blood flow is calculated by the same formula used in the standard Fick equation:

$$ Q_p (L/min) = \frac{O_2 \text{ consumption} (mL/min)}{PV O_2 \text{ content (mL/L)} - PA O_2 \text{ content (mL/L)}} \quad (12.1) $$

If a pulmonary vein (PV) has not been entered, systemic arterial oxygen content may be used in the preceding formula, if systemic oxygen saturation is ≥95%. If systemic oxygen saturation is <95%, one must determine whether a right-to-left intracardiac shunt is present. If there is an intracardiac right-to-left shunt, an assumed value of 98% oxygen capacity for the pulmonary venous oxygen content should be used in calculating pulmonary blood flow. If arterial desaturation is present and is not owing to a right-to-left intracardiac shunt, the observed systemic arterial oxygen saturation should be used to calculate pulmonary blood flow.

**Example**

Let us suppose that a patient is found to have an atrial septal defect (ASD) with a left-to-right shunt clearly detected by oximetry run. Furthermore, the catheter crosses the defect and a pulmonary vein is entered, from which a blood sample shows O2 saturation of 98%. Let us further suppose that systemic arterial blood saturation, however, is 90% and that this is owing to chronic pulmonary disease. After ruling out a right-to-left shunt by any of the various methods (e.g., inhalation of 100% oxygen, indocyanine green dye injection in inferior vena cava, echocardiogram-bubble study), should we use 98% or 90% for pulmonary venous blood O2 saturation in the calculation of Qp?

As indicated earlier, because arterial desaturation is not caused by a right-to-left intracardiac shunt, the observed systemic arterial O2 saturation (90%) should be used because this sums all the pulmonary veins draining both lungs, not just the one with 98% O2 saturation.

**Calculation of Systemic Blood Flow (Qs)**

Use the following equation for systemic blood flow:

$$ Q_s (L/min) = \frac{O_2 \text{ consumption} (mL/min)}{[\frac{SA O_2 \text{ content (mL/L)}}{MV O_2 \text{ content (mL/L)}}]} \quad (12.2) $$

The key to proper measurement of systemic blood flow in the presence of an intracardiac shunt is that the mixed venous oxygen content must be measured in the chamber immediately proximal to the shunt, as shown in Table 12.2.

The formula generally used by cardiologists who treat adults for the calculation of venous content in the presence of an ASD was derived by Flamm and coworkers. They found that systemic blood flow calculated from mixed venous oxygen content as determined from the formula listed in Table 12.2 most closely approximates systemic blood flow as measured by left ventricular to brachial artery (BA) dye curves in patients with atrial septal defect studied at rest. It should be noted that Flamm’s formula weights blood returning from the superior vena cava more heavily than might be expected on the basis of relative flows in the superior and inferior cavae. The success of this empirical weighting of the relatively desaturated superior vena cava blood (O2 saturation is almost always less in blood from the superior as opposed to the inferior vena cava) probably reflects the fact that the third contributor to mixed venous blood—desaturated coronary sinus blood—is not sampled during the oximetry run and therefore cannot be included directly in the formula. The formula (3 SVC O2 + IVC O2)/4 was validated by Flamm and associates for mixed venous oxygen content at rest: In 18 patients without shunt, this value agreed closely with pulmonary artery

<table>
<thead>
<tr>
<th>Location of Shunt as Determined by Site of O2 Step-Up</th>
<th>Mixed Venous Sample to be Used in Calculating Systemic Blood Flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Pulmonary artery (e.g., patent ductus arteriosus)</td>
<td>Right ventricle, average of samples obtained during oximetry run</td>
</tr>
<tr>
<td>2. Right ventricle (e.g., ventricular septal defect)</td>
<td>Right atrium, average of all samples during oximetry run</td>
</tr>
<tr>
<td>3. Right atrium (e.g., atrial septal defect)</td>
<td>( \frac{3(SVC \text{ O}_2 \text{ content}) + 1(IVC \text{ O}_2 \text{ content})}{4} )</td>
</tr>
</tbody>
</table>
blood oxygen content at rest. During supine bicycle exercise, however, a different relationship was found to apply, in which mixed venous (pulmonary artery) oxygen content in patients without shunt was best approximated as 
\[ (\text{SVC } O_2 + \frac{2}{3} \text{IVC } O_2) / 3 \] . This formula was then used for patients with atrial septal defect during exercise, and it reliably predicted systemic blood flow measured by left ventricular to BA dye-dilution curve. Therefore, for patients with left-to-right shunt at the atrial level, the formula in Table 12.2 should be used only for calculation of resting mixed venous \( O_2 \) content.

Obviously, calculations based on the formula in Table 12.2 would be changed a little in many cases by ignoring inferior vena cava blood altogether, and this is done in some laboratories (especially those involved in pediatric catheterization). Flamm and associates, however, examined the effects of assuming that superior vena cava oxygen content equaled mixed venous oxygen content and concluded that this method was somewhat less accurate (both in the 18 subjects without shunt and in the 9 patients with atrial septal defect and left-to-right shunt) than the formula given in Table 12.2.³

Calculation of Left-to-Right Shunt

If there is no evidence of an associated right-to-left shunt, the left-to-right shunt is calculated by

\[ L \to R \text{ shunt} = Q_p - Q_r \text{ (measured in L/min)} \quad (12.3) \]

Examples of Left-to-Right Shunt Detection and Quantification

Some examples of oximetry runs are presented to illustrate interpretation.

Atrial Septal Defect

In the example seen in Figure 12.1, there is a step-up in oxygen saturation in the mid-right atrium. The average or mean value for the vena caval samples in this patient is calculated as \( (3 \text{SVC} + 1 \text{IVC}) / 4 \). SVC is the average of SVC samples (i.e., 67.5% in this example), and IVC is the value for the IVC sample taken at the level of the diaphragm only (i.e., 73%). Thus the vena caval mean \( O_2 \) saturation for the example illustrated in Figure 12.1 is \( (3 \times 67.5 + 1 \times 73) / 4 = 69\% \). The right atrial mean \( O_2 \) saturation for this patient is \( (74 + 84 + 79) / 3 = 79\% \). The 10% step-up in mean \( O_2 \) saturation from vena cava to right atrium is higher than the 7% value listed in Table 12.1 as a criterion for a significant step-up at the atrial level. Note that for this example, the highest-to-highest approach (highest right atrial \( O_2 \) saturation to highest vena caval \( O_2 \) saturation) would barely meet the criteria for a significant step-up, because of the high value of IVC saturation (73%) as compared with SVC saturation. Thus for the detection of a significant step-up at the atrial level using the highest-to-highest approach, it is better to use the highest RA and SVC samples. In this case, the result would be \( (84\% - 68\%) = 16\% \), which is clearly above the 11% value listed in Table 12.1 for detection of a significant step-up. Also, the screening samples that we recommend for all right heart catheterizations (a single sample each from SVC and PA) would have strongly indicated a shunt at some level in the right heart, since \( \Delta O_2 \) saturation from SVC to PA is 12% to 13%, well above the 8% value for a significant step-up.

To calculate pulmonary and systemic blood flows for the example given in Figure 12.1, we need to know \( O_2 \) consumption and blood \( O_2 \) capacity. If the patient’s \( O_2 \) consumption is 240 mL \( O_2 \)/minute and the blood hemoglobin concentration is 14 g%, pulmonary and systemic blood flows may be calculated as follows:

\[ Q_p = \frac{O_2 \text{ consumption (mL/min)}}{\left( \frac{\text{PV } O_2 \text{ content (mL/L)}}{\text{PA } O_2 \text{ content (mL/L)}} \right) - \left( \frac{\text{PV } O_2 \text{ content (mL/L)}}{\text{PA } O_2 \text{ content (mL/L)}} \right)} \quad (12.4) \]

PV \( O_2 \) content was not measured, but left ventricular (LV) and arterial blood \( O_2 \) saturation was 96% (effectively ruling out a right-to-left shunt), and therefore it may be assumed that PV blood \( O_2 \) saturation was 96%. As described in Chapter 11, oxygen content of PV blood is calculated as follows:

\[ 0.96 \left( \frac{14 \text{ g Hgb}}{100 \text{ mL blood}} \right) \times \left( \frac{1.36 \text{ mL } O_2}{\text{g Hgb}} \right) = 18.3 \text{ mL } O_2/100 \text{ mL blood} = 183 \text{ mL } O_2/\text{liter} \quad (12.5) \]
Similarly, PA \(O_2\) content is calculated as
\[
0.80(14)1.36 \times 10 = 152 \text{ mL } O_2/\text{liter} \tag{12.6}
\]
Therefore,
\[
Q_s = \frac{240 \text{ mL } O_2/\text{min}}{[183 - 152] \text{ mL } O_2/L} = 7.74 \text{ L/min} \tag{12.7}
\]
Systemic blood flow for the example illustrated in Figure 12.1 is calculated as
\[
Q_s = \frac{240 \text{ mL } O_2/\text{min}}{(0.96 - 0.69) 14(1.36) 10} = 4.7 \text{ L/min} \tag{12.8}
\]
For this calculation, mixed venous \(O_2\) saturation was derived from the formula given in Table 12.2 as 69%. Thus the ratio of \(Q_p/Q_s\) in this example is 7.74/4.7 = 1.65, and the magnitude of the left-to-right shunt is 7.7 - 4.7 = 3 L/min. This patient has a small to moderate atrial septal defect.

**Ventricular Septal Defect**

Figure 12.2 shows another example of findings in an oximetry run. In this case, the patient has a large \(O_2\) step-up in the right ventricle, indicating the presence of a ventricular septal defect. If \(O_2\) consumption is 260 mL/minute and hemoglobin is 15 g%, then
\[
Q_p = \frac{260}{(0.97 - 0.885) 15(1.36)10} = 15 \text{ L/minute} \tag{12.9}
\]
\[
Q_s = \frac{260}{(0.97 - 0.66) 15(1.36)10} = 4.1 \text{ L/minute} \tag{12.9}
\]
\[
Q_p/Q_s = 15/4.1 = 3.7
\]
\[
L \rightarrow \text{ shunt} = 15 - 4.1 = 10.9 \text{ L/minute}
\]
In this case, the \(O_2\) saturation of mixed venous blood is calculated by averaging the right atrial \(O_2\) saturations because the right atrium is the chamber immediately proximal to the \(O_2\) step-up.

**Flow Ratio**

The ratio \(Q_p/Q_s\) gives important physiologic information about the magnitude of a left-to-right shunt. In addition, because it factors out other variables (e.g., \(O_2\) consumption), the ratio can be calculated from knowledge of blood \(O_2\) saturation alone. A \(Q_p/Q_s\) ratio of <1.5 signifies a small left-to-right shunt and is often a motivation to argue against operative correction, particularly if the patient has an otherwise uncomplicated atrial or ventricular septal defect. A ratio of \(>=2.0\) indicates a large left-to-right shunt and is generally considered sufficient evidence to recommend surgical repair of the defect, to prevent late pulmonary vascular disease as well as other complications of prolonged circulatory overload. Flow ratios between 1.5 and 2.0 are obviously intermediate in magnitude; surgical correction is generally recommended if operative risk is low. A flow ratio of <1.0 indicates a net right-to-left shunt and is often a sign of the presence of irreversible pulmonary vascular disease.

A simplified formula for the calculation of flow ratio can be derived by combining the equations for systemic and pulmonary blood flow to obtain
\[
\frac{Q_p}{Q_s} = \frac{(SA O_2 - MV O_2)}{(PV O_2 - PA O_2)} \tag{12.10}
\]
where \(SA O_2\), \(MV O_2\), \(PV O_2\), and \(PA O_2\) are systemic arterial, mixed venous, pulmonary venous, and pulmonary arterial blood oxygen saturations, respectively. For the case illustrated in Figure 12.1,
\[
Q_p/Q_s = (96% - 69%)/(96% - 80%) = 1.69.
\]

**Calculation of Bidirectional Shunts**

A simplified approach to the calculation of simultaneous right-to-left and left-to-right (also known as bidirectional) shunts makes use of a hypothetic quantity known as the
**Limitations of the Oximetry Method**

There are several limitations and potential sources of error in the calculation of blood flow using the data obtained from an oximetry run. A primary source of error may be the absence of a steady state during the collection of blood samples. That is, if the oximetry run is prolonged because of technical difficulties, if the patient is agitated, or if arrhythmias occur during the oximetry run, the data may not be consistent.

An important limitation of the oxygen step-up method for detecting intracardiac shunts is that it lacks sensitivity. Most shunts of a magnitude that would lead to a recommendation for surgical closure of a ventricular septal defect or patent ductus arteriosus are detected by this method. Small shunts, however, are not consistently detected by this technique.

As pointed out by Antman and coworkers, the normal variability of blood oxygen saturation in the right heart chambers is strongly influenced by the magnitude of systemic blood flow. High levels of systemic flow tend to equalize the arterial and venous oxygen values across a given vascular bed. Therefore, elevated systemic blood flow will cause the mixed venous oxygen saturation to be higher than normal, and interchamber variability owing to streaming will be blunted. Even a small increase in right heart oxygen saturation under such conditions might indicate the presence of a significant left-to-right shunt; larger increases would indicate voluminous left-to-right shunting of blood. For a patient with a systemic blood flow index of 3.0 L/minute per M², minimum shunt sizes that could be detected reliably by oximetry are listed in Table 12.1.

Fundamental to the oximetric method of shunt detection is the fact that left-to-right shunting across an intracardiac defect will cause an increase in blood O₂ saturation in the chamber receiving the shunt proportional to the magnitude of the shunt. The increase in blood O₂ content in the chamber receiving the shunt, however, depends not only on the magnitude of the shunt but also on the O₂-carrying capacity of the blood (i.e., the hemoglobin concentration). As reported by Antman and colleagues, the influence of blood hemoglobin concentration may be important when blood O₂ content (rather than O₂ saturation) is used to detect a shunt (Table 12.3).

Thus, the same shunt giving the same blood O₂ saturation step-up would give markedly different blood O₂ content step-ups if the blood hemoglobin concentration varied significantly. Accordingly, when evaluating oximetric data for shunt detection, it is a more precise method to exclude the potential influence of blood O₂-carrying capacity and use only O₂ saturation data. This is especially true in pediatric cases where the normal blood O₂-carrying capacity may vary from 20 to 28 vol% in the neonate to 12 to 16 vol% in infancy. To minimize errors and maximize the physiologic strengths of the oximetry method for shunt detection and quantification, the guidelines listed in Table 12.4 should be followed.

**Other Indicators**

Many other more sensitive techniques are available for detecting smaller left-to-right shunts. These include indocyanine green dye curves, radionuclide techniques, contrast angiography, and echocardiographic methods. Some of these

**Expected Value of O₂ Content (Volumes Percent) for Various Levels of O₂ Step-Up and Blood Hemoglobin Concentration**

<table>
<thead>
<tr>
<th>Increase in O₂ Saturation (%)</th>
<th>Hemoglobin Concentration (g/100 mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>0.68</td>
</tr>
<tr>
<td>12</td>
<td>0.82</td>
</tr>
<tr>
<td>15</td>
<td>1.02</td>
</tr>
<tr>
<td>20</td>
<td>1.36</td>
</tr>
<tr>
<td>24</td>
<td>1.63</td>
</tr>
<tr>
<td>30</td>
<td>2.04</td>
</tr>
<tr>
<td>40</td>
<td>2.45</td>
</tr>
<tr>
<td>50</td>
<td>3.06</td>
</tr>
<tr>
<td>60</td>
<td>4.08</td>
</tr>
</tbody>
</table>


\[
Q_{\text{of}} = \frac{O_{\text{2 consumption (mL/min)}}}{\left[\frac{\text{PV } O_{\text{2 content (mL/L)}}}{\text{MV } O_{\text{2 content (mL/L)}}}\right]}
\]

\[
Q_{\text{of}} = \left[\frac{\text{PV } O_{\text{2 content (mL/L)}}}{\text{MV } O_{\text{2 content (mL/L)}}}\right]
\]

\[
R \rightarrow L = \frac{Q_{\text{of}} \times (\text{PV } O_{\text{2 content (mL/L)}} \times \text{MV } O_{\text{2 content (mL/L)}})}{(\text{SA } O_{\text{2 content (mL/L)}} \times \text{MV } O_{\text{2 content (mL/L)}})}
\]

\[
L \rightarrow R = \frac{Q_{\text{of}} \times (\text{MV } O_{\text{2 content (mL/L)}} \times \text{PA } O_{\text{2 content (mL/L)}})}{(\text{PV } O_{\text{2 content (mL/L)}} \times \text{PA } O_{\text{2 content (mL/L)}})}
\]
Table 12.4 Guidelines for Optimum Use of the Oximetric Method for Shunt Detection and Quantification

1. Blood samples at multiple sites should be obtained rapidly.

2. Blood $O_2$ saturation data rather than $O_2$ content data are preferable to identify the presence and location of a shunt.

3. Comparison of the mean of all values obtained in the respective chambers is preferable to comparison of the highest values in each chamber.

4. Because of the significant influence of systemic blood flow on shunt detection, exercise should be used in equivocal cases where a low systemic blood flow is present at rest.


* if pulmonary vein is not entered, use 98% × $O_2$ capacity.

Methods (e.g., green dye) were discussed extensively in previous editions of this textbook, and the interested reader is referred there for details. For discussion of other predominantly non-catheter-based methods (e.g., echo, radionuclide) the reader is referred to textbooks devoted to those techniques. We will give only one example here of one of the older methods.

Early Recirculation of an Indicator

Standard indicator-dilution curves method, performed by injection of indocyanine green into the pulmonary artery with sampling in a systemic artery, is rarely used today, and most laboratories are not even equipped to perform this technique. In the presence of a left-to-right shunt, however, a green dye curve produced by this technique will demonstrate early recirculation on the downslope of the dye curve* (Figure 12.3).

This technique can detect left-to-right shunts too small to be detected by the oxygen step-up method,a Thus if there is no evidence of a left-to-right shunt by this method, there is no need to perform an oximetry run. The studies of Castillo and coworkers suggest that left-to-right shunts as small as 25% of the systemic output can be detected by standard pulmonary artery to systemic artery dye curves.

Although a simple pulmonary to systemic artery indocyanine green dye curve may detect the presence of a shunt, it does not localize it. That is, a pulmonary artery to systemic artery dye curve will show evidence of early recirculation in the presence of a left-to-right shunt owing to an atrial septal defect, ventricular septal defect, or patent duc tus arteriosus.

Angiography

Selective angiography is effective in visualizing and localizing the site of left-to-right shunts. Angiographic demonstration of anatomy has become a routine part of the preoperative evaluation of patients with congenital or acquired shunts and is useful in localizing the anatomic site of the shunt. Actually, the use of angiography in this fashion should be considered an indicator-dilution method, with the radiographic contrast agent being the indicator and the cinefluoroscopy unit serving as the densitometer.

In general, assessment of the patient with a left-to-right shunt virtually always includes a left ventriculogram. If this is performed in the left anterior oblique projection with cranial angulation (or done as a biplane study with both left and right anterior oblique views), excellent visualization of the interventricular septum, sinuses of Valsalva, and ascending and descending thoracic aorta will allow diagnosis and localization of essentially all the causes of left-to-right shunt other than atrial septal defect and anomalous pulmonary venous return.

![Figure 12.3](image-url) Left-to-right shunt. This indicator-dilution curve, obtained by injecting indocyanine green into the pulmonary artery with sampling in the brachial artery, demonstrates early recirculation on the downslope, indicating a left-to-right shunt. Injection was at time zero. This technique does not localize the site of the left-to-right shunt.
Complicated lesions (e.g., endocardial cushion defects, coronary artery/right heart fistulas, ruptured aneurysms at the sinus of Valsalva) commonly require angiographic delineation before surgical intervention can be undertaken. Angiography also helps to assess the “routine” cases more completely. For instance, does the patient with secundum atrial septal defect have associated left ventricular dysfunction or mitral valve prolapse? Does the patient with ventricular septal defect have associated aortic regurgitation (caused by prolapse of the medial aortic leaflet) or infundibular pulmonic stenosis?

Angiography, however, cannot replace the important physiologic measurements that allow quantitation of flow and vascular resistance. Without quantitative evaluation of pulmonary and systemic flows ($Q_p$ and $Q_s$) and their associated resistances (PVR and SVR), appropriate decisions regarding patient management cannot be made, nor can prognosis be assessed.

**DETECTION OF RIGHT-TO-LEFT INTRACARDIAC SHUNTS**

The primary indication for the use of techniques to detect and localize right-to-left intracardiac shunts is the presence of cyanosis or, more commonly, arterial hypoxemia. The presence of arterial hypoxemia raises two specific questions: first, is the observed hypoxemia owing to an intracardiac shunt, or is it owing to a ventilation/perfusion imbalance secondary to a variety of forms of intrinsic pulmonary disease? This problem is particularly important in patients with coexistent congenital heart disease and pulmonary disease. Second, if hypoxemia is caused by an intracardiac shunt, what is its site and what is its magnitude?

Attempts to measure right-to-left shunts in patients with cyanotic heart disease date back at least to 1941. Prinzmetal, in a series of ingenious experiments, expanded the earlier observation of Benenson and Hitzig that ether injected intravenously in patients with cyanotic heart disease will cause a prickly, burning sensation of the face. This sensation is caused by the entry of ether into the systemic circulation of patients with right-to-left shunts. In normal subjects without right-to-left shunts, the ether is eliminated by the lungs and thus does not reach the systemic circulation. Prinzmetal then measured the time necessary for an intravenous injection of a dilute solution of saccharin to be tasted. This time is equal to the transit time from a peripheral vein through the lungs, through the left heart, and then to the systemic circulation. By increasing the concentration of saccharin, he found that a second, much shorter appearance time occurred in patients with cyanotic heart disease because of the presence of a right-to-left shunt bypassing the pulmonary circulation. He then estimated the percent right-to-left shunt by the following formula:

$$\% \text{ R \rightarrow L Shunt} = \frac{A}{A + C}$$

(12.13)

where $A$ is the smallest concentration of saccharin to be tasted by way of the long circuit and $C$ is the smallest concentration of saccharin to be tasted by way of the short circuit.

Our current methods of documenting and quantitating right-to-left shunts may not be as ingenious and certainly are not as sweet, but they are nonetheless effective.

**Angiography**

With appropriate techniques, angiography may be used to detect right-to-left intracardiac shunts. This method is particularly important in detecting right-to-left shunting caused by a pulmonary arteriovenous fistula. In this circumstance, the shunt cannot be detected by indicator-dilution curves on the basis of a shortened appearance time. That is, the difference in transit time when the pulmonary capillaries are bypassed is not perceptible by standard indicator-dilution techniques. Although angiography may localize right-to-left shunts, it does not permit quantification.

**Oximetry**

The site of right-to-left shunts may be localized if blood samples can be obtained from a pulmonary vein, the left atrium, left ventricle, and aorta. The pulmonary venous blood of patients with arterial hypoxemia caused by an intracardiac right-to-left shunt is fully saturated with oxygen. Therefore, the site of a right-to-left shunt may be localized by noting which left heart chamber is the first to show desaturation (i.e., a step-down in oxygen concentration). Thus if left atrial blood oxygen saturation is normal but desaturation is present in the left ventricle and in the systemic circulation, the right-to-left shunt is across a ventricular septal defect. The only disadvantage of this technique is that a pulmonary vein and the left atrium must be entered. This is not as easy in adults as it is in infants, in whom the left atrium may be entered routinely by way of the foramen ovale.

**Echocardiography**

Echocardiographic methods have been proved sensitive enough for the detection and localization of left-to-right and right-to-left shunts. The so-called echocardiographic contrast or “bubble study” using agitated saline solution with microbubbles or some of the newer specifically designed echo contrast agents can detect small shunts, and the use of two-dimensional echocardiographic techniques can usually localize the site of the shunt to the atrial or ventricular septum. Combined echocardiographic and cardiac catheterization studies involve injection of the echo contrast agent into the right or left heart chambers sequentially, thus permitting localization of the shunt and determination of whether it is unidirectional or bidirectional. Echo-Doppler techniques can also be used to detect and localize intracardiac shunts. In this regard, color Doppler echocardiography is particularly useful in detecting and localizing small intracardiac shunts without the need for injection of an echo contrast agent. An example of the use of the echo-contrast technique for the detection of an atrial septal defect with left-to-right shunting is shown in Figure 12.4.
Section III Hemodynamic Principles

Figure 12.4 Two-dimensional echo showing right ventricular (RV) inflow tract (top), short axis views at the base (middle) (AO = aorta), and four-chamber apical view (bottom) in a patient with an atrial septal defect (ASD), shown at cardiac catheterization to be associated with a $Q/Q_s$ of 3.0. **Left views.** The anatomy before echo contrast injection. Following an intravenous injection of agitated saline solution (right views), a negative contrast effect (black arrows) is seen within the right atrium (RA), compatible with entry of unopacified blood from the left atrium (LA) across the ASD into the RA. The ASD is visualized (white arrow) as an area of septal dropout. (Reproduced from Come PC, Riley M. Contrast echocardiography. In: Come PC, ed. Diagnostic Cardiology: Noninvasive Imaging Techniques. Philadelphia, PA: JB Lippincott, 1984:294, with permission.)

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The normal cardiac valve offers little resistance to blood flow. As valvular stenosis develops, there is progressively more resistance to flow, causing a pressure drop (pressure gradient) across the valve. For any stenotic orifice size, a stronger flow across the orifice yields a higher pressure gradient. Using two fundamental hydraulic formulas, Dr. Richard Gorlin and his father developed a formula for the calculation of cardiac valvular orifices from flow and pressure-gradient data.

THE GORLIN FORMULA

The first hydraulic formula that the Gorlins used was based on Torricelli's law, which describes flow across a round orifice:

\[ F = AVC_c \]  

(13.1)

where \( F \) is the flow rate, \( A \) is the orifice area, \( V \) is the velocity of flow, and \( C_c \) is the coefficient of orifice contraction. The constant \( C_c \) compensates for the physical phenomenon that, except for a perfect orifice, the area of a stream flowing through an orifice will be less than the true area of the orifice.

Rearranging the terms,

\[ A = \frac{F}{VC_c} \]  

(13.2)

The second hydraulic principle used in the derivation of the Gorlin formula relates pressure gradient and velocity of flow according to Torricelli's law:

\[ V^2 = (C_v)^2 \cdot 2gh \quad \text{or} \quad V = (C_v)\sqrt{2gh} \]  

(13.3)

where \( V \) is the velocity of flow; \( C_v \) is the coefficient of velocity, correcting for the energy loss as pressure energy is converted to kinetic or velocity energy; \( h \) is the pressure gradient in cm H₂O, and \( g \) is the gravitational constant (980 cm/second²) for converting cm H₂O to units of pressure.

Combining the two equations,

\[ A = \frac{F}{C_v \sqrt{2gh} \cdot C_c} = \frac{F}{C_c C_v \sqrt{2 \cdot 980 \cdot h}} = \frac{F}{(C)(44.3)\sqrt{h}} \]  

(13.4)

where \( C \) is an empirical constant accounting for \( C_v \) and \( C_c \), and the expression of \( h \) in mmHg (rather than cm H₂O), and correcting the calculated valve area to the actual valve area measured at surgery or autopsy.

It is obvious that antegrade flow across the mitral and tricuspid valves occurs only in diastole, whereas that across the aortic and pulmonic valves occurs only in systole. Accordingly, the flow, \( F \), in Eq. (13.4) is the total cardiac output expressed in terms of the number of seconds per minute during which there is actually forward flow across the valve. For the mitral and tricuspid valves, this is calculated by multiplying the diastolic filling period (seconds per beat) by the heart rate (beats per minute [bpm]), yielding the number of seconds per minute during which there is diastolic flow. The cardiac output in milliliters per minute (or cm³/minute) is then divided by the number of seconds per minute during which there is flow, yielding diastolic flow in cubic centimeters per second. For the aortic and pulmonic valves, the systolic ejection period is substituted for the diastolic filling period. The manner in which the diastolic filling period and systolic ejection period are measured is shown in Figure 13.1. The diastolic filling period begins at mitral valve opening.
Figure 13.1 Left ventricular (LV), aortic (Ao), and pulmonary capillary wedge (PCW) pressure tracings from a patient without valvular heart disease, illustrating the definition and measurement of diastolic filling period (DFP) and systolic ejection period (SEP). (See text for discussion.)

and continues until end-diastole. The systolic ejection period begins with aortic valve opening and proceeds till the dicrotic notch or some other evidence of aortic valve closure.

Thus the final equation for the calculation of valve orifice area $A$ (in cm$^2$) is

$$ A = \frac{CO/(DFP \text{ or } SEP)(HR)}{44.3 \sqrt{\Delta P}} $$

(13.5)

where $CO$ is the cardiac output (cm$^3$/minute), $DFP$ is the diastolic filling period (seconds/beat), $SEP$ is the systolic ejection period (seconds/beat), $HR$ is the heart rate (beats/minute), $C$ is an empirical constant, and $P$ is the pressure gradient. $DFP$ is measured directly from left ventricular (LV) versus pulmonary capillary wedge (PCW) or left atrial pressure tracings as shown in Figure 13.1.

An empirical constant of 0.7 (later adjusted to 0.85) was derived by comparing the calculated and actual mitral valve areas.$^{12}$ With the use of this constant, the maximum deviation of the calculated valve area from the measured valve area was 0.2 cm$^2$. The empirical constant for the aortic, tricuspid and pulmonic valves has never been derived because of lack of data comparing actual with calculated valve areas for these valves; the constant for these valves has been assumed to be 1.0 (i.e., $1.0 \times 44.3 = 44.3$). Nonetheless, the Gorlin formula remains the gold standard for assessing the severity of stenosis in cardiac valves.

**MITRAL VALVE AREA**

By rearranging the terms of Eq. (13.5), one sees that for the mitral valve,

$$ \Delta P = \left[ \frac{CO/(HR)(DFP)}{(MVA)(44.3)(0.85)} \right]^2 $$

(13.6)

where $\Delta P$ is the mean transmural pressure gradient and MVA is the mitral valve area. Thus, by doubling cardiac output one will quadruple the gradient across the valve, if heart rate and diastolic filling period remain constant. The normal mitral orifice in an adult has a cross-sectional area of 4.0 to 5.0 cm$^2$ when the mitral valve is completely open in diastole. Considerable reduction in this orifice area can occur without symptomatic limitation, but when the area is 1.0 cm$^2$ or less, a substantial resting gradient will be present across the mitral valve and any demand for increased cardiac output will be met by increases in left atrial and pulmonary capillary pressure that lead to pulmonary congestion and edema.

Figure 13.2 demonstrates that a cardiac output of 5 L/minute can be maintained with only a minimal mitral diastolic gradient as the mitral orifice area contracts from its normal 4.0 to 5.0 cm$^2$ to a moderately stenotic area of 2.0 cm$^2$. After that, the gradient rises so that, at an orifice area of 1.0 cm$^2$, a resting gradient of 8 to 10 mmHg is required to maintain the cardiac output at 5 L/minute with a normal resting heart rate of 72 bpm (Figure 13.2A). Note that even at this level of cardiac output, substantial increases in gradient may occur in response to tachycardia (Figure 13.2B, C), which reduces the total time per minute available for diastolic filling. Thus, 1.0 cm$^2$ is generally viewed as the critical mitral valve area because even small increases in cardiac output lead to pulmonary congestion and severe dyspnea. However, some allowance needs to be made for the patient's size in assessing critical valve area. Larger patients need stronger flows than needed by smaller patients to maintain tissue perfusion, and they also have higher gradients because of higher cardiac output for any given valve orifice area. Thus 1.2 cm$^2$ could be a critical mitral valve area for a large patient. Currently, no uniform agreement exists on indexing critical valve area to body size.

**Example of Valve Area Calculation in Mitral Stenosis**

Figure 13.3 shows PCW and LV pressure tracings in a 40-year-old woman with rheumatic heart disease and severe mitral stenosis. This woman also had hypertension and significant elevation of her LV diastolic pressure. The valve orifice area is calculated with the aid of a form reproduced as Table 13.1. In this patient, five beats were chosen from the recordings taken closest in time to the Fick cardiac output determination. Planimetry of the area between PCW and LV pressure tracings (Figure 13.3) was done for these five beats, and these areas were divided by the length of the diastolic
Figure 13.2 Relationship between cardiac output and mean diastolic pressure gradient in patients with mitral stenosis, calculated using Eq. (13.6), derived from the Gorlin formula. Curves represent orifice areas of 4.0, 2.0, 1.0, 0.7, and 0.5 cm². A to C. Flow-gradient relations at differing heart rates and diastolic filling periods (see text for discussion). (Courtesy of Dr. James J. Ferguson III.)

Figure 13.3 Pulmonary capillary wedge (PCW) and left ventricular (LV) pressure tracings in a 40-year-old woman with severe mitral stenosis. This woman also had systemic arterial hypertension and significant elevation of her LV diastolic pressure. (See text for discussion.)

Filling periods for each beat, giving an average gradient deflection in millimeters. The mean gradient in millimeters of mercury (Table 13.1, part B) was calculated as the average gradient deflection in millimeters multiplied by the scale factor (mmHg/mm deflection). In this case, the mean gradient was 30 mmHg. Next, the average diastolic filling period was calculated (Table 13.1, part C) using the average measured length between initial PCW-LV crossover in early diastole and end-diastole (peak of the R wave by ECG). This average length in millimeters was divided by the paper speed (mm/second) to give the average diastolic filling period, which in this case was 0.40 second. Heart rate and cardiac output (Table 13.1, parts D and E) are recorded, ideally from data collected simultaneously with the recording of the PCW-LV pressure gradient. Heart rate was 80 bpm and cardiac output was 4,680 cm³/minute in the case illustrated in Figure 13.3. It should be noted that cardiac output must be expressed in cubic centimeters per minute if valve area is expressed in square centimeters of cross-sectional area.

Entering these values in the formula given in Table 13.1, part F, and using a constant of 0.85(44.3) = 37.7 for the mitral valve, we get

\[
\text{Mitral orifice area} = \frac{(4.680\text{ cm}^3/\text{min})(80 \text{ beats/min})(0.40 \text{ sec/beat})}{37.7 \text{ cm}^2/30 \text{ mmHg}}
\]

\[
= 0.71 \text{ cm}^2
\]  

(13.7)

Because the accuracy of the method to hundredths of a square centimeter has not been demonstrated, the resulting valve area is rounded off and expressed as 0.7 cm².
### Table 13.1  Valve Orifice Area Determination

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Unit number</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complex no.</td>
<td>Area of gradient (mm²) / Length of diastolic or systolic period (mm)</td>
<td>= Average gradient (deflection, mm)</td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>2.</td>
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<td>3.</td>
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</tr>
<tr>
<td>4.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

B. Mean gradient = Average gradient (mm deflection) × scale factor (mmHg/mm deflection)

\[
= \frac{\text{Average gradient (mm deflection)}}{\text{scale factor (mmHg/mm deflection)}} = \text{mmHg}
\]

C. Average diastolic or systolic period = average length (mm)/paper speed (mm/sec)

\[
= \frac{\text{average length (mm)}}{\text{paper speed (mm/sec)}} = \text{sec/beat}
\]

D. Heart rate = _________ beat/min

E. Cardiac output (Fick or indicator dilution) = _________ mL/min

\[
\text{cardiac output/(heart rate} \times \text{avg. diastolic or systolic period) = cardiac output/heart rate} \times \text{avg. diastolic or systolic period)
\]

F. \[\text{valve constant}^a \times \sqrt{\text{mean gradient}}\]

\[
= \text{valve constant}^a \times \sqrt{\text{mean gradient}} = \text{cm}^2
\]

G. Valve area index = valve area/body surface area = _________ cm²/m²

---

**Pitfalls**

**Pulmonary Capillary Wedge Tracing**

In most cases, PCW pressure is substituted for left atrial pressure under the assumption that a properly confirmed wedge pressure accurately reflects left atrial pressure. Nishimura et al. found that transmitral gradient was overestimated by 3.3 to 3.5 mmHg when a Swan-Ganz catheter was used to measure the wedge pressure in comparison with actual left atrial pressure. However, these “wedge” pressures were not confirmed as true wedge pressures, using the techniques described in Chapter 6. Conversely, Lange et al. measured left atrial pressure directly (trans-septal) and compared it with oximetrically confirmed wedge pressure obtained using a stiff woven Dacron catheter. In this study, overestimation of true left atrial pressure was only 1.7 ± 0.6 mmHg. Hence we and others believe that the weight of evidence and our own experience support the use of PCW pressure as a satisfactory substitution for left atrial pressure, except in some patients with pulmonary veno-occlusive disease or cor triatratum. Failure to wedge the catheter properly may, however, cause one to compare a dampened pulmonary artery pressure with the LV pressure, yielding a falsely high gradient. To ensure that the right heart catheter is properly wedged, one should verify that

1. The mean wedge pressure is lower than the mean pulmonary artery pressure

2. Blood withdrawn from the wedged catheter is ≥95% saturated with oxygen, or at least equal in oxygen saturation to arterial blood.
Alignment Mismatch

Alignment of the PCW and LV pressure tracings does not match alignment of simultaneous left atrial and LV tracings because there is a time delay in the transmission of the left atrial pressure signal back through the pulmonary venous and capillary beds. The resulting pressure mismatch is small when PCW pressure is measured in the distal pulmonary arteries using a 7F or 8F Cournand or Goodale-Lubin catheter, but may be larger when wedge pressure is measured more proximally in the pulmonary arterial tree using a balloon-tipped flow-directed catheter. The A and V waves in an optimally damped PCW tracing are delayed typically by 50 to 70 milliseconds as compared with a simultaneous left atrial pressure tracing. Thus, ideally, the wedge pressure should be realigned with the LV pressure (using tracing paper) by shifting it leftward by 50 to 70 milliseconds.

The V wave, which is normally present in the left atrium (where it represents pulmonary venous return), peaks immediately before the downstroke of the LV pressure tracing. With a wedge pressure measured distally using a 7F Goodale-Lubin catheter (Figure 13.3), the peak of the V wave is bisected by the rapid downstroke of LV pressure decline. Realignment of the wedge tracing in such a way that the V wave peak is bisected by (or slightly to the left of) the downstroke of LV pressure is a practical method for achieving better physiologic realignment.

Calibration Errors

Failure to calibrate the pressure transducers properly and adjust them to the same zero reference point may yield an erroneous gradient. A quick way to check the validity of an unexpected transmitral pressure gradient is to switch the left and right heart catheters to the opposite transducers, which if calibrated correctly will yield the same gradient.

Cardiac Output Determination

Cardiac output must be determined accurately using the techniques described in Chapter 11. The cardiac output used in valve area calculation should be the value measured simultaneously with the gradient determination. The measurement used in the valve area formula is usually the forward cardiac output determined by the Fick method or the thermodilution method. If mitral valvular regurgitation exists, the gradient across the valve will reflect not only the net forward flow but forward plus regurgitant or total transmural diastolic flow. Therefore, using only the net forward flow to calculate the valve orifice area will underestimate the actual anatomic valve area in cases where regurgitation coexists with stenosis. It is worth noting that many patients with mitral stenosis have coexistent tricuspid regurgitation. As indicated in Chapter 11, tricuspid regurgitation may cause the thermodilution technique for measuring cardiac output to be inaccurate.

Early Diastasis

Even when left atrial and LV pressures equalize (diastasis) before the end of diastole, there will generally still be a flow through the mitral valve after the point of diastasis. The diastolic filling period to be used in valve area calculation should include all of nonisovolumic diastole, not just the period during which a gradient is present.

AORTIC VALVE AREA

An aortic valve area of 0.7 cm² or less is generally considered severe enough to account for the symptoms of angina, syncope, or heart failure in a patient with aortic stenosis. Because the development of symptoms in patients with aortic stenosis portends an abrupt worsening of prognosis, this valve area is termed critical. However, it must be pointed out that no unique critical valve area has been established and that even an aortic valve area as large as 1.0 cm² can cause symptoms and thus be critical, especially in a large individual. Conversely, smaller calculated valve orifice areas in a totally asymptomatic patient may not be critical. For this reason the AHA/ACC Guidelines for the Management of Patients with Valvular Heart Disease avoided the use of the word “critical.” Instead, they define “severe” as an AVA of ≤1.0 cm², recognizing that one can define “severe,” without defining “critical.” Figure 13.4 illustrates the relationship between cardiac output and aortic pressure gradient over a range of values of aortic valve area and at three different values of heart rate and systolic ejection period. For the aortic valve, Eq. (13.4) can be rearranged as

\[
\Delta P = \left( \frac{\text{CO}/(\text{HR})(\text{SEP})}{44.3 \text{ AVA}} \right)^2
\]

As can be seen in Figure 13.4A, at a normal resting cardiac output of 5.0 l/minute, an aortic orifice area of 0.7 cm² will result in a pressure gradient of approximately 33 mmHg across the aortic valve. Doubling of the cardiac output, as might occur with exercise, would increase the gradient by a factor of 4 to 132 mmHg if the systolic time per minute did not change. This increase in gradient would require a peak LV pressure in excess of 250 mmHg to maintain a central aortic pressure of 120 mmHg. Such a major increase in LV pressure obviously increases myocardial oxygen demand and limits ejection performance. These factors contribute to the symptoms of angina and congestive heart failure, respectively. The limitations in cardiac output imposed by high afterload may contribute to hypotension when peripheral vasodilation occurs during muscular exercise.

Actually, the systolic time per minute does not remain constant during the increase in cardiac output associated with exercise. As heart rate increases during exercise, the systolic ejection period tends to become shorter, but the tendency is counteracted by both increased venous return and systemic...
arteriolar vasodilation, factors that normally help to maintain LV stroke volume constant (or even allow it to increase) during exercise. Thus, the heart rate is increasing but the systolic ejection period is diminishing only slightly so that their product (the systolic ejection time per minute) increases. This is the counterpart of the decrease in diastolic filling time per minute during exercise discussed earlier. Examining Eq. (13.8), it can be seen that the increase in cardiac output will be partially offset by the increase in the term (HR)(SEP) so that the gradient will not quadruple with a doubling of cardiac output during exercise.

Figure 13.4B and C show that with decreasing heart rate, the gradient increases in aortic stenosis for any value of cardiac output. This is opposite to the effect of heart rate in mitral stenosis and reflects the opposite effects of heart rate on systolic and diastolic time per minute. Viewed another way, as the heart rate slows in aortic stenosis, the stroke volume increases if cardiac output remains constant. Thus the flow per beat across the aortic valve increases and so does the pressure gradient.

As with mitral stenosis, some allowance must be made for body size in defining a critical valve area in patients with aortic stenosis; larger patients who require higher output may become symptomatic even at somewhat larger valve areas. Thus, a man with a very large body surface area of 2.4 m² and a cardiac index of 3.0 L/minute/m² would have a cardiac output of 7,200 mL/minute. At a heart rate of 68 bpm (Figure 13.4C), this man might have a 50 mmHg aortic valve gradient with an orifice area of 0.9 to 1.0 cm². Thus, for him, this might be the critical valve area.

**Example**

Figure 13.5 demonstrates simultaneous pressure tracings from the left ventricle (LV) and right femoral artery (RFA) in a patient with exertional syncope. Because the pulse wave takes a finite period of time to travel from the left ventricle to the femoral artery, the femoral artery tracing is somewhat delayed (Figure 13.5A). Figure 13.5B shows the LV and RFA tracings realigned to correct for the delay in transmission time. This is accomplished by using tracing paper and aligning the arterial upstroke to coincide with the LV upstroke. After such an alignment, the mean pressure gradient can now be obtained by planimetry, and the orifice area can be calculated using the form given in Table 13.1. For this example, the average aortic pressure gradient is 40 mmHg, the systolic ejection period is 0.33 second, the heart rate is 74 bpm, and the cardiac output is 5,000 mL/minute. Using these values together with an aortic valve constant of (1)(44.3) = 44.3 in the equation in Table 13.1 gives

\[
\text{Aortic valve area} = \frac{5,000 \text{ cm}^3/\text{min}}{(74 \text{ beats/min})(0.33 \text{ sec/beat})} = 0.7 \text{ cm}^2
\]
As discussed in Chapter 10, peripheral arterial pressure waveforms are distorted in ways other than time delay. These distortions include systolic amplification and spreading out (widening) of the pressure waveform. To assess possible errors introduced by the use of peripheral arterial pressure as a substitute for ascending aortic pressure, Folland et al. compared the \( \text{LV-ascending aortic (LV-Ao)} \) mean gradient with the \( \text{LV-femoral artery (LV-FA)} \) systolic gradient, with and without realignment (Figure 13.6), in 26 patients with aortic stenosis. Without realignment of the LV-FA gradient, the LV-Ao gradient was overestimated by about 9 mmHg. In contrast, aligned LV-FA gradient underestimated the LV-Ao gradient by about 10 mmHg, possibly because peak systolic arterial pressure is higher in peripheral arterial pressure tracings than in central aortic tracings so that the planimetered gradient is smaller when using LV-FA. Without realignment, this effect is offset by the fact that much of the arterial systolic waveform falls outside and to the right of the LV pressure tracing (Figure 13.6). A second error in gradient measurement can occur if the LV catheter is placed in the LV outflow tract. As shown in Figure 13.7, a gradient usually exists between the body of the left ventricle and the outflow tract, produced as blood accelerates when it enters this relatively narrow portion of the left ventricle. A catheter tip placed in the LV outflow tract will measure a typical LV pressure tracing, but can underestimate the true LV-aorta gradient by 30 mmHg.

Assey et al. measured the transaortic valve gradients in 15 patients from eight different combinations of catheter locations using the schema shown in Figure 13.8. The average mean gradient recorded between positions 1 and 3 was the highest, whereas the gradient between positions 1 and 5 recorded using the alignment technique produced the smallest value. In some patients, the differences in gradient among the different measurement sites were as much as 45 mmHg. In calculating aortic valve area, the gradient between sites 1 and 3, which records the gradient before pressure recovery, is probably the most accurate reflection of the pressure drop across the valve. When the aortic catheter is placed at a more distal site, it records the effect of pressure recovery, which reduces the gradient as blood flow again becomes laminar. The more proximal aortic position is probably the ideal location for measuring the gradient for the valve area calculation; the more distal positions may better reflect the actual overload on the myocardium. When the transvalvular gradient recorded from positions 1 and 5a in Figure 13.8 is larger than 60 mmHg, these differences are of little clinical importance. When a small transvalvular gradient is present in conjunction with a low cardiac output, however, the differences between aligned and unaligned tracings and between gradients recorded at different catheter locations may affect the decision about whether to replace the valve. In such instances, the problem can be obviated by placing a second catheter in the proximal ascending aorta without the need for alignment (Figure 13.6A). As an alternative, the difference between peak central aortic pressure and peripheral arterial pressure is added to the planimetered gradient measured during the
Figure 13.7

A. Pressure tracings recorded from two catheters placed within the body of the left ventricular (LV) chamber. Tracings are nearly identical. B. Pressures recorded by two catheters, one placed in the body of the left ventricular chamber and the other placed in the left ventricular outflow tract (LVOT), proximal to the aortic valve (AO). Both catheters recorded characteristic left ventricular pressure tracings; however, there is a substantial pressure gradient between the body of the left ventricle and the outflow tract. This is not owing to anatomic subvalvular stenosis but rather to acceleration of blood as it enters the relatively narrow outflow tract. C. Pressures recorded from one catheter in the body of the left ventricle and a second catheter in the proximal aorta. These tracings demonstrate the gradient across the aortic valve and outflow tract. (Reproduced from Paspoularides A. Clinical assessment of ventricular ejection dynamics with and without outflow obstruction. J Am Coll Cardiol 1990;15:859, with permission.)

Fick output determination. This compensates for the fact that the planimetered gradient with realignment (Figure 13.6C) underestimates the true gradient (Figure 13.6A). Another approach to increasing the accuracy of transaortic valve gradient measurement using simultaneously recorded LV and femoral artery pressures has been introduced by Krueger et al.\textsuperscript{12} at the University of Utah. As seen in Figure 13.9, the mean LV systolic pressure during the interval A and the mean FA systolic pressure during the interval B are determined by planimetry. Their difference was nearly identical to the gradient measured by planimetry of simultaneously recorded LV and central aortic pressures and was more accurate than the other techniques commonly used.\textsuperscript{12}

The most accurate approach, however, involves the use of a second catheter positioned in the ascending aorta, as discussed earlier, or the use of dual lumen catheters. In particular, we have found that dual lumen catheters, such as the Langston catheter (Vascular Solutions Inc, Minneapolis, MN), provide today an excellent option for simultaneous and accurate measurements of LV and ascending aortic pressure.

If a second catheter or a dual lumen catheter is not used to obtain simultaneous LV and peripheral pressures, the gradient may be obtained by recording the LV pressure and superimposing it on the aortic pressure obtained immediately after the LV catheter is pulled back into the aorta.

It should be noted that the current AHA/ACC guidelines\textsuperscript{6} make crossing the aortic valve in a patient with aortic stenosis...
a class III recommendation (potentially harmful, not beneficial) if the severity of aortic stenosis is clear from noninvasive testing. Conversely, it is a class I recommendation (indicated, beneficial) to cross the valve if the diagnosis and severity are in doubt. Thus the pressure gradient, obtained by whatever means, must be as accurate as possible because crucial management decisions will be based upon it.

Pitfalls

Transducer Calibration

As with calculation of mitral valve area, attention to cardiac output determination and transducer calibration is critical. Assurance that proper transducer calibration has been accomplished can be obtained by comparing the left heart catheter pressure with the peripheral arterial catheter pressure before insertion of the left heart catheter into the left ventricle. Because in the absence of peripheral stenosis the mean arterial pressure will be the same throughout the arterial tree, the mean pressures recorded by both catheters should be identical, confirming identical transducer calibration. Further gradient verification is done by comparing the LV pressure with aortic pressure obtained by the left heart catheter during catheter pullback. In this case, both the LV and the aortic pressure are recorded by the same catheter and transducer, eliminating the second transducer as a source of error.

Pullback Hemodynamics

When the aortic valve area is diminished to 0.6 cm² or less, a 7F or 8F catheter placed retrograde across the valve takes up a significant amount of the residual orifice area, and the catheter may actually increase the severity of stenosis. Conversely, removal of the catheter reduces the severity of stenosis. We have observed that a peripheral pressure rise occurs in severe aortic stenosis when the LV catheter is removed from the aortic valve orifice. In our experience, an augmentation of more than 5 mmHg in peripheral systolic pressure at the time of LV catheter pullback indicates that significant aortic stenosis is present. This sign is present in >80% of patients with an aortic valve area of 0.5 cm² or less, a point that is discussed further in Chapter 40.

AREA OF TRICUSPID AND PULMONIC VALVES

Because of the rarity of tricuspid and pulmonic stenosis in adults, no general agreement exists as to what constitutes a critical orifice area for these valves. In general, a mean gradient of 5 mmHg across the tricuspid valve is sufficient to cause symptoms of systemic venous hypertension. Gradients across the pulmonic valve of <50 mmHg are usually well tolerated, but gradients of >100 mmHg indicate a need for surgical correction. Between 50 and 100 mmHg, decision regarding surgical correction depends on the clinical features of each case.

ALTERNATIVES TO THE GORLIN FORMULA

A simplified valve formula for the calculation of stenotic cardiac valve areas was proposed by Hakki et al. and tested in 100 consecutive patients with either aortic or mitral stenosis. The simplified formula is

\[
\text{Valve area} = \sqrt{\frac{\text{cardiac output (liters/min)}}{\text{pressure gradient}}} \quad (13.10)
\]

and is based on their observation that the product of heart rate, SEP or DFP, and the Gorlin formula constant was nearly the same for all patients whose hemodynamics were measured in the resting state, and that the value of this product was close to 1.0. For the examples given earlier in this chapter,
the simplified formula works reasonably well. Thus for the patient with mitral stenosis (Figure 13.3) with a cardiac output of 4.680 mL/minute and a mitral diastolic gradient of 30 mmHg, mitral valve area is 4.68 divided by the square root of 30, or 0.85 cm², using the simplified formula as opposed to the value of 0.71 cm² calculated using the Gorlin formula. For the patient with aortic stenosis whose tracings are shown in Figure 13.5 (cardiac output 5 L/minute, aortic gradient 40 mmHg), the aortic valve area by the simplified formula is 5 divided by the square root of 40, or 0.79 cm², as opposed to 0.73 cm² calculated using the Gorlin formula. Because the percentage of time per minute spent in diastole or systole changes substantially at higher heart rates, the simplified formula may be less useful in the presence of substantial tachycardia. This point, however, has not been tested adequately.

ASSESSMENT OF AORTIC STENOSIS IN PATIENTS WITH LOW CARDIAC OUTPUT

In a patient with a forward cardiac output of 3 L/minute, a mean transvalvular gradient of 20 mmHg will yield a calculated valve area of 0.7 cm², indicating critical aortic stenosis. However, not all such patients actually have severe aortic stenosis. Valve calculations made using the Gorlin formula are flow dependent: That is, as cardiac output increases, calculated area increases, and as cardiac output decreases, calculated area decreases. Two potential mechanisms exist by which calculated valve orifice area increases with cardiac output: (a) Increased flow through the stenotic aortic valve in conjunction with increased LV pressure physically opens the valve to a larger orifice area, and thus the valve orifice really is wider during increased flow, and (b) inaccuracies in the Gorlin formula cause the calculated area (but not necessarily the actual orifice area) to be flow dependent. The Gorlins themselves had noted that they had no data based on which they could derive an empirical constant for the aortic valve. Indeed, such a constant has never been derived but has been assumed to be 1.0 by the cardiology community. The issue remains in doubt, but in all probability both explanations are correct in part.

On the one hand, Tardif and coworkers have shown that two-dimensional transthoracic echocardiographic imaging of the stenotic aortic valve has failed to demonstrate true changes in valve orifice area when increased flow caused calculated area to increase. Their data suggest that the relationship between calculated area and flow resides within the calculation rather than in representing a true change in area. However, it remains unclear whether the echocardiographic method used is sensitive enough to detect tiny (0.2 to 0.4 cm²) changes in actual valve area. On the other hand, Voelker and colleagues working in vitro concluded that changes in calculated orifice area with changes in flow were probably owing to actual changes in valve area. Flow dependence of calculated valve orifice area appears to be less in bicuspid than in tricuspid valves, but is more at lower flows than at higher flows.

These problems in assessing stenosis severity have substantial clinical importance. Consider a patient with a reduced cardiac output and low LV ejection fraction who has both cardiomyopathy and mild aortic stenosis. Despite a calculated valve area of 0.7 cm², such a patient will probably not benefit from aortic valve replacement because aortic stenosis was not the cause of the LV dysfunction. On the other hand, although patients with low aortic valve gradients are generally at higher risk for perioperative death associated with aortic valve replacement, many patients with low gradients may improve substantially following surgery. It is likely that such patients have truly severe aortic stenosis, which is the cause of their hemodynamic decompensation; in these patients, correcting the aortic stenosis is beneficial.

Preliminary data from four studies suggest that cautious hemodynamic manipulation in the catheterization laboratory can distinguish between these two different clinical entities. In patients with mild aortic stenosis, an infusion of nitroprusside or dobutamine increases forward output substantially, but may actually decrease the transvalvular gradient. In such cases, the calculated aortic valve area increases dramatically and is no longer within the critical range. On the other hand, in patients with truly severe aortic stenosis, infusion of nitroprusside widens the transvalvular gradient and increases the calculated aortic valve area only slightly, if at all. The results of nitroprusside infusion in a patient with mild aortic stenosis are presented in Table 13.2. The patient's initial calculated valve orifice area was 0.6 cm², which would indicate a need for surgery. However, following nitroprusside infusion, the gradient actually fell and calculated valve area increased. The patient improved on chronic vasodilator therapy, usually contraindicated in aortic stenosis unless the disease is mild. It must be emphasized that infusion of nitroprusside in patients with suspected aortic stenosis must be performed with great caution, because if true aortic stenosis is present, hypotension may result. If it is known that the patient has normal coronary arteries, dobutamine, which produces similar changes in cardiac output, can be infused instead of nitroprusside. However, dobutamine infusion may be dangerous in patients who also have coronary disease, in whom it may precipitate ischemia. Importantly, patients with true aortic stenosis in whom stroke volume is augmented by at least 20% during dobutamine infusion have a much lower surgical mortality than observed in patients who fail to show inotropic reserve (see also Chapter 20).

Usually patients with low flow and low transaortic gradient also have a low ejection fraction. However, recently, low flow and low gradient with normal ejection fraction has been observed in a group of patients. Such patients have small concentrically hypertrophied left ventricles so that a normal ejection from a small LV yields a low stroke volume and thus a low gradient. In these cases the practitioner may
be misled by the low gradient into believing that the aortic stenosis is mild or moderate in severity when in fact it is severe. Severity is confirmed by a low valve area, and if the patient is symptomatic the prognosis is dire without aortic valve replacement.

### VALVE RESISTANCE

Valve resistance is simply the mean aortic valve gradient divided by the cardiac output per second of systolic flow. It has the advantage of being calculated from two directly obtained pieces of data (output and gradient) and requires no discharge coefficient. A simplified formula for calculating aortic valve resistance is

\[
\text{Valve resistance (dyn sec/cm}^5\rangle = \frac{(\text{Mean gradient}) 
\times (\text{Systolic ejection period})}{(\text{Heart rate}) \times \text{Cardiac output (liters/min)}} \times 1.33
\]

Valve resistance has been shown by Cannon et al. to help separate patients with severe aortic stenosis from those patients who had similarly small calculated aortic valve areas but were subsequently demonstrated to have mild disease. Resistance appears to be less flow dependent than valve area. Resistance is unlikely to supplant the Gorlin formula in assessing stenosis severity, but may be an important adjunct to it in patients with low cardiac output.

Currently, we recommend cautious hemodynamic manipulation with dobutamine or nitroprusside for patients with a cardiac output of <4.5 L/minute and who have a transvalvular gradient of <40 mmHg and a valve resistance of <275 dyn second/cm². If patients respond with a substantial increase in the measured gradient, they probably have truly severe aortic stenosis and may benefit from aortic valve replacement. However, if cardiac output increases substantially but gradient increases only slightly or actually declines, the aortic stenosis is mild and the patient is unlikely to benefit from aortic valve replacement.

### REFERENCES


### ACKNOWLEDGMENTS

We would like to express our appreciation to Dr. James J. Ferguson III, who supplied Figures 13.2 and 13.4, constructed by him through computer simulation.
Chapter 13 Calculation of Stenotic Valve Orifice Area


Acquisition of cardiac catheterization hemodynamic data has been revolutionized by the automation of hemodynamic measurement and recording since the first edition of this book was published. For the pioneers who worked in the middle part of the 20th century, assessment of intravascular and intracardiac pressures required far more than just development of catheters and methods to access the various cardiac chambers. Much time was spent dealing with fundamental flaws in the equipment used for pressure measurement (see Chapter 10). Transducers had inherently unstable electronic circuits, and they required repeated rebalancing to barometric pressure—by convention, the “zero” pressure that is the baseline for all hemodynamic recordings. Transducer drift also meant that calibration had to be performed, typically against mercury manometers, at least once per case if not more often. In addition, characteristics of the mechanical recording systems interfered with accurate recording of waveforms. In the modern era, pressure transducers are disposable, published drift is theoretically only 1 mmHg per 8 hours of use, and assumed error rates are <2%; in practice, the actual mean calibration error is <0.1 ± 0.8%. Modern recording systems have eliminated a slew of mechanical errors introduced by the use of analog pen on paper or even needle on drums (the kymograph) covered by a layer of carbon (see Chapter 10, Figure 10.2). Unfortunately, in the wake of automation, accuracy still requires attention to basics that are largely no longer taught, and as a result the modern cardiac catheterization laboratory can generate reams of sometime useless and occasionally wholly erroneous data. This chapter will highlight a variety of pitfalls in hemodynamic measurements.

There are several categories of potential error in cardiac hemodynamic measurements. First, artifacts can be induced by mechanical or operator errors, including unrecognized transducer failure, incorrect transducer positioning, inadequate balancing, and under- or overdamping. Second, and probably more significant, is misinterpretation of recordings, including failure to recognize catheter location (e.g., pulmonary wedge versus pulmonary artery); failure to understand the influence of loading conditions; and failure to understand the implications of incorrectly recorded tracings. Finally, standardized software provided with hemodynamic recording equipment assumes that each laboratory follows the common practices of data acquisition, which may not always be a valid assumption, thus resulting in erroneous reporting.

As an example of the first category, the hemodynamic tracings in Figure 14.1 show right atrial pressures that reflect normal hemodynamics and moderate or severe right heart pressure elevation in the setting of constrictive physiology with a steep Y descent. The mean RA pressures are 6, 17, and 24 mmHg, respectively. Importantly, they were all taken within 1 minute of each other, and merely reflect zeroing of the transducer at heights above, at and below the patient’s right atrium. Few laboratories use the leveling stick required to get this right as depicted in Chapter 10. The most compulsive laboratories measure the anterior-posterior diameter of the patient’s chest and place the manifold at half this distance above the top of the catheterization table. Even this approach has been a subject of debate: it may be more appropriate to
**Figure 14.1** A, B, C. Three sets of right atrial pressures in a patient with severe aortic stenosis and radiation-induced pericardial disease s/p pericardectomy. The panels reveal normal, moderately elevated, and severely elevated right atrial pressures, all recorded on a 5 mmHg scale. The tracings were taken a few seconds apart, with the transducers positioned above, at, and below the level of the patient’s heart. Failure to compulsively align the transducer with the level of the patient’s heart produces substantial error in hemodynamic recordings. Note the steep Y descent, which falsely appears to have an excursion below zero in the tracing at left (A).

place the transducer at the level of the top of the chamber the pressure of which is being measured, resulting in a difference of several mmHg depending on the vascular structure being assessed.2

Failure to adequately balance transducers results in the very common recording of negative diastolic pressures, largely a physiologic impossibility, in the cath lab. Grossly negative diastolic pressures are not possible under ordinary physiological circumstances. Negative left ventricular end-diastolic pressure would reflect net reversal of blood flow. Figure 14.2A shows hemodynamics of a patient with a newly diagnosed dilated cardiomyopathy presenting with heart failure, dutifully interpreted as an LVEDP of −1 mmHg. Figures 14.2B and C show the effect of recording left ventricular pressure through compliant tubing and with damping due to air in the line, respectively. Figures 14.2D and E show the difference between high-fidelity micromanometer-tipped catheter recordings and fluid-filled catheter recordings; micromanometer catheter recordings are primarily used for research purposes, even though they provide much more accurate data.

Finally, an example of generic assumptions made by software vendors is the recording of left ventricular versus systemic pressure in a patient with aortic stenosis (Figure 14.3A). The tracing grossly underestimates the gradient and shows systemic pressure rising before left ventricular contraction, a physiologic impossibility.3

**TRANSVALVULAR GRADIENT**

The common reliance on valve gradients to assess severity of valve disease ignores the role of loading conditions, systolic and diastolic filling periods, and transvalvular flow on the gradient measurement. Examples in Figure 14.5 show underestimation of the severity of valvular stenosis in the setting of volume depletion and sedation, corrected by volume infusion and exercise, respectively. This patient had severe mitral stenosis by clinical assessment and noninvasive imaging. She was given no fluids after midnight and was not catheterized until late afternoon, thereby leading to dehydration combined with decreased cardiac output in the setting of sedation. Infusion of only 100 mL of saline and exercise consisting of lifting 1 L IV bags with both arms, respectively, were sufficient to demonstrate the hemodynamic alternations shown in the figure. The disproportionate rise in gradient associated with increasing heart rates in mitral stenosis reflects the disproportionate fall in the diastolic filling period that occurs simultaneously; this is seen even with mild mitral stenosis and includes rise in left atrial pressure, gradient, and pulmonary artery pressure.4 The relationship of gradient to valve area is shown in Chapter 13, Figures 13.2 and 13.4. Even in the normal range of valve areas, there is a minimal gradient induced by very high cardiac outputs, reflecting the intrinsic size of the valvular annulus. With increasing flow across the
A. Left ventricular pressure tracing of a 63-year-old patient presenting with congestive heart failure with a newly diagnosed cardiomyopathy. The left ventricular end-diastolic pressure of −1 mmHg is an obvious artifact, though it was dutifully included in the patient’s assessment. This has occurred almost certainly owing to the transducer having been mounted well above the patient’s heart. In addition to the negative pressures, the hemodynamics are inconsistent with the patient having a newly diagnosed cardiomyopathy. This is an example of a fundamental flaw in modern hemodynamic assessment and reporting: blind repetition of numbers reported by machine. B, C. Two other examples of distorted left ventricular pressure recordings (200 mmHg scale). The tracing in panel B was obtained with overly compliant tubing attached to the diagnostic catheter, whereas for the tracing in panel C, air was present in the tubing between the catheter and the manifold. (Figure courtesy of Dr. John Hirshfeld, University of Pennsylvania.). D, E. Left ventricular (LV) versus central aortic pressure with high-fidelity pressure recordings using micromanometer catheters (D). In contrast, tracing E shows the loss of fidelity inherent in using fluid-filled catheters; the last two beats reflect a left ventricle–to–central aortic pullback. The femoral arterial pressure upstroke is delayed, and because of harmonics and possibly the height of the LV transducer, the femoral arterial pressure appears to be substantially higher than LV systolic pressure. Similar to B above, the LV pressure tracing is underdamped. (Tracings courtesy of Dr. Morton Kern, University of California, Irvine.)
The aortic pressure tracing was thus moved forward in time, creating the artifact seen which depicts systemic pressure rise occurring prior to left ventricular contraction, a physiologic impossibility (in the absence of certain types of cardiac assist devices that would have a quite different signature). The gradient was reported as 11 mmHg and the calculated aortic valve area as 1.7 cm². B. With the elimination of the phase shift, the gradient is now reported as 20 mmHg and the valve area as 1.3 cm². (Figure courtesy of Dr. John Hirshfeld, University of Pennsylvania.)
Figure 14.4   Tracings from the first report of transcatheter aortic valve replacement (TAVR) in a human. The results of this first TAVR are actually even better than the tracings would suggest at first glance. The tracing in panel A depicts systemic pressure rise commencing prior to the rise of left ventricular pressure, an example of the phenomenon shown in Figure 14.3. The tracing thus underestimates the pre-TAVR gradient and overestimates the valve area. The tracing in panel B demonstrates left ventricular versus femoral pressure, in this case artificially increasing the apparent gradient and underestimated the resultant valve area. Note the late rise in systemic pressure upstroke. In patients such as this one, who have severe peripheral vascular disease, the severity of aortic stenosis may be underestimated when femoral rather than central aortic pressure is used because of higher systemic peak pressure, reflecting the recruitment of harmonics as the pressure waveform passes through a long area of stiff blood vessels. The systemic pressure will also show a higher dP/dt than if it were recorded in the ascending aorta. (Reproduced from Elchaninoff H, Tron C, Cribier A. Percutaneous implantation of aortic valve prostheses in patients with calcific aortic stenosis: technical aspects. *J Interv Cardiol* 2003;16(6):515–521.)

valve, exponential rises are noted with fixed severe stenosis, whereas in the setting of mild to moderate disease, further opening of the stenotic valve results in blunting of the gradient rise. These findings in turn allow the use of maneuvers that increase transvalvular flow, such as dobutamine infusion, vasodilators, and other interventions, to help assess equivocal valve disease severity (see Figure 14.6).

**EFFECTS OF CATHETER LOCATION**

The classic parvus et tardus carotid pulse upstroke taught to medical students is elegantly reflected in the catheterization laboratory. Figure 14.7 shows simultaneous left ventricular, aortic, and left atrial pressure on 200 mmHg scale. The primary pitfall in aortic stenosis pressure measurement relates to comparison of pressures at levels other than either side of the aortic valve. Measurement of left ventricular versus femoral artery pressure is particularly common: because of reflected harmonics, the phasic waveform difference between femoral and central aortic pressure is substantial even though under ordinary circumstances the mean pressure will be the same (see Chapter 10). Figure 14.8A and B show the effect of measuring LV pressure against central aortic pressure and femoral artery pressure, respectively (see also Chapter 13, Figure 13.6). The latter remains a common technique along with simple pullback measurement across the aortic valve; both techniques are fraught with errors. Figure 14.8C–E were recorded in a patient with no aortic stenosis and merely reflect transducer balancing artifact. In this context, the reader is referred to the discussion in Chapter 13 regarding
**Figure 14.5** Response to 100 cc saline (A) and to arm exercise (B) in a patient undergoing cardiac catheterization in the late afternoon after having been NPO overnight. In the setting of a compliant left atrium, dehydration can result in substantial underestimation of the severity of mitral stenosis; the gradient on the right side of panel A has approximately doubled. Because of the disproportionate fall in diastolic filling period with increasing heart rate, and the effect of increasing flow across the valve with exercise, even relatively modest exertion can have a substantial effect on the gradient, which roughly tripled in the right side of panel B. (See text for discussion.) LV, left ventricle; PAW, pulmonary artery wedge pressure; EX, exercise.

**Figure 14.6** Left ventricular versus pulmonary wedge pressure in a patient with mitral stenosis, sedated and somewhat dehydrated (40 mmHg scale). Baseline tracing is shown in panel A and tracing during dobutamine infusion in B. This intervention is typically applied for patients with aortic stenosis, but can readily be applied to assess all stenotic orifices with variable blood flow.
Figure 14.7  

**A.** Left ventricular (LV), central aortic (Ao), and left atrial (LA) pressures, all on 200 mmHg scale. Peak left ventricular pressure is approximately 100 mmHg higher than systemic pressure. Note the prominent anacrotic notch (arrow) characteristic of severe aortic stenosis, and the classic parvus et tardus (weak and delayed) upstroke, corresponding to the blunted carotid upstroke notable on physical examination. Left atrial pressure is high, with a V wave of >40 mmHg. Note the location of the peak of the V wave (double arrow; see text) and diastasis in early diastole (dashed arrow). **B.** The same tracing with superimposed lines showing the first derivatives of left ventricular and central aortic pressures over time (dP/dt), green and blue lines, respectively. The systolic and diastolic pressures are shown by horizontal dotted lines with the red arrow depicting the pulse pressure. **C.** After valvuloplasty with a 20 mm balloon, the gradient is substantially lower, central aortic dP/dt is much improved, and systemic systolic and pulse pressure are dramatically higher. Although the gradient has been lowered by at least 50%, the patient still has severe aortic stenosis, a common result after balloon dilatation.

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Figure 14.8  

**A, B.** Left ventricular (LV) versus central aortic pressure and LV versus femoral artery pressure. The tracings were recorded a few seconds apart. Note the dramatically higher gradient in **A** with classic features of severe aortic stenosis. In contrast, tracing **B** shows lower peak-to-peak gradient, and much higher aortic dP/dt and pulse pressure. Using femoral artery pressure as a proxy for central aortic pressure can result in substantial underestimation of the severity of aortic stenosis. **C.** Left ventricular versus femoral artery pressure in a patient with a systolic ejection murmur billed as having aortic stenosis. A substantial gradient is seen. **D.** However, the dP/dt (dotted diagonal lines) of the left ventricular and femoral pressure upstrokes are identical and the pulse pressure (horizontal dashed lines) is high. This tracing is not consistent with aortic stenosis. **E.** Rebalancing of the femoral sheath transducer reveals normal hemodynamics.
the errors in gradient and valve area assessment inherent in recording LV versus femoral artery pressure with or without phase adjustment.6

The primary pitfalls in mitral stenosis assessment again reflect the importance of pressures measured on either side of the mitral valve. A substantial artificial gradient results from indirect measurement of left atrial pressure across the pulmonary vascular bed. Exponential rise in resistance to pressure transmission is caused by the small caliber of the pulmonary arteriolar circulation, according to Poiseuille’s law. Figure 14.9 shows the inherent gradient when left atrial and pulmonary wedge pressures are recorded simultaneously. In the example in Figure 14.10A, the gradient between wedge and LV pressures was incorrectly interpreted as showing severe mitral stenosis. In fact, it reflects mild mitral stenosis with severe mitral insufficiency. Figure 14.10B shows left

Figure 14.8 (Continued)

Figure 14.9 Simultaneous left atrial and wedge pressures in a patient with severe mitral insufficiency. The mean pressures are the same, but the A and V waves are blunted when pressures are recorded via a pulmonary catheter wedged in the pulmonary arterial circulation. The gradients shown in blue and red are thus artifactual—the fall in diastolic pressure as the left atrium is decompressed is transmitted with a significant delay. The gradient between wedge and left atrial pressure in diastole results in underestimation of the mitral valve area in mitral stenosis, and of the height of the V wave in mitral insufficiency. Note the diastasis by the end of the diastolic cycle.
This patient was referred for percutaneous balloon mitral valvuloplasty based on echocardiographic findings of severe mitral stenosis and mild mitral insufficiency. The tall V wave and diastasis at late cycle in the left ventricle versus wedge pressure tracing (A) are suspicious for severe mitral insufficiency and mild mitral stenosis, respectively. Left ventricle versus left atrial pressure (B) shows early decompression of the left atrium consistent with mild mitral stenosis. The patient in fact had severe mitral insufficiency as her primary mitral valve pathology. Note the exaggerated gradient across the mitral valve in A consistent with recording left atrial decompression across the high-resistance pulmonary arteriolar bed.

atrial and LV pressures recorded concurrently—most of the gradient was eliminated. Thus, when noninvasive data are inadequate, and determination of the gradient is essential for clinical decision making, a direct left atrial pressure measurement is superior to wedge pressure measurement, albeit direct left atrial pressure measurement is associated with the increased risk of trans-septal catheterization as well as of clot formation and air embolism.7 Prior studies have shown that reliance on wedge pressure results in overestimation of the gradient and of valve dysfunction.8,9

OTHER CONSIDERATIONS

Both heart rate, as already discussed, and heart rhythm can have significant influence on hemodynamics, in both left and right heart catheterization.10 An example of the effect of paced rhythm is seen in Figure 14.11. The pitfalls of hemodynamic measurement include practices as simple as adequate flushing of the catheter (Figure 14.12). Phase shifting and frequency filters can distort measurements. Air bubbles, clots, compliance of the tubing, and introduction of contrast (which affects viscosity and therefore resistance) all influence the recordings made through fluid-filled systems. Keeping tubing length short, having the transducer as close to the end of the catheter as possible, and flushing the system adequately and repeatedly are all important elements.

CONCLUSION

Over the past two decades, advancements in technology have automated and simplified hemodynamic measurements. However, conceptual understanding of cardiac physiology, proper use of recording apparatus, and rejection of artifact are still essential for arriving at accurate diagnosis in the cardiac catheterization laboratory.
The effect of pacing on mitral valve gradient in a patient with mitral stenosis. The tracing in panel A shows a gradient of approximately 12 mmHg: the effect of the heart rate of 82 beats per minute. The tracing in panel B shows the absence of significant gradient with the pacemaker shut off and a much slower heart rate. Note also the establishment of diastasis late in the cardiac cycle. Absence of atrial contraction with ventricular pacing exacerbates mitral stenosis gradient.

Figure 14.12 A, B. Left ventricular pressure versus aortic pressure taken a few minutes apart. Note the dramatic difference in area and gradient. This patient had aortic sclerosis, not stenosis, with a small gradient. The pressures were recorded through a 6F dual lumen catheter—the aortic pressure lumen is extremely small and damps easily from flow stasis and platelet sludging (A). Flushing the catheter resulted in resolution of most of the gradient (B).
REFERENCES

The initial attempts to perform coronary angiography used nonselective injections of contrast media into the aortic root to opacify both the left and right coronary arteries simultaneously as the angiographic images were recorded on serial conventional sheet films. The focus on nonselective angiography was prompted by animal studies, which had shown that selective injection of contrast media in a coronary artery would induce ventricular fibrillation. To improve contrast delivery into the coronary ostia, some early investigators used transient circulatory arrest induced by the administration of acetylcholine or by elevation of intrabronchial pressure, followed by occlusion of the ascending aorta by gas-filled balloons and injection of the contrast bolus. Unfortunately, all these techniques were associated with risks and did not provide a clear opacification of the coronary artery tree. The realization that selective coronary angiography could be performed safely in humans was the result of a serendipitous event that occurred in the Cleveland Clinic Cardiac Catheterization Laboratory in 1958. As described by Dr. Mason Sones in his recollection of that day, he had just performed with his assistant a left ventriculogram and was proceeding to perform an aortogram in a young patient with rheumatic heart disease:

“I asked my associate to withdraw the catheter tip across the aortic valve into the ascending aorta so that we could complete the procedure by performing an aortogram with the catheter tip in the ascending aorta. My associate complied and we relied on the pressure change from the left ventricle to the ascending aorta without sliding the table top back under the 5 inch amplifier to confirm the exact location of the tip. I didn’t think this was necessary because I was quite certain that the catheter tip lay in the ascending aorta just above the aortic valve. My associate, Dr. Royston Lewis, made an injection of 40 cc of 90% Hypaque through the catheter. About one second before the injection was initiated, I had the switch to initiate a cine run. When the injection began, I was horrified to see the right coronary artery become heavily opacified and realized the catheter tip was actually inside the orifice of the dominant right coronary artery ostium.”

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The contribution of William Grossman and Donald Baim to this chapter in prior editions is gratefully acknowledged.
coronary artery. I shouted, “Pull it out.” Our combined reaction times to accomplish withdrawal of the catheter consumed 3–4 seconds which meant that approximately 30 cc of 90% Hypaque had been delivered into the right coronary artery. I was of course horrified because I was certain the patient would develop ventricular fibrillation. At that time we did not have direct current defibrillators and knew nothing about the application of closed chest cardiac massage. I climbed out of the hole and ran around the table looking for a scalpel to open his chest in order to defibrillate him by direct application of the paddles of an alternating current defibrillator. I looked at the oscilloscope tracing of his electrocardiogram and it was evident that he was in asystole rather than in ventricular fibrillation. I knew that an explosive cough could produce a very effective pressure pulse in the aorta and hoped that this might push the contrast media through his myocardial capillary bed. Fortunately, he was still conscious and responded to my demand that he cough repeatedly. After 3–4 explosive coughs, his heart began to beat again with initially a sinus bradycardia which accelerated into a sinus tachycardia within 15 to 20 seconds. He then made a perfectly uneventful recovery with no neurological deficit or other sequelae.”

Fortunately, the patient did not develop ventricular fibrillation, and that inadvertent injection allowed Dr Sones to realize that selective injection of contrast media in coronary arteries was feasible. Two days later, he performed a planned selective injection that marked the beginning of a new era in cardiac catheterization1 (Figure 15.1). For further details on the history and evolution of coronary angiography, interested readers are referred to excellent reviews available in the literature.3·5

As of today, diagnostic coronary angiography remains the principal component of cardiac catheterization. The goal is to examine the entire coronary tree (both native vessels and any surgically constructed bypass grafts) while recording details of the coronary anatomy, which include the following: the pattern of arterial distribution, anatomic or functional pathology (atherosclerosis, thrombosis, congenital anomalies, or focal coronary spasm), and the presence of intercoronary and intracoronary collateral connections. The procedure is typically performed in 30 minutes or less, under local anesthesia, on an outpatient basis, with a procedure-related major complication rate (death, stroke, myocardial infarction, see Chapter 4) of <0.1%. By performing a series of intracoronary contrast injections in carefully chosen angulated views using current high-resolution x-ray imaging (see Chapter 2), it is possible to define all portions of the coronary arterial circulation down to vessels as small as 0.3 mm, free of any artifacts owing to vessel overlap or foreshortening.

There is currently no other imaging technique that gives as detailed a view of the coronary circulation, although noninvasive techniques such as magnetic resonance angiography (MRA) and coronary computed tomographic angiography (CCTA) have improved their temporal and spatial resolution and emerged as effective screening tests for coronary artery disease, for the evaluation of coronary anomalies and patency of surgical bypass grafts, and more recently for providing additional information regarding nonobstructive coronary artery disease and atherosclerosis burden.6·9 However, for patients with compelling ischemic symptoms, what begins as a diagnostic procedure can quickly shift to a definitive therapy (percutaneous coronary intervention or PCI, see Chapters 28–31) performed through the same access site. Even so, coronary angiography is limited to examination of only the coronary lumen and not of the endothelial surface, plaque content, vessel wall, or (except indirectly) coronary flow physiology. When features related to the above are in question, coronary angiography may be supplemented by intravascular ultrasound, optical computerized tomography, angioscopy, or intracoronary pressure and flow measurements (see Chapters 24 and 25). Despite these limitations, selective coronary angiography still remains the clinical gold standard for evaluating coronary anatomy. Performance of high-quality coronary angiography to safely define each and every coronary stenosis in an optimal view is an important measure of an operator’s skill in cardiac catheterization and is the foundation on which the ability to perform successful coronary intervention is based.
CURRENT INDICATIONS

The various current indications for coronary angiography are summarized comprehensively in the AHA/ACC guidelines for coronary angiography and in the recent Appropriate Use Criteria for Diagnostic Cardiac Catheterization. Although the details of these indications continue to evolve as new applications of catheter-based therapy are developed, they are still best summarized by the principle stated by F. Mason Sones—coronary arteriography is indicated when a problem is encountered whose resolution may be aided by the objective demonstration of the coronary anatomy, provided competent personnel and adequate facilities are available and the potential risks are acceptable to the patient and physician.

The most frequent indication is the further evaluation of patients in whom the diagnosis of coronary atherosclerosis is almost certain and in whom anatomic correction by means of coronary bypass surgery or PCI is contemplated. Angiographic evaluation of coronary anatomy in such patients provides the crucial information needed to select the most appropriate treatment strategy—catheter intervention (see Chapters 28–31), bypass surgery, or medical therapy. Included in this category are patients with stable angina pectoris refractory to medical therapy.

Even asymptomatic patients with noninvasive evidence of myocardial ischemia also benefit from revascularization and are thus candidates for coronary angiography. In patients with unstable angina (new onset, progressive, or rest pain), intensive drug therapy (beta-blocker, calcium channel blocker, nitrate, heparin, aspirin, clopidogrel or a platelet glycoprotein IIb/IIa receptor blocker) may be temporizing, but more than two-thirds of such patients will come to angiography within 6 weeks of presentation anyway owing to ongoing clinical symptoms or a positive exercise test. In most cases, therefore, such patients are brought to early coronary angiography, with same-procedure PCI if their anatomy is suitable. Patients with acute myocardial infarction routinely undergo immediate coronary angiography followed by same-procedure primary angioplasty. However, the role of routine post-MI coronary angiography in the asymptomatic postinfarct patient who was managed medically or with thrombolysis has not been established. The most recent AHA/ACC guidelines for the role of coronary angiography in stable angina, unstable angina, and acute myocardial infarction are available on the Internet at http://www.cardiosource.org/.

A second group of potential candidates for coronary angiography consists of patients in whom the presence or absence of coronary artery disease is unclear. This includes patients with troublesome chest pain syndromes but ambiguous noninvasive test results, patients with unexplained heart failure or ventricular arrhythmias, survivors of out-of-hospital cardiac arrest, patients with suspected or proven variant angina, and patients with risk factors for coronary artery disease who are being evaluated for major abdominal, thoracic, or vascular surgery. This category also includes patients scheduled for correction of congenital or valvular pathology. Patients with congenital defects such as tetralogy of Fallot frequently have anomalies of coronary distribution that may lead to surgical complications if unrecognized, whereas patients older than age 45 years with valvular disease may have advanced coronary atherosclerosis without clinical symptoms. Although younger patients with valvular disease are commonly operated on without prior coronary angiograms, given the extraordinary low risk of diagnostic catheterization and the potential benefit of knowing the coronary anatomy, most surgical center personnel believe it is best to perform a preoperative diagnostic catheterization to identify (and then correct) significant coronary lesions, so as to provide the best and safest outcome during concurrent valve replacement.

Finally, coronary angiography is frequently performed when a patient develops recurrent angina after coronary intervention (to detect and treat restenosis) or after bypass surgery (to detect vein graft failure, which might require catheter intervention or reoperation). Routine follow-up angiography 6 months after catheter intervention is not indicated clinically, but may play an important role in the research evaluation of new technologies or drug therapies targeted at reducing restenosis or atherosclerosis burden.

GENERAL ISSUES

In the early years, coronary angiography used to be performed using the brachial artery cutdown approach. The development of preshaped catheters and advancements in vascular access techniques have led to a progressive adoption of the percutaneous approach from the femoral, brachial, or radial artery, and as of today brachial cutdown (Chapter 8) is rarely performed. Importantly, over the past 10 years the radial artery percutaneous approach (Chapter 7) has emerged as an alternative to the femoral artery approach. As discussed in detail in Chapter 7, the radial artery approach may offer a selective advantage in patients with severe peripheral vascular disease, morbid obesity, or known abdominal aortic aneurysm, and additional advantages regarding bleeding complications and early ambulation. Regardless of the approach, however, it is important for the catheterization team to meet the patient before the actual procedure to evaluate the best access site, to gain an appreciation of the clinical questions that need to be answered by coronary angiography, to uncover any history of adverse reaction to medications or organic iodine compounds, and to explain the procedure and its risks in detail.

Coronary angiography was traditionally performed with hospitalization for the night after the procedure and sometimes for the night prior to the scheduled procedure as well. In contrast, most patients now come in on the morning of their scheduled procedure, with no oral intake (except for medications and limited quantities of clear liquid) for 6 to 8 hours.
before catheterization. A mild sedative premedication (such as diazepam, 5–10 mg orally) may be given prior to the procedure, or intravenous conscious sedation may be administered as needed during the procedure itself. Outpatient coronary angiography for low- to moderate-risk patients began in the 1990s and is now the dominant practice. However, patients with major comorbidities (e.g., heart failure, valve disease, renal insufficiency, peripheral vascular disease), or those who have sustained a procedural complication might be expected to stay overnight in the hospital following a diagnostic coronary angiogram. If the angiogram shows significant disease and PCI is appropriate, this may be done during the same procedure followed by an overnight hospital stay. Some day hospital discharge following PCI is currently undergoing further evaluation. Patients needing revascularization but not found to be suitable for PCI at the time of coronary angiography may go for a bypass surgical operation within 24 to 48 hours or may be discharged home to return for surgery, depending on clinical acuity and availability of surgical time. At least 2 hours of bed rest is required after a percutaneous femoral procedure unless a puncture sealing device is used (see Chapter 6) to allow earlier ambulation and discharge.

**THE FEMORAL APPROACH**

As described in Chapter 6, the femoral approach to left heart catheterization involves insertion of the catheter either directly over a guidewire or through an introducing sheath. A series of preformed catheters are used, starting with a pigtail catheter for left ventriculography followed by separate catheters (either Judkins or Amplatz shapes) for cannulation of the left and right coronary arteries and any surgical bypass grafts. Coronary catheters are available in 4F, 5F, 6F, 7F, or 8F end-hole designs that may taper further near the tip. They may be constructed of polyethylene (Cook Inc, Bloomington, IN), polyurethane (Cordis, Miami, FL), or other high-strength polymer materials such as Trilon (TM, Boston Scientific Natick, MA), which resist softening in the body. They contain steel braid, nylon, or other reinforcing materials (Kevlar, carbon fiber) within the catheter wall to provide the excellent torque control needed for coronary cannulation. Current catheters have a soft distal tip to minimize the risk of arterial dissection. In the 1970s, 8F catheters predominated because they provided excellent torque control and permitted rapid contrast delivery. In the 1980s, improvements in the design of 7F catheters allowed for a lumen diameter comparable to that in standard 8F catheters, making them the standard in most laboratories. Smaller (6F and even 5F and 4F coronary angiographic catheters are now available that use technology similar to that used in guiding catheters to provide thinner catheter walls and larger lumens (6F lumens up to 0.071 inches for guiding catheters), exceeding the lumen size once available in 8F diagnostic catheters. We now use such 6F catheters for all of our routine diagnostic procedures and most interventional procedures. Some of the catheters used for native coronary injection via the femoral or brachial approach are shown in Figure 15.2.

**Insertion and Flushing of the Coronary Catheter**

The selected catheter is inserted into the femoral sheath and advanced around the arch and into the ascending aorta before the guidewire is removed. Alternatively, the catheter can be advanced to the level of the left mainstem bronchus over the guidewire. This alternative approach, while having the potential to reduce the risk of complications secondary to improper flushing, can result in snagging the catheter tip on aortic wall plaques and irregularities. After removal of the guidewire, the catheter is attached to a specially designed manifold system that permits the maintenance of a closed system during pressure monitoring, catheter flushing, and contrast agent administration (Figure 15.3). The catheter is immediately double-flushed—blood is withdrawn and discarded, after which heparinized saline flush is injected through the catheter lumen. Difficulty in blood withdrawal suggests apposition of the catheter tip to the aortic wall, which can be rectified by slight withdrawal or rotation of the catheter until free blood aspiration is possible. If blood cannot be aspirated despite repositioning the catheter, the catheter should be removed from the body and flushed on a towel, as we have occasionally seen thrombus collected in the catheter during exchanges over a guidewire. The lumen of the introducing sheath should also be flushed immediately before and after each catheter insertion and every 5 minutes thereafter to prevent the encroachment of blood into the sheath. Such encroachment can result in the formation of thrombus, which is then “collected” by the catheter tip during insertion of the catheter in the sheath. Alternatively, the side arm of the sheath may be connected to a 30 ml/hour continuous flow regulator.

Once the catheter has been flushed with saline solution, tip pressure should be displayed on the physiologic monitor at all times (except during actual contrast injections). Recording this baseline pressure before contrast administration serves as an important baseline reference point. Next, the catheter lumen should be gently filled with contrast agent under fluoroscopic visualization, avoiding selective contrast administration into small branches such as the lumbar arteries if filling is performed in the descending aorta. Filling with contrast results in slight attenuation of high-frequency components in the aortic pressure waveform, the new shape of which should be carefully noted. Any subsequent alteration in that waveform during coronary angiography (see damping and ventricularization, below) may signify an ostial coronary stenosis or an unfavorable catheter position within the coronary artery. Once these measures are completed, the coronary angiographic catheter is advanced into the aortic root in preparation for selective engagement of the desired coronary ostium.
Damping and Ventricularization of the Pressure Waveform

A fall in overall catheter tip pressure (damping) or a fall in diastolic pressure only (ventricularization, Figure 15.4) during catheter engagement in a coronary ostium indicates obstruction of the catheter tip or interference with coronary inflow. The catheter tip may have been inserted across a proximal coronary stenosis or may have an adverse catheter lie that places it against the coronary wall. If either of these phenomena is observed, the catheter should be withdrawn into the aortic root immediately until the operator can analyze the situation further. The catheter may be reengaged and a cautious small-volume contrast injection made to further clarify the situation. This may disclose a proximal occlusion of the vessel, against which the tip of the coronary catheter is resting, in which case a cine run should be performed to document this finding. The test injection may also
Catheter techniques

Figure 15.3

A. Four-port coronary manifold. This manifold provides a closed system with which blood can be withdrawn from the catheter and discarded. The catheter can be filled with either flush solution or contrast medium, and the catheter pressure can be observed, all under the control of a series of stopcocks. The fourth port is connected to an empty plastic bag and is used as a discard port (for blood from the double flush, air bubbles) so that the syringe need not be disconnected from the manifold at any time during the procedure. As an alternative, a discard/flush system can allow attaching the flush solution and the discard system to the same port, thus leaving one port available for infusion of drugs or for blood sampling. Attachment of the transducer directly to the manifold allows optimum pressure waveform fidelity (see Chapter 10), and the fluid-filled reference line allows zeroing of the transducer to midchest level. B. The Bracco Acist device consists of a contrast-filled power injector, controlled by a sterile pneumatic actuator to deliver contrast in amounts and rates up to the limits preprogrammed on the digital panel. A power flushing system and a pressure transducer are also included, duplicating many of the functions of the traditional four-port manifold. (Courtesy of ACIST Medical Systems, Inc. Eden Prairie, MN.)

indicate ostial stenosis with absent reflux into the aortic root or retention of the injected contrast in the proximal- and midportion of the vessel. Lack of reflux indicates that the catheter tip is severely restricting or occluding ostial inflow and mandates that only a gentle injection be performed followed by immediate removal of the catheter at the end of the cine run to restore antegrade flow. Actually, continuing with injection and filming as the catheter is removed from the ostium may capture the few frames that show the ostial lesion clearly.

Another approach to evaluating such ostial lesions is to perform a nonselective injection into the sinus of Valsalva in an appropriate view (that displays the ostium of the vessel in question with no overlap by the sinus of Valsalva). Or the standard end-hole diagnostic catheter may be exchanged for an end- and side-hole angioplasty guiding catheter to overcome damping by preserving partial antegrade flow into the side holes, through the lumen of the catheter, and into the coronary artery, even though the catheter tip may be obstructing entry of blood into the ostium itself (see discussion of cannulation of the right coronary ostium, below). Vigorous injection despite a damped or ventricularized pressure waveform should be avoided, however, since it predisposes to ventricular fibrillation or dissection of the proximal coronary artery with major ischemic sequelae. Such a dissection is detected by tracking of contrast down the vessel over the course of the injection and failure of contrast to clear on fluoroscopy after the injection is terminated (Figure 15.5). Prompt repair by catheter-based intervention or bypass surgery should be considered if creation of such a dye stain is associated with impeded antegrade coronary flow and signs of myocardial ischemia.
Chapter 15 Coronary Angiography

The Judkins technique for engaging the right coronary ostium requires slightly more catheter manipulation than required for cannulation of the left coronary ostium. After being flushed and filled with contrast in the descending aortic segment, the catheter is advanced into the right coronary sinus as previously described. In the occasional patient with a short or narrow aortic root, the catheter may lie nearly horizontally across the aortic root with the tip pointing vertically against the roof of the left main artery, or the catheter may even refold into its packaged shape during advancement into the aortic root. In this case, a left Judkins catheter with a larger (JL4.5, JL5, or even JL6) curve should be selected. In the long run, changing to a larger catheter under these circumstances may end up saving time as compared with trying to make an unsuitable catheter work.

In the occasional patient with a short or narrow aortic root (usually a younger female, particularly if of short stature), even the 4-cm Judkins curve may be too long. When brought down into the aortic root, the catheter arm may lie nearly vertically with the tip pointing downward below the left coronary ostium. The left ostium may still be engaged despite this somewhat unfavorable situation by pushing the catheter down into the left sinus of Valsalva for approximately 10 seconds to tighten the tip angle and then withdrawing the catheter slowly. Having the patient take a deep breath during this maneuver also helps by pulling the heart into a more vertical position to assist in engagement of the left ostium. The most satisfactory approach, however, is to exchange for a JL3.5 catheter with a shorter curve.

On rare occasions, the left coronary ostium lies out of plane (typically high and posterior), as seen in the right anterior oblique (RAO) projection where the ostium is seen to be posterior to the catheter tip. In this case, limited counterclockwise rotation of the left Judkins catheter may help orient the catheter’s tip posteriorly and facilitate engagement. Too much rotation of this catheter, however, may result in a refolded catheter that requires guidewire reinsertion to straighten. In that case, it may be helpful to step up to the next larger Judkins curve. Alternately, some operators prefer to switch to a left Amplatz shape (Figure 15.2: available in progressively larger curves—1, 2, 3, 4). Amplatz catheters are more tolerant of rotational maneuvering and allow easy engagement of left coronary ostia that lie out of the conventional Judkins plane, as well as subselective engagement of the left anterior descending and circumflex coronary arteries in patients with short left main coronary segments or separate left coronary ostia. The left Amplatz is advanced around the arch oriented toward the left coronary ostium (Figure 15.7). The tip of the catheter usually comes to rest in the sinus of Valsalva below the coronary ostium. As the catheter is advanced farther, however, the Amplatz shape causes the tip of the catheter to rise up the wall of the sinus until it engages the ostium. At that point, slight withdrawal of the catheter causes deeper engagement of the coronary ostium, whereas further slight advancement causes paradoxical retraction of the catheter tip.

Cannulation of the Left Coronary Ostium

Engagement of the left coronary ostium is usually quite easy with the Judkins technique. As Judkins himself has stated, “No points are earned for coronary catheterization—the catheters know where to go if not thwarted by the operator.” If a left Judkins catheter with a 4-cm curve (commonly referred to as a JL4) is simply allowed to remain en face as it is advanced down into the aortic root, it will engage the left coronary ostium without further manipulation in 80% to 90% of patients (Figure 15.6). Engagement should take place with the arm of the catheter traversing the ascending aorta at an angle of approximately 45°, the tip of the catheter in a more or less horizontal orientation, and with no change in the pressure waveform recorded from the catheter tip.

In patients with a widened aortic root owing to aortic valve disease or long-standing hypertension, the 4-cm left Judkins curve may be too short to allow successful engagement. The catheter arm may lie nearly horizontally across the aortic root with the tip pointing vertically against the roof of the left main artery, or the catheter may even refold into its packaged shape during advancement into the aortic root (Figure 15.6D). In this case, a left Judkins catheter with a larger (JL4.5, JL5, or even JL6) curve should be selected. In the long run, changing to a larger catheter under these circumstances may end up saving time as compared with trying to make an unsuitable catheter work.

In the occasional patient with a short or narrow aortic root (usually a younger female, particularly if of short stature), even the 4-cm Judkins curve may be too long. When brought down into the aortic root, the catheter arm may lie nearly vertically with the tip pointing downward below the left coronary ostium. The left ostium may still be engaged despite this somewhat unfavorable situation by pushing the catheter down into the left sinus of Valsalva for approximately 10 seconds to tighten the tip angle and then withdrawing the catheter slowly. Having the patient take a deep breath during this maneuver also helps by pulling the heart into a more vertical position to assist in engagement of the left ostium. The most satisfactory approach, however, is to exchange for a JL3.5 catheter with a shorter curve.

On rare occasions, the left coronary ostium lies out of plane (typically high and posterior), as seen in the right anterior oblique (RAO) projection where the ostium is seen to be posterior to the catheter tip. In this case, limited counterclockwise rotation of the left Judkins catheter may help orient the catheter’s tip posteriorly and facilitate engagement. Too much rotation of this catheter, however, may result in a refolded catheter that requires guidewire reinsertion to straighten. In that case, it may be helpful to step up to the next larger Judkins curve. Alternately, some operators prefer to switch to a left Amplatz shape (Figure 15.2: available in progressively larger curves—1, 2, 3, 4). Amplatz catheters are more tolerant of rotational maneuvering and allow easy engagement of left coronary ostia that lie out of the conventional Judkins plane, as well as subselective engagement of the left anterior descending and circumflex coronary arteries in patients with short left main coronary segments or separate left coronary ostia. The left Amplatz is advanced around the arch oriented toward the left coronary ostium (Figure 15.7). The tip of the catheter usually comes to rest in the sinus of Valsalva below the coronary ostium. As the catheter is advanced farther, however, the Amplatz shape causes the tip of the catheter to rise up the wall of the sinus until it engages the ostium. At that point, slight withdrawal of the catheter causes deeper engagement of the coronary ostium, whereas further slight advancement causes paradoxical retraction of the catheter tip.

Cannulation of the Right Coronary Ostium

The Judkins technique for engaging the right coronary ostium requires slightly more catheter manipulation than required for cannulation of the left coronary ostium. After being flushed and filled with contrast in the descending
Guide catheter-induced coronary dissection and treatment with stent placement. Panel A displays a cranial left anterior oblique image showing the aggressive selective cannulation of the left circumflex coronary artery with an extra back-up catheter. Panel B shows an occlusive dissection and contrast staining in the left circumflex in right anterior oblique. Note that the wire position was preserved throughout the case. Panel C shows the final result with complete restoration of flow after stent placement. (Reproduced with permission from: Cohen MG, Rossi JS. Coronary dissection, side branch occlusion and abrupt closure. In Moscucci M, ed. Complications of Cardiovascular Procedures: Risk Factors, Management and Bailout Techniques. Lippincott Williams & Wilkins; 2011.)
Figure 15.6  Judkins technique for catheterization of the left and right coronary arteries as viewed in the left anterior oblique (LAO) projection. In a patient with a normal-size aortic arch, simple advancement of the JL4 catheter leads to intubation of the left coronary ostium (A–C). In a patient with an enlarged aortic root (D), the arm of the JL4 may be too short, causing the catheter tip to point upward or even flip back into its packaged shape (dotted catheter). A catheter with an appropriately longer arm (a JL5 or JL6) is required. To catheterize the right coronary ostium, the right Judkins catheter is advanced around the aortic arch with its tip directed leftward, as viewed in the LAO projection, until it reaches a position 2 to 3 cm above the level of the left coronary ostium (E). Clockwise rotation causes the catheter tip to drop into the aortic root and point anteriorly (F). Slight further rotation causes the catheter tip to enter the right coronary ostium (G).

aorta (with the catheter tip directed anteriorly to avoid injection into the intercostal arteries), the right Judkins catheter with a 4-cm curve (JR4) is brought around the aortic arch with the tip facing inward until it comes to lie against the right side of the aortic root with its tip aimed toward the left coronary ostium (Figure 15.6). In a left anterior oblique (LAO) projection, the operator slowly and carefully rotates the catheter clockwise by nearly 180° to engage the right coronary artery. The tip of the right Judkins catheter tends to drop more deeply into the aortic root when the catheter

Figure 15.7  Catheterization of the left coronary ostium with an Amplatz catheter. The catheter should be advanced into the ascending aorta with its tip pointing downward so that the terminal catheter configuration resembles a diving duck. As the Amplatz catheter is advanced into the left sinus of Valsalva, its tip initially lies below the left coronary ostium (left). Further advancement causes the tip to ride up the aortic wall and enter the ostium (center). Slight withdrawal of the catheter causes the tip to seat more deeply in the ostium (right).
is rotated, as the tertiary curve of the right Judkins shape aligns with the top of the aortic arch. To compensate for this effect, the operator must either begin the rotational maneuver with the tip 2 to 3 cm above the coronary ostium or withdraw the catheter slowly during rotation. Care must be taken to avoid over-rotation of the catheter, which tends to cause the catheter tip to engage too deeply into the right coronary artery. To avoid this common technical error, the operator should be prepared to apply a small amount of counterclockwise torque immediately as the tip of the catheter enters the ostium. Catheters with smaller (3.5 cm) or larger (5 or 6 cm) Judkins curves or right Amplatz catheters (AR1 or AR2) may be of value if aortic root configuration and proximal right coronary anatomy make engagement difficult.

Sometimes, the right coronary ostium lies high and anterior above the commissure of the left and right aortic valve leaflets rather than in the middle of the right sinus. If it had not been possible to engage the right coronary with the approach described above, a nonselective injection should be performed into the right sinus of Valsalva. This will show the high-anterior origin and trigger a change to a left Amplatz (either AL0.75 or AL1) as required to make contact with the aortic wall at that ostium location.

Damping and ventricularization are far more common in the right coronary artery than in the left. The cause may be (a) the generally smaller caliber of the vessel (particularly in nondominant vessels; see below), (b) ostial spasm around the catheter tip, (c) selective engagement of the conus branch, or (d) true ostial stenosis. These problems in right coronary engagement can usually be elucidated by nonselective injections into the right sinus of Valsalva or cautious injections in the damped position with immediate postinjection withdrawal of the catheter. As mentioned above, a 6F or 7F guiding catheter with side holes near the tip may be used to allow uninterrupted coronary perfusion between contrast injections, if necessitated by true ostial or proximal right coronary disease.

**Cannulation of Saphenous Vein and Arterial Grafts**

Despite the high initial rate of anginal relief following bypass surgery, 3% to 12% of saphenous vein grafts occlude within the first month. Additional veins occlude between 1 month and 1 year after surgery owing to exaggerated neointimal hyperplasia. By far the dominant failure mode of saphenous vein graft failure beyond 1 year, however, is diffuse graft atherosclerosis, which accounts for a 50% graft closure rate by 7 years. Free arterial grafts (free radial or free internal mammary) are sometimes used instead of saphenous vein grafts, and these have an intermediate long-term patency between that of saphenous vein grafts and pedicled internal mammary grafts (see below). An increasing number of patients thus develop recurrent angina after prior bypass surgery owing to vein graft or progressive native vessel disease, and these patients account for an increasing number of diagnostic procedures.

The proximal anastomosis of a vein graft or free arterial graft is usually placed on the right or left anterior aortic surface, several centimeters above the sinuses of Valsalva. Because many surgeons still resist the practice of placing radiopaque markers on the proximal graft, the operator must generally rely on the surgeon's operative report or diagram, as well as on knowledge of usual surgical practice in his/her own institution. The operative report always should be obtained before elective angiography on any patient with prior bypass surgery, but is absolutely essential for patients who underwent their operation at another medical center (where local preference may include practices like proximal anastomosis to the right posterior surface of the aorta [see below] or even proximal anastomosis to the descending aorta in patients with aortic root disease). It may thus be quite frustrating to embark on coronary angiography in a patient with prior bypass surgery without a detailed graft map, operative note, or prior detailed catheterization report/films in hand. In addition, searching for proximal anastomosis while not knowing the number of anastomosis or their location increases the risk of stroke and increases the total amount of contrast media needed to perform the procedure, thus also increasing the risk of contrast-induced nephropathy.

If no markers have been provided, the catheter tip should be oriented against the appropriate aortic wall and slowly advanced and then withdrawn until its tip catches in a graft ostium. The graft is injected in multiple projections that show its origin, shaft, distal anastomosis, and the native vessels beyond the anastomosis. This process must then be repeated until all graft sites have been identified. Grafts should not be written off as occluded unless a clear stump is demonstrated. If the myocardial territory supplied by a graft assumed to be occluded is still contracting, and there is no evident native or collateral blood supply to that territory, there may be a missed graft—the myocardium cannot function without a visible means of support! In that case, it may be valuable to perform an aortogram in an appropriate view to try to demonstrate flow in and locate the origin of such a missed graft. The emergence of effective therapies for focal lesions in vein grafts has placed a premium on being able to find and fix such diseased grafts before they occlude (Figure 15.8; see Chapters 29, 31, and 33).

**Left Coronary Artery Grafts**

Most commonly, grafts to the left coronary arise from the left anterior surface of the aorta, with grafts to the circumflex system usually placed somewhat higher on the aorta than those to the left anterior descending or diagonal branches. Alternatively, some surgeons prefer to route grafts to the circumflex through the transverse sinus behind the heart, in which case the circumflex graft may originate from the posterior surface of the aorta. Our preferred view for engagement of
Figure 15.8  
A. Sample of saphenous vein graft angiography, showing an occluded graft to the circumflex, filled with thrombus (top left, open arrow). A drug-infusion catheter (Tracker, Target Therapeutics) was placed (bottom left, curved arrow) and used to administer Urokinase (50,000 IU/hour) overnight. The following morning (top right), the thrombus had been dissolved, revealing the underlying ulcerated culprit lesion. This was treated with a single Palmaz-Schatz coronary stent (bottom right), reestablishing full patency.  
B. Saphenous vein graft with its origin localized by a ring marker implanted at the time of surgery.

Left coronary artery grafts is the right anterior oblique view, with the tip of the catheter pointing anteriorly (to the right of the angiographic view). Alternatively, the left anterior oblique view can also be used.

Right Coronary Artery Grafts

Grafts to the right coronary (or the distal portions of a dominant circumflex) usually originate from the right anterior surface of the aorta, above and somewhat behind the plane of the native right coronary ostium. We generally use a right Judkins (JR4) or an Amplatz (AL1) catheter to engage anterior (i.e., left) coronary grafts. Special left coronary bypass, internal mammary, or hockey stick catheters may be required for left grafts that originate with an upward trajectory (Figure 15.9). For downward-pointing right coronary grafts, we prefer a soft catheter with no primary curve (a multipurpose, Wexler, or JR3.5 short-tip catheter), which provides...
better alignment with the proximal portion of the graft and thus better opacification. The Wexler catheter can also be used for grafts originating from the left or posterior surface of the aorta. Since its tip remains in contact with the aortic wall, the shaft of this catheter can be rotated or the tip can be flexed to bring it into alignment with the proximal graft once the ostium has been engaged. Our preferred view for engagement of right coronary artery grafts is the left anterior oblique view, with the tip of the catheter pointing downward and toward the right of the aortic wall (left in the angiographic view).

Internal Mammary Artery Cannulation

Based on their superior demonstrated 10-year patency, the pedicled left and right internal mammary arteries (IMAs, also known as internal thoracic arteries [ITAs]) have become the conduits of choice. The proximal end of this graft remains attached to the subclavian artery (supplying the nutritional needs of the graft itself), as the vessel is freed up from its lower sternal attachments and anastomosed to the target coronary artery (usually the left anterior descending). More than 90% of current elective bypass procedures involve placement of at least one internal mammary graft.

Successful cannulation requires knowledge of the left subclavian and brachiocephalic trunk as well as the right subclavian arteries, as shown in Figure 15.10A. It is also important to understand some of the common anatomic variants in the internal mammary artery, including more proximal origin in the vertical portion of the subclavian, or origin as a common vessel with the thyrocervical trunk.

Although uncommon, these grafts can develop significant lesions, making it important to evaluate such grafts during any postbypass catheterization. In patients with early recurrence of angina (within the first 6 months after surgery), most commonly the lesion is located at the distal mammary–coronary anastomosis. It occurs usually owing to local intimal hyperplasia rather than atherosclerosis and responds well to balloon angioplasty. Flow-limiting kinks may also be present in the midgraft, and ostial lesions at the origin of the internal mammary from the subclavian may also occur. In patients years postbypass, significant lesions may develop in the native coronary artery beyond the internal mammary touchdown. In addition to establishing the patency of the internal mammary itself, it may also be important to look for large nonligated side branches that may divert flow from the coronary circulation and occlusion of which (in the occasional patient) may be required for angina relief. It is also important to look for stenoses in the subclavian artery before the take-off of the internal mammary, which may compromise the inflow to the graft and thereby cause myocardial ischemia (Figure 15.11). Such lesions may require construction of a carotid-to-subclavian graft, or more commonly stent placement.
Figure 15.10  Internal mammary angiography. A. Aortic arch injection shows the left internal mammary artery (LIMA) originating from the left subclavian (LS), just opposite the thyrocervical trunk (TCT) and distal to the right vertebral artery (VERT). The right internal mammary artery (RIMA) originates from the right subclavian (RS) just distal to the bifurcation of the right carotid from the brachiocephalic trunk (BT). B. Schematic diagram shows the corresponding arch vessel origins. Note that the left subclavian originates just inside the patient’s leftmost edge of the wedge-shaped shadow cast by the upper mediastinal structures in the left anterior oblique projection. Catheter manipulation in this projection facilitates advancement of a guidewire into the LS (step 1), facilitating selective cannulation of the LIMA during catheter withdrawal and slight counterclockwise rotation (step 2, see text). C. Variant in which internal mammary originates in common with thyrocervical trunk, resulting in poor opacification. An angioplasty guide wire was placed down the internal mammary through a 6F diagnostic catheter and used to advance the tip of the diagnostic catheter selectively down the IMA. From that position, sufficient opacification was obtained to demonstrate occlusion of the distal left anterior descending (LAD) beyond the anastomosis as the cause of the patient’s recurrent angina.

to restore normal flow to the internal mammary and vertebral branches of the subclavian artery (see Chapters 19 and 34).

Although mammary grafts can be studied easily from the ipsilateral brachial approach, we prefer the femoral approach using a soft-tip preformed internal mammary catheter, which resembles a right Judkins catheter except for a tighter primary curve. This used to be a time-consuming (up to 20 minutes for some operators) process, but the required time can be reduced to less than 3 minutes by adoption of a systematic strategy (see Figure 15.10B). In the LAO projection, cannulation of the left internal mammary artery begins by advancement of this catheter into the aortic arch until it
lies just inside the left edge of the wedgelike density formed by the shadow of the upper mediastinum against the lung fields. With 1 to 2 cm of J guidewire protruding from its tip, the mammary catheter is rotated counterclockwise and slowly pulled back until it falls into the subclavian artery origin. From there, the wire can be advanced well out into the axillary artery. The mammary catheter is then advanced over the wire, into the midsubclavian, where the guidewire is then removed and the catheter is flushed and filled with contrast. A low-osmolar contrast agent should be used to avoid causing CNS toxicity by reflux of hyperosmolar ionic contrast up the vertebral arteries. Switching to the straight AP projection, the catheter is rotated counterclockwise slightly (to make the tip point slightly anteriorly) as it is withdrawn slowly until the internal mammary is engaged. Intermittent gentle puffs of contrast will help localize the mammary origin during this withdrawal. Great care should be taken to avoid catheter tip trauma/dissection of the relatively delicate mammary vessel.

If selective cannulation is difficult because of tortuosity or anatomic variations, a variety of superselective or nonselective techniques can be used to permit angiographic evaluation. Nonselective injections into the subclavian will generally allow adequate opacification to see whether the internal mammary is open, but generally not to provide detailed information about the distal native vessel. Inflation of a blood pressure cuff on the ipsilateral arm may help reduce runoff through the axillary artery and improve opacification of the internal mammary in cases where selective cannulation is difficult. When selective cannulation proves difficult, a Y connector can be attached to the hub of the diagnostic internal mammary catheter and a 0.014-inch soft-tipped coronary angioplasty guidewire can be advanced into the mammary to serve as a support for catheter advancement.

Cannulation of the right internal mammary artery may be slightly more difficult because of the need to avoid the right carotid before entering the right subclavian itself. Again in the LAO projection, the upper mediastinal wedge is identified. The mammary catheter with protruding J wire is taken to the right edge of this shadow and rotated counterclockwise until it falls into the brachiocephalic trunk. The wire is then advanced toward the right subclavian artery. Predilection for the wire to advance into the right carotid artery may require removing the guidewire and performing a nonselective contrast injection in the brachiocephalic trunk to identify the origin of the subclavian branch. The RAO-caudal projection often gives the best spatial resolution of the right carotid and right subclavian origins, after which a steerable Wholey guidewire (Mallinckrodt) can be used to cannulate the subclavian. Once the wire is firmly out of the subclavian artery, the mammary catheter is advanced as described above. For cannulation of the right internal mammary artery, however, the catheter is rotated slightly clockwise during withdrawal to point its tip anteriorly.

**Gastroepiploic Graft Cannulation**

Taken together, the left and right internal mammary arteries can be used to revascularize most lesions in the left anterior descending, proximal circumflex, and proximal right coronary arteries. Even with sequential distal anastomoses,
however, the fact that there are only two internal mammary arteries means that most revascularization procedures still suffer the long-term limitations associated with the use of saphenous veins. Free segments of radial artery have also been used as bypass conduits, either from the ascending aorta (like a saphenous vein) or from the descending thoracic aorta in some patients undergoing repeat bypass surgery. Although the radial artery may have slight benefit over the saphenous vein, it is prone to spasm in the early postop period and does not match the long-term patency record of the internal mammary artery (because it does not retain its blood supply and innervation when used as a free graft). The effort to perform all-arterial bypass has brought back the right gastroepiploic artery (as an arterial pedicle graft) for anastomosis to the posterior descending or other vessels on the inferior surface of the heart. The right gastroepiploic normally supplies most of the greater curvature of the stomach, but can be dissected free from that organ and tunneled through the diaphragm to reach the inferior wall of the heart. Angiography of this vessel is possible using standard visceral angiographic catheters (e.g., Cobra) designed to enter visceral arteries such as the celiac axis. From there, the catheter can be advanced into the common hepatic (as opposed to the splenic) artery and then turned downward into the gastroduodenal artery (Figure 15.12). A 0.025-inch Glidewire (Terumo) can then be used to cannulate the right gastroepiploic (as opposed to the superior pancreaticoduodenal artery) if more selective injection is desired.

### THE BRACHIAL OR RADIAL APPROACH

The technique of brachial artery cutdown was the first approach used for selective coronary angiography, as described in Chapter 8. Dr. F. Mason Sones, Jr., designed the original catheter for this approach—a thin-walled radiopaque woven Dacron catheter with a 2.67-mm (SF) shaft diameter, tapering to 5F external diameter at a point 5 cm from its tip. In addition to the open tip, current models include side holes that are arranged in opposed pairs within 7 mm of the distal end. As Sones stated, this provides a “flexible finger” that may be curved upward into the coronary orifices by pressure of the more rigid shaft against the aortic valve cusps. This enables the Sones catheter to be used for cannulation of both the left and right coronary arteries, as well as for entry into the left ventricle for ventriculography. The standard Sones catheter is available in lengths of 80, 100, and 125 cm and 6F to 8F diameters. Most operators now use a different Sones-type coronary catheter constructed of polyurethane and made by Cordis Corporation. This catheter traverses a tortuous subclavian system with much greater facility and smoothness than does the woven Dacron catheter, and its enhanced torque control and reduced coefficient of friction ease engagement of the coronary ostia. See Figure 15.2 for a variety of preshaped coronary catheters, which are also effective from the brachial approach. In general, similar techniques as described above for the femoral approach apply for use of standard Judkins and Amplatz shapes from the left brachial or radial arteries. From the right brachial or radial arteries, smaller left Judkins curves or special catheter shapes are preferable (see Chapters 7 and 8).

When the Sones method is used from the right arm, catheter tip pressure should be monitored continuously once the catheter enters the brachial artery. Further passage of the catheter into the subclavian and brachiocephalic arteries should be accomplished under both pressure monitoring and fluoroscopic visualization. Occasionally, it may be difficult to pass the catheter from the subclavian artery to the aortic arch, but a simple maneuver by the patient—such as a deep inspiration, shrugging the shoulders, or turning the head to the left—often facilitates passage of the catheter into the ascending aorta. If passage of the catheter from the subclavian artery to the ascending aorta is not accomplished immediately and with complete ease, the operator should stop catheter manipulation and use a soft J-tipped 0.035-inch guidewire. Once the catheter is in the ascending aorta, the guidewire is removed and the catheter is aspirated, flushed, and reconnected to the rotating adapter of the manifold, either directly or by a short length of large-bore flexible connecting tubing.

With the Sones technique, selective engagement of the left coronary artery is accomplished as follows. In a left anterior oblique projection, the sinus of Valsalva containing the ostium of the left coronary artery lies to the left, and the sinus containing the ostium of the right coronary artery lies to the right. The noncoronary sinus lies posteriorly. The operator advances the catheter to the aortic valve and then continues to advance the catheter until its tip bends cephalad and points toward the left coronary ostium. When the catheter is properly positioned with its tip bent cephalad, slightly advancing or rotating the catheter usually results in selective engagement of the left coronary ostium, which is verified by a small injection of radiographic contrast agent. Occasionally, a deep breath taken by the patient will facilitate this selective engagement. Our usual approach, as described in Chapter 8 and illustrated in the upper left panel of Figure 15.13, involves forming a smooth shallow loop and gradually inching up to the ostium from below. If the distal 2 to 3 mm of the catheter tip bends downward during this inching-up process, the tip may enter the left coronary artery, giving a cobra head appearance (see Figure 15.13, top right) similar to that achieved with the left Amplatz catheter (see Figure 15.7). For the high take-off left coronary ostium, the catheter may have the appearance (as in Figure 15.13, bottom) in which the catheter tip is lying across the ostium at right angles to the course of the left main coronary artery. During contrast injection in this instance, coronary blood flow generally carries the contrast agent down the vessel, giving good opacification of the entire left coronary artery. Once the catheter tip has engaged the coronary ostium and no damping of pressure...
A1 and A2. Gastroepiploic graft anatomy. The common hepatic artery (CHA) originates with the splenic artery (SA) from the celiac trunk (CT). The gastroduodenal artery (GDA) originates from the CHA, which then becomes the proper hepatic artery (PHA). The terminal branches of the GDA are the pancreatoduodenal (PD) and the right gastroepiploic artery (GEA), shown here undergoing angioplasty of a lesion at its anastomosis to the right coronary artery (RCA). B. Free radial graft from the descending aorta to an obtuse marginal graft, cannulated using a Cobra visceral angiographic catheter. Localization of the graft ostium was aided by the presence of multiple surgical clips used to ligate small side branches of the radial artery at the time of bypass.

from the catheter tip is observed, cineangiography may be performed with selective injection of radiopaque material in a variety of views, as described below.

Selective engagement of the right coronary orifice may be accomplished as illustrated in steps 1 to 3 of Figure 15.14. In the shallow LAO projection, the catheter is curved up
usually makes an abrupt turn into the right coronary ostium, at which time the operator must release all torque to prevent the catheter tip from continuing its sweep past the ostium. On occasion, the Sones catheter literally leaps into the right coronary artery and will be 4 to 5 cm down its lumen. If this occurs, the catheter should be gently withdrawn until its tip is stable just within the ostium.

Another technique for catheterizing the right coronary artery involves a more direct approach by way of the right coronary cusp. With the catheter in the right sinus, the operator should make a small curve on the tip, directed rightward. A small dose of contrast material in the right sinus of Valsalva will allow visualization of the right coronary orifice and thus facilitate selective engagement. Occasionally, a deep inspiration by the patient accompanied by gentle advancement of the catheter to the right of the aortic root results in selective engagement of the right coronary artery. Cannulation of the coronary arteries using the radial artery approach presents challenges similar to those in the brachial artery approach. The reader is directed to Chapter 7 for a detailed description.

### Adverse Effects of Coronary Angiography

Once the coronary vessels have been engaged, optimal selective angiography requires transient but nearly complete replacement of blood flow with the radiopaque contrast agent. A wide variety of iodine-containing agents are currently used for coronary angiography and have already been discussed in greater detail in Chapter 2. Older high-osmolar contrast agents had a number of potentially deleterious effects during coronary injection (see Chapters 2 and 4) including (a) transient (10 to 20 second) hemodynamic depression marked by arterial hypotension and elevation of the left ventricular end-diastolic pressure, (b) electrocardiographic effects with T-wave inversion or peaking in the inferior leads (during right and left coronary injection, respectively), sinus slowing or arrest, and prolongation of the PR, QRS, and QT intervals, (c) significant arrhythmia (asystole or ventricular tachycardia/fibrillation), (d) myocardial ischemia owing to interruption of oxygen delivery or inappropriate arteriolar vasodilatation (coronary “steal”), (e) allergic reaction, and (f) cumulative renal toxicity. Some (but not all) of these adverse effects are eliminated by use of a low-osmolar contrast agent, albeit at a modestly increased expense.

Although newer low-osmolar contrast agents have less prominent side effects, patients undergoing coronary angiography should always be monitored continuously in terms of clinical status, surface electrocardiogram, and arterial pressure from the catheter tip. In patients with baseline left ventricular dysfunction or marked ischemic instability, we also like to perform a right heart catheterization, and display pulmonary artery pressure continuously on the same scale as that of the arterial pressure as an early indicator of procedural problems.

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**Figure 15.13**

Selective catheterization of the left coronary artery using the Sones catheter. The standard approach involves forming a smooth shallow loop and gradually “inching up” to the ostium from below. If the distal 2 to 3 mm of the catheter tip bends downward during this inching-up process, the tip may enter the left coronary artery, giving a cobra head appearance (upper right). When the left coronary ostium originates high in the left sinus of Valsalva (high take-off left coronary artery), the catheter may have the appearance seen in the bottom panel, where the tip is lying across the ostium at right angles to the course of the left main coronary artery. During coronary injection in this instance, coronary blood flow usually carries the contrast agent down the vessel, giving good opacification of the entire left coronary artery. Toward the left coronary artery (step 1) and clockwise torque is applied. While the operator is gradually applying clockwise torque, a gentle to-and-fro motion of the catheter (the to-and-fro excursions are not more than 5 to 10 mm in length) helps to translate the applied torque to the catheter tip. When the tip starts moving in its clockwise sweep of the anterior wall of the aorta, the operator maintains (but does not increase) a clockwise torque on the catheter and simultaneously pulls the catheter back slightly (step 2, Figure 15.14) because the position of the ostium of the right coronary artery is lower than that of the left coronary artery. At this point, the catheter...
Selective catheterization of the right coronary artery using the Sones catheter. In the shallow left anterior oblique (LAO) projection, the catheter is curved upward and to the left (1) and clockwise torque is applied. While the operator is gradually applying clockwise torque, a gentle to-and-fro motion of the catheter helps to translate the applied torque to the catheter tip. When the tip starts moving in its clockwise sweep of the anterior wall of the aorta, the operator maintains (but does not increase) a clockwise torque tension on the catheter and simultaneously pulls the catheter back slightly (2), because the position of ostium of the right coronary artery is lower than that of the left coronary artery. At this point, the catheter usually makes an abrupt leap into the right coronary ostium (3), at which time the operator must release all torque to prevent the catheter tip from continuing its sweep and passing by the ostium. See text for details and alternative methods.

or progressive decompensation. A significant rise in pulmonary artery mean or diastolic pressure should prompt temporary suspension of angiography and initiation of treatment (e.g., intravenous furosemide, nitroglycerin, nitroprusside) before frank pulmonary edema develops. The venous sheath also provides a ready route for rapid administration of fluids or medication through its side arm and allows rapid insertion of a temporary pacing electrode if needed. Prophylactic placement of temporary pacing electrodes in patients undergoing coronary angiography is not indicated, since most episodes of bradycardia or asystole are brief and are resolved promptly by having the patient give a forceful cough, which elevates central aortic pressure and probably helps wash residual contrast out of the myocardial capillary bed. Similarly, prophylactic drugs are not given routinely to prevent ventricular tachyarrhythmias, although appropriate drugs (lidocaine, amiodarone, atropine, epinephrine, and so on), a defibrillator, and airway management equipment are always kept at the ready and can be brought into play within seconds.

One of the most common adverse effects seen during coronary angiography is the provocation of myocardial ischemia, particularly in patients with unstable angina. In unstable patients or when the primary indication for cardiac catheterization is assessment of coronary artery disease, we have modified our usual practice of performing the left ventriculogram before coronary angiography (lest an adverse reaction to the ventriculogram compromise the more crucial coronary study). When myocardial ischemia does occur during coronary angiography, the best course of action is to remove the catheter from the coronary ostium and temporarily suspend injections until angina resolves. If this takes more than 30 seconds, we typically administer nitroglycerin (200 mg bolus, repeated at 30-second intervals up to a total of 1,000 mg) into either the involved coronary artery or the pulmonary artery catheter. If marked arterial hypertension is present and fails to respond to nitroglycerin, we may administer other vasodilators as needed to bring the blood pressure down. In patients with inappropriate tachycardia in the setting of angina and reasonable systolic left ventricular function, intravenous metoprolol (5 mg every 5 minutes to a total dose of 15 mg) or an infusion of a short-acting beta-blocking agent (esmolol) is frequently beneficial. Only rarely (in patients with severe three-vessel and/or left main coronary disease and those whose ischemia is associated with hypotension) is myocardial ischemia severe enough and refractory to the above management program to prompt placement of an intra-aortic counterpulsation balloon in the contralateral femoral artery before completion of coronary angiography (see Chapter 27). In any patient with prolonged or refractory ischemia during diagnostic coronary angiography, it may be worthwhile to perform limited reexamination of the coronary vessels to determine whether the angiographic procedure has caused a problem (spasm, dissection, thrombosis) that might require immediate treatment with additional vasodilators, coronary intervention, thrombolysis, or emergency bypass surgery.

Severe allergic reactions are uncommon during coronary angiography and are best prevented by 13 to 24 hours of premedication (see Chapter 4) and use of a nonionic contrast agent in patients with a history of prior allergic reaction to radiographic contrast. When a severe unexpected reaction does occur, it usually responds promptly to the intravenous
administration of epinephrine (see Chapter 4 for a detailed protocol). Acute kidney injury (AKI) may develop after coronary angiography, particularly in patients who are hypovolemic, who receive large volumes of contrast (more than 5 mL/kg body weight divided by serum creatinine in mg/dL),43 or who have had prior renal insufficiency, diabetes, or multiple myeloma. In these patients, every effort should be made to give adequate hydration preprocedure and postprocedure (see also Chapters 2 and 4). Use of low-osmolar or iso-osmolar contrast media has been shown to reduce the incidence of acute kidney injury when compared to use of high-osmolar contrast media (Chapter 4). Given the additional adverse effects on hemodynamics, conduction, and contractility, high-osmolar contrast media are no longer used.

Air embolization is a rare complication of coronary angiography, and it occurs always owing to poor technique (see below). Intracoronary administration of nitroglycerin, intra-coronary saline flushes, administration of 100% oxygen, and attempts to aspirate the injected air have been proposed as interventions to revert the acute ischemic changes associated with this complication.44

**INJECTION TECHNIQUE**

As mentioned previously, high-quality coronary angiography requires selective injection of radiographic contrast at an adequate rate and volume to transiently replace the blood contained in the involved vessel with slight but continuous reflux into the aortic root. Too timid an injection permits intermittent entry of nonopaque blood into the coronary artery (producing contrast dilution or streaming, which makes interpretation of lesions difficult) and fails to allow visualization of the coronary ostium and proximal coronary branches. On the other hand, too vigorous an injection may cause coronary dissection or excessive myocardial blushing, and too prolonged an injection may contribute to increased myocardial depression or bradycardia.

We train our fellows to adjust the rate and duration of manual contrast injection to match the observed filling pattern of the particular vessel being injected to. Injection velocity should be built up gradually during the first second until the injection rate is adequate to completely replace antegrade blood flow into the coronary ostium (Figure 15.15). The rate and volume of injection required to accomplish this goal have been measured45 and found to average 7 mL at 2.1 mL/second in the left and 4.8 mL at 1.7 mL/second in the right coronary. In patients with occlusion, much lower rates and volumes are required, and in patients with left ventricular hypertrophy (e.g., aortic stenosis, hypertrophic myopathy) much larger volumes and higher rates of injection may be required. In addition, visualization of the right coronary artery can often be achieved with <4 mL of contrast. Thus, the injection should be maintained until the entire vessel is opacified. If there is any question about whether the body of the injection has provided adequate reflux to visualize the coronary ostium, an additional burst of contrast (extra reflux) should be given before the injection is terminated. The injection should then be terminated abruptly by turning the manifold stopcock back to monitor pressure, although cine filming should continue until opacification of distal vessels or late-filling branches is complete. The operator should monitor for excessive bradycardia or hypotension, review the video loop, and set up the gantry angles for the next injection. To avoid problems, each injection should begin with a completely full (and bubble-free) injection syringe, held with the handle slightly elevated so that any microbubbles will drift up toward the plunger. The injection syringe should be managed in such a way as to avoid mixing of blood and contrast, because such mixing may promote formation of thrombi (particularly when non-ionic contrast agents are used).

Although manual contrast injection is the standard technique in coronary angiography, some operators favor the use of a power injector (as used in left ventriculography or aortography) to perform coronary injections.46 The injector is preset to a rate to match the involved vessel (2–3 mL/second for the right and 3–4 mL/second for the left coronary) and activated by a foot switch for sufficient time to fill the coronary with contrast (generally 2–3 seconds). This approach
allows a single operator to perform injections and move the table, and has proved safe in thousands of procedures. A special power injector has also been introduced (Acist, Bracco, Eden Prairie, MN) that can perform such power injections under rate control by finger pressure on a sterile control handle, reverting automatically to pressure monitoring when the injection is terminated. This may be of value when a single operator must perform injections as well as panning the table during diagnostic coronary angiography.

Right-Dominant Circulation

The right coronary artery gives rise to the conus branch (which supplies the right ventricular outflow tract) and one or more acute marginal branches (which supply the free wall of the right ventricle), whether or not the circulation is right dominant. In the 85% of patients who have a right-dominant coronary artery, it goes on to form the AV nodal artery, the posterior descending, and the posterolateral left ventricular branches that supply the inferior aspect of the interventricular septum (see Figure 15.16). After a short (but variable) distance, the left main trunk branches into the left anterior descending and the circumflex coronary arteries. The left anterior descending artery gives rise to septal branches that curve down into the interventricular septum, as well as to diagonal branches that wrap over the anterolateral free wall of the left ventricle.

Some patients have a twin left anterior descending system, in which one trunk (frequently intramyocardial) supplies the entire septum and the other trunk runs on the surface of the heart supplying all the diagonal branches. The circumflex artery courses clockwise in the AV groove (viewed from the apex) as it gives rise to one or more obtuse marginal branches that supply the lateral free wall of the left ventricle, but does not reach the crux in patients with a right-dominant circulation. In some patients, a large intermedius or ramus medianus branch (neither a diagonal nor a marginal) may originate directly from the left main trunk, bisecting the angle

Coronary Anatomy

The coronary angiographer must develop a thorough familiarity with the normal coronary arterial anatomy and its common variants. For individuals just learning coronary anatomy, the main coronary trunks can be considered to lie in one of two orthogonal planes (Figure 15.16). The anterior descending and posterior descending coronary arteries lie in the plane of the interventricular septum, whereas the right and circumflex coronary trunks lie in the plane of the atrioventricular valves. In the 60° left anterior oblique (LAO) projection, one is looking down the plane of the interventricular septum, with the plane of the AV valves seen en face; in the 30° right anterior oblique (RAO) projection, one is looking down the plane of the AV valves, with the plane of the interventricular septum seen en face. The major segments and branches have each been assigned a numerical identification in the BARI modification of the CASS nomenclature (Figure 15.17).
between the left anterior descending and circumflex arteries, to create a trifurcation pattern of the left main coronary artery. Regardless of whether the patient is right or left dominant, the sinus node originates as a proximal branch of the right coronary in 60% of patients and as a left atrial branch of the circumflex in the remaining 40% of patients.

**Left-Dominant Circulation**

In 8% of patients, the coronary circulation is left dominant; that is, the posterolateral left ventricular, posterior descending, and AV nodal arteries are all supplied by the terminal portion of the left circumflex coronary artery. In such patients, the right coronary artery is small and supplies only the right atrium and right ventricle. It may be important to visualize this, as a potential source of right-to-left collaterals, but the small diameter of a nondominant right coronary artery predisposes it to damping and catheter-induced spasm (see below), which make limited injections advisable.

**Balanced-Dominant Circulation**

In about 7% of hearts, there is a codominant or balanced system, in which the right coronary artery gives rise to the posterior descending artery and then terminates, and the circumflex artery gives rise to all the posterior left ventricular branches and perhaps also a parallel posterior descending branch that supplies part of the interventricular septum. In some patients, the supply to the inferior wall may be further fractionated among a short posterior descending branch of the right coronary (which supplies the inferobase), branches of the distal circumflex (which supply the midinferior wall), and branches of the acute marginal (which extend to supply the inferopapex).

**Anatomic Variants**

Although these basic concepts describe the general pattern of the coronary circulation, it must be noted that there is considerable patient-to-patient variability in the size and position of different coronary arterial branches. In 1% to 2% of patients, these coronary anatomic features are sufficiently divergent to qualify as coronary anomalies (see Chapter 16). Every operator must be thoroughly familiar with these anatomic anomalies and continually vigilant for their occurrence, lest failure to recognize an anomaly result in an incomplete and therefore inadequate examination. In a review of 126,595 cases from the Cleveland Clinic, the most common of these anomalies was separate ostia of the left anterior descending and left circumflex arteries (0.41%). When separate ostia of the left anterior descending and left circumflex are present, the catheter will generally sit with its tip in the left anterior descending, although there is generally adequate spillover to opacify the circumflex. If not, separate cannulation of the circumflex may be necessary, using the next larger size left Judkins catheter (e.g., JL5 instead of JL4) or a left Amplatz catheter. A similar situation may exist in the right coronary artery, where the conus branch may have a separate ostium and separate
cannulation of it may be necessary to demonstrate important collaterals when reflux during the right coronary injection does not provide adequate reflux to opacify the conus.

The next most common anomaly is origin of the circumflex from the right coronary artery or right sinus of Val- solda (0.37%). This should be suspected when the left main is unusually long and a paucity of vessels to the lateral wall is identified. Careful review of the RAO left ventriculogram may show a dot of contrast just behind the aortic valve when the anomalous circumflex runs posterior to the aorta.50 If an anomalous circumflex is not filled adequately during right coronary injection, it must be cannulated separately (generally with an ALL catheter). We have seen patients in whom the only coronary lesion was located in such an anomalous circumflex, and failure to identify and opacify this vessel would have led to failure to diagnose and treat the problem.

In another common variant, anomalous vessels (particularly the right coronary artery) may originate unusually high in the aortic root or out of the normal coronary plane (Figure 15.18), making them easier to cannulate using left Amplatz rather than right Judkins catheters. The left coronary may originate from the right sinus of Valsalva (Figure 15.19), either as a separate ostium51 or as part of a single coronary.52 Origin of a coronary artery from the noncoronary sinus of Valsalva is rare but has been reported.49,53 The main effect of these coronary anomalies is to test the patience, knowledge, and resourcefulness of the angiographer. Other anomalies, however, may themselves cause myocardial ischemia (even in the absence of atherosclerotic stenosis) and are described in Chapter 16.

Angiographic Views

Accurate coronary diagnosis requires coronary injections in multiple views to make sure that all coronary segments are seen clearly without foreshortening or overlap. The angulation of each view is defined using two terms. The first term denotes rotation; for example, the term right anterior oblique (RAO) designates a view where the image intensifier is positioned over the patient’s right anterior chest wall, and left anterior oblique (LAO) designates a view where the image intensifier is positioned over the patient’s left anterior chest wall. The second term denotes skew, that is, the amount of angulation toward the patient’s head (cranial) or foot (caudal). Although the full nomenclature of skew specifies first the source of the beam and then the location of the imaging device (e.g., caudocranial, to denote that the x-ray tube is toward the patient’s feet while the image intensifier is located toward the patient’s head), in practice this is simplified to give just the location of the imaging device. The term RAO caudocranial is thus stated as RAO-cranial.

When cradle systems were in use in the 1970s, these views were usually limited to different degrees of left or right anterior obliquity in the transverse plane, including the classic 60° LAO and 30° RAO projections (see Figure 15.16 and 15.20). To allow concurrent cranial angulation of the x-ray beam, cradle systems were later modified by propping the patient’s shoulders up on a foam wedge—hence the name sit-up view—to provide compound LAO-cranial projection. In the 1980s, cradle systems were abandoned in favor of parallelogram or rigid U-arm systems supported by a rotating pedestal that allow compound beam angulation in any combination of conventional transverse (LAO, RAO) with skew (cranial, caudal) angulation up to 45°. Although these views place increased demands on the generator and increase the scattered radiation, there is no doubt that they have improved our ability to define coronary anatomy44,55 (Figure 15.20).

It is not necessary to perform all potential views in a given patient to constitute an adequate study. Rather, a series of screening views should be used as the foundation of the

Figure 15.18 Multidetector computed tomographic image of a patient with anomalous origin of the right coronary artery from the left sinus of Valsalva and a course between the aorta and pulmonary artery. RCA, right coronary artery; LAD, left anterior descending; LC, left circumflex; AO, aorta; RVOT, right ventricular outflow tract.
study, adjusted or supplemented by one or more additional views selected to more completely define suspicious areas. This requires the operator to interpret the coronary anatomy as each injection is made or by digital review—it is not acceptable to simply shoot a series of routine views and hope that the study will prove adequate when reviewed later. Although some laboratories rely on a single technician to set up shots and pan the table during coronary angiography, each operator should know how to do this himself/herself to develop a good understanding of how the choice of gantry angulation influences the projected coronary anatomy. One valuable training tool in this respect is a simple wire model of the coronary anatomy, which is viewed as it is moved into different angles56 (Figure 15.21). Although there is no substitute for this type of hands-on learning, the discussion below is provided as a rough introduction.
Right Anterior Oblique Projections

For historic reasons relating to cradle systems, the screening views used in many laboratories were the straight LAO–RAO angulations. With the availability of more modern gantry systems, it became clear that certain cranial and caudal angulated views offer far better anatomic definition. Thus, we generally avoid the straight 30° RAO projection of the left coronary, because it suffers from overlap and foreshortening of both the left anterior descending and the circumflex vessels (see Figure 15.20). Instead, our initial view of choice is the RAO-caudal projection (0–10° RAO and 15–20° caudal), since it provides an excellent view of the left main bifurcation, the proximal left anterior descending artery, and the proximal to midcircumflex artery. The second view we perform is a shallow RAO-cranial projection (0–10° RAO and 25–40° cranial), which provides a superior view of the mid and distal left anterior descending artery, with clear visualization of the origins of the septal and diagonal branches. This shallow RAO cranial view is also quite good for examination of the distal right coronary artery or distal circumflex, since it effectively unstacks the posterior descending and posterolateral branches and projects them without foreshortening. However, it seldom provides any useful information about the left main or circumflex coronary artery, because it causes them to be overlapped and foreshortened.

Left Anterior Oblique Projections

The conventional 60° LAO projection is limited by overlap and foreshortening of the left coronary artery, although it is very useful in the evaluation of the proximal and midright coronary artery. The LAO-cranial view, created by the addition of 15 to 30° of cranial angulation, elongates the left
main and proximal left anterior descending arteries while projecting the intermedius or first diagonal branch downward off the proximal circumflex. If radiographic penetration in this view is difficult, reducing the LAO angulation to 30 to 40° will usually allow the left anterior descending artery to fall into the lucent wedge between the right hemidiaphragm and the spine. Performing the angiographic run during a sustained maximal inspiration will usually pull the diaphragm down and improve x-ray penetration. The LAO-caudal view (40–60° LAO and 10–20° caudal) projects the left coronary artery upward from the left main in the appearance of a spider (hence the older term, spider view), and usually offers improved visualization of the left main, proximal left anterior descending (LAD), and proximal circumflex arteries. It is particularly valuable in patients whose heart has a horizontal lie, that is, the origin of the left main artery projects at or below the proximal left anterior descending artery in the standard LAO projection. This view can often be enhanced by filming during maximal expiration, which accentuates a horizontal cardiac position and allows a better look from below, although it poses a challenge to the radiographic capability of most of the older installations. A shallow LAO-cranial view will also allow optimal visualization of the distal right coronary artery, its bifurcation into the posterior descending artery and the posterolateral artery, and of the complete posterior descending artery and posterolateral artery systems.

Posteroanterior and Left Lateral Projections

The straight posteroanterior (PA, or “0–0”) and left lateral projections tend to be underused in the era of complex angulation. Because the left main coronary artery curves from a more leftward to an almost anterior direction along its length, the PA projection (sometimes referred to incorrectly as the AP projection) frequently provides the best view of the left main ostium. On the other hand, the shallow RAO-caudal view frequently provides a better look at the more distal left main artery. The left lateral projection is particularly useful in examining the proximal circumflex and the proximal and distal left anterior descending arteries, particularly when combined with slight (10–15°) cranial angulation. This projection also provides the best look at the anastomosis of a left internal mammary graft to the mid-distal left anterior descending and offers an excellent look at the midportion of the right coronary artery, free of the excessive motion seen when this portion of the vessel is viewed in the straight RAO projection. The left lateral projection also has the advantage of allowing easy radiographic penetration in most patients when it is performed with both of the patient’s hands positioned behind the head, although it generates the highest degree of backscatter given the proximity of the beam entry point on the patient’s right side to the operator.

A uniform sequence of these views, adjusting the exact angles slightly in each patient as dictated by test puffs of contrast, can thus be adopted, and it can result in optimum visualization of coronary anatomy while minimizing use of contrast media and radiation exposure. Beginning with the left coronary artery, these views include the following:

1. RAO-caudal to visualize the left main, proximal LAD, and proximal circumflex
2. RAO-cranial to visualize the mid and distal LAD without overlap of septal or diagonal branches
3. LAO-cranial to visualize the mid and distal LAD in an orthogonal projection
4. LAO-caudal to visualize the left main and proximal circumflex

One or more supplemental views (PA, lateral-cranial, lateral-caudal) may then be taken to clarify any areas of uncertainty. The right coronary catheter is then placed, after which three screening views are obtained:

1. LAO to visualize the proximal and mid right coronary artery (RCA)
2. LAO cranial to visualize the distal right coronary artery and its bifurcation into the posterior descending and posterolateral branches
3. RAO-cranial to visualize the posterior descending and posterolateral branches
4. Lateral to visualize the mid-RCA

Lesion Quantification

To quantify a coronary stenosis accurately, it must be seen in profile, free from artifact related to foreshortening or obfuscation by a crossing vessel. Multiple views are important, because many lesions have a markedly eccentric (elliptical rather than round) lumen. When seen across its major axis, the width of the lumen may appear nearly normal, but a clue to the presence of a severe degree of narrowing in the other axis may be marked lucency caused by thinning of the contrast column. Any such suspicious lesions must be examined in a variety of other projections to reveal their true severity and to distinguish the lucency caused by eccentric stenosis from a similar lucency that may be seen adjacent to an area of denser contrast (caused by tortuosity or overlapping vessels in the absence of any true abnormality at the site) owing to a perceptual artifact known as the Mach effect. The ability of coronary angiography to quantify the degree of stenosis at different points in the coronary circulation is fundamentally limited by the fact that it consists of a “lumen-o-gram,” in which each stenosis can be evaluated only by comparison to an adjacent reference segment that is presumed to be free of disease. In fact, both intravascular ultrasound (see Chapter 25) and pathologic examination show that even segments that appear smooth on angiography may harbor substantial plaque. It is thus important to have a sense of the normal caliber of the major coronary arteries (4.5 ± 0.5 mm for the left main, 3.7 ± 0.4 mm for the left anterior descending, 3.4 ± 0.5 mm for a nondominant versus 4.2 ± 0.6 mm for a dominant circumflex, and 3.9 ± 0.6 mm...
for a dominant versus 2.8 ± 0.5 mm for a nondominant right coronary artery). By comparing the diameter of a presumably disease-free segment of coronary artery to the size of the diagnostic catheter (6F equals 2 mm), the operator can identify vessels that fall below these normal size ranges and may thus be diffusely diseased.

In addition to the difficulty in finding a disease-free reference segment, a major problem in the interpretation of a coronary angiogram is deciding the severity of any given stenosis. Both animal data and human data show that a stenosis that reduces the lumen diameter by 50% (and hence cross-sectional area by 75%) is hemodynamically significant in that it reduces the normal threefold-to-fourfold flow reserve of a coronary bed (Figure 15.22), whereas a 70% diameter stenosis (90% cross-sectional area) eliminates virtually any ability to increase flow above its resting level (see Chapter 24). Stenoses that reduce the lumen diameter by 90%, however, rarely exist without reducing antegrade flow (i.e., TIMI [Thrombolysis in Myocardial Infarction] grade 1 or 2, rather than TIMI grade 3 normal flow).

Instead of the subjective TIMI flow grading system, Gibson et al. have created norms for the number of cine frames (at 30 frames per second [fps]) required for contrast to leave the catheter tip and reach standardized distal landmarks in each coronary artery (the LAD “mustache,” the first posterolateral branch of the right coronary). Contrast normally reaches these points in 20 frames for the RCA and 36 frames for the LAD, with TIMI 2 (partial) flow corresponding to more than a doubling of these frame counts. Of course, even more precise data about hemodynamic lesion significance can be obtained by performance of flow or pressure gradient measurements, at rest and during arteriolar vasodilation (e.g., after adenosine administration), to calculate the coronary flow or fractional flow reserve. Lesions that permit a flow increase of more than twofold, or have a ratio of distal pressure to aortic pressure of >0.75 in the setting of peak flow after adenosine injection, are generally considered to be hemodynamically insignificant. Angiographically borderline (40–60%) lesions for which there is no clear objective evidence of ischemia (e.g., exercise test, perfusion scan) should thus be investigated further with intravascular ultrasound or pressure wire measurements before considering intervention (see Chapters 24 and 25).

In clinical practice, however, the degree of lesion stenosis is usually just estimated visually from the coronary angiogram. The operator must thus develop a sense of what constitutes a 50%, 70%, and 90% diameter stenosis (see Figure 15.23). Although the process of visually estimating the degree of coronary stenosis may seem straightforward, it is subject to significant operator variability (the standard deviation for repeat estimates is ±18%) as well as a systematic form of “stenosis inflation” that causes operators to estimate a diameter stenosis roughly 20% higher than that measured by quantitative coronary angiography (QCA). A stenosis that measures 50% will thus typically be called 70%, whereas a stenosis that measures 70% will be called 90%.

![Figure 15.22](image_url) Effect of coronary stenosis on myocardial blood flow and coronary vasodilator reserve. Top. Resting flow (open circles) is well maintained at approximately 1 mL/minute per gram of myocardium throughout the range of evaluated diameter stenosis. The ability to increase flow during vasodilator stimulus (closed circles), however, becomes impaired for stenosis >50% and is virtually abolished >70%. Bottom. The vasodilator reserve (dilated flow/resting flow), which has a normal value of 3 to 4 but is reduced with stenosis >50% and falls to 1 at >70%. (From Uren, et al. Relation between myocardial blood flow and the severity of coronary artery stenosis. N Engl J Med 1994;330:1782, with permission.)

Tools are available to resolve this problem. The simplest is to project the coronary image on a wall-mounted viewing screen and to use inexpensive digital calipers (available from machinist supply houses) to measure the relative diameters of the stenotic and reference segments. Percent stenosis then can be calculated as $100 \times [1 - (\text{stenosis diameter}/\text{reference diameter})]$ to provide a more accurate estimate of stenosis.
This technique also reduces the standard deviation for diameter stenosis estimates to 6% to 8%. Even greater precision can be obtained by using computer-assisted algorithms to perform automated edge detection on digitally acquired images to measure the coronary lumen with a standard deviation <5%. The amounts of variation in diameter stenosis estimates in one study using these different methods concurrently is shown in Figure 15.24. Most cardiac catheterization angiographic systems today include software for the quantitative analysis of coronary artery stenosis.

The good news is that angiographers who have trained their eye in actual stenosis quantification (by using digital calipers or computer-assisted quantitative coronary angiography) can then actually give visual estimates much closer to true measurements. This would allow angiographers to be more uniform in their visual estimates and move away from reporting physiologically impossible findings like a 95% stenosis with normal distal flow! It has also become important to evaluate lesion morphology more accurately from the coronary angiogram. Features such as eccentricity, ulceration, and thrombus may be associated with unstable clinical patterns, whereas features such as calcification, eccentricity, or thrombus may influence the choice of catheter intervention. Many of these features can be recognized from careful study of high-quality cineangiograms, although angiography is clearly not as sensitive to these features as intravascular ultrasound or angioscopy (for thrombus or dissection). Angiographers may also have trouble predicting the physiologic significance of a coronary lesion, in which case angiography may need to be supplemented by other techniques such as direct flow or distal pressure measurements. Finally, the absence of lesions narrowing the coronary lumen by >50% does not necessarily confer immunity from subsequent coronary events, since it is frequently a less severe stenotic lesion with a large lipid core and thin fibrous cap that may predispose to subsequent plaque rupture and the resulting coronary thrombosis. Despite these recognized limitations in quantification and morphology assessment, contrast coronary angiography remains the clinical standard by which lesions are evaluated and decisions are made regarding the need for (and best mode of providing) revascularization in the patient with ischemic heart disease.

**Coronary Collaterals**

In reviewing the coronary angiogram, one basic principle is that there should be evident blood supply to all portions of the left ventricle. Previously occluded vessel branches usually manifest as truncated stumps, but a stump may not be evident if there has been a flush occlusion at the origin of the involved vessel. These occluded or severely stenotic vessels will frequently be seen to fill late in the injection by antegrade (so-called bridging) collaterals or collaterals that originate from the same (intracoronary) or an adjacent (intercoronary) vessel; these collaterals are reviewed in an excellent paper by Levin and illustrated in Figures 15.25 through 15.27. Finally, coronary occlusion may present in some patients simply as an angiographically arid area to which there is no evidence of either antegrade or collateral flow and no evident vascular stump. However, if such an area fails to show regional hypokinesis on the left ventriculogram, the operator should search carefully for blood supply by way of anomalous vessels or unopacified collaterals (i.e., a separate origin conus branch that was not opacified during the main right coronary injections), because the myocardium cannot continue to function normally with no visible means of support. Functioning collaterals, however, can maintain a coronary wedge pressure that averages nearly 40% of mean aortic pressure, thereby maintaining myocardial viability in the collateral-fed distribution. Along with other measures of retained or augmented wall motion, redistributing defects on perfusion imaging, and positron emission tomographic (PET) evidence of ongoing glucose metabolism, the angiographic presence of collateral flow to an area in the distribution of an occluded coronary artery is one of the strongest evidences of ongoing myocardial viability and an important factor in determining the best revascularization strategy.

Although it is uncommon, what appears as a network of collaterals may be the vascular supply to an organized thrombus (in the left ventricle or left atrium) or a cardiac tumor. Those entities should be suspected when filling of an apparent collateral network is seen in the absence of occlusion or severe stenosis of the normal supply to a myocardial territory.
In a series of 227 patients with single-vessel disease, visual estimates (right curve, average nearly 90%) were consistently higher than either caliper measurements (average nearly 80%) or computer-assisted quantitative angiography by either geometric or densitometric techniques (left curves, average nearly 70% diameter stenosis). (From Folland ED, Vogel RA, Hartigan P, et al. Relation between coronary artery stenosis assessed by visual, caliper, and computer methods and exercise capacity in patients with single-vessel coronary artery disease. Circulation 1994;89:2005, with permission.)

exposure (see Chapter 2). In addition, particularly in high-risk patients with underlying renal insufficiency and other comorbidities, administration of contrast media can result in the development of acute kidney injury (see Chapter 4). There have been several studies aimed toward identifying ways to reduce radiation exposure and the total amount of contrast media required for image acquisition. Biplane coronary angiography requires by definition the use of a biplane cardiac cath lab, and it involves obtaining two views during a single injection using the frontal and lateral planes positioned in orthogonal views. Usually, the lateral plane is positioned in a left cranial or caudal view and the frontal plane is positioned in the contralateral cranial or caudal view (LAO cranial–RAO caudal and LAO caudal–RAO cranial). This simplifies panning during acquisition of the angiographic images. Biplane angiography can result in a reduction in the amount of contrast media required for angiography, although radiation exposure is the same or can be slightly higher because of the additional fluoroscopy time needed for appropriate positioning of the frontal and lateral planes.

High-speed rotational angiography is an alternative technique that has been evaluated in several small randomized clinical trials. In this technique, the c-arm and the detector rotate around the patient at a high speed during a single contrast injection and the corresponding image acquisition. Two rotations in caudal and cranial angulation (LAO to RAO) are usually performed for the left coronary artery system while a single rotation (LAO to RAO) is usually performed for the right coronary artery system. The newest technology has the ability to perform dual axis rotation (Dual Axis Rotational Coronary Angiography or DARA), in which the c-arm is preprogrammed to make a single-run rotation along a curved trajectory around the patient, acquiring all the views in a single rotation. It has been shown that rotational angiography can result in a significant reduction in contrast dose, radiation exposure, and image acquisition time when compared to conventional angiography, without compromising the quality of imaging. Thus, when available and in selected patients, rotational angiography can be considered as an alternative to standard coronary angiography.

Although atherosclerotic stenosis is far and away the most common pathologic process responsible for myocardial ischemia, the angiographer must be aware of various other
potential causes. These include certain congenital anomalies of coronary origin—for example, an anomalous coronary that courses between the aorta and pulmonary artery (Figure 15.18), in which flow may be compromised by deformation of the ostium or compression of the proximal vessel, potentially even causing sudden death. In patients with such anatomy and objective evidence of ischemia on medical therapy, bypass surgery or stenting of the anomalous segment may be considered.

Other abnormalities include coronary fistulae (Figure 15.28), coronary aneurysms, and muscle bridges (Figure 15.29). Coronary fistulae, connections mostly from a coronary artery to the right ventricle, right atrium, pulmonary artery, or coronary sinus, are found in roughly 0.1% of patients coming for cardiac catheterization. When they are large (or in the setting of proximal coronary disease), these fistulae may cause chronic volume overload or myocardial ischemia and must be closed, using surgery or newer catheter techniques (embolization coils, covered stents). Smaller, asymptomatic fistulae may close spontaneously, however, and can be managed conservatively. Muscle bridges are sections of a coronary artery (almost always the left anterior descending) that run under a strip of left ventricular muscle, which compresses the lumen during ventricular systole despite a normal appearance during diastole. Similar systolic compression of the first septal branch (saw-toothing) is also seen in many patients with hypertrophic cardiomyopathy. When one of these congenital anomalies is present in a patient with ischemic symptoms in whom catheterization has failed to demonstrate the expected finding of coronary atherosclerosis, the angiographer should be able to recognize it as a potential cause of ischemia and recommend additional functional testing with an eye toward surgical or catheter-assisted repair (fistula coil embolization, muscle bridge stent placement).

The coronary arteries may also be affected by medium-vessel vasculitis, including polyarteritis nodosa and the mucocutaneous lymph node syndrome (Kawasaki disease). The latter is largely a childhood illness, in which coronary
Seven collateral pathways observed in patients with left coronary artery obstruction. Abbreviations and format are the same as in Figure 15.25. (From Levin DC. Pathways and functional significance of the coronary collateral circulation. *Circulation* 1974;50:831. By permission of the American Heart Association, Inc.)

arteritis may lead to aneurysm, stenosis, or thrombosis, which often turns fatal (usually in the first month of the illness) before the use of high-dose gamma globulin to treat the acute illness. When coronary aneurysms are found in adults, it may thus be difficult to determine if they represent atherosclerotic damage to the vessel wall or are the remainders of childhood Kawasaki disease. The treatment for the stenotic lesions (bypass or catheter-based intervention), however, are the same regardless of the etiology.

Although not an arteritis, cardiac allograft vasculopathy is one of the most troublesome long-term complications of heart transplantation. The mechanism seems to be an immune-mediated diffuse vascular proliferative response involving distal as well as proximal coronary arteries, with superimposed focal lesions of the proximal vessels. The latter may be amenable to catheter-based revascularization. Patients who have received prior mantle radiation therapy for Hodgkin's disease may be at risk for radiation-induced coronary stenosis, particularly of the left and right coronary ostia and the proximal left coronary artery, up to 20 years after completing their course of therapy. The pathology is most commonly fibrotic contraction of the vessel wall, rather than intimal proliferation or plaque formation.

Finally, some patients who come for catheterization have no demonstrable coronary abnormality to account for their clinically suspected ischemic heart disease. Although anginalike pain can be seen in patients with noncoronary cardiac abnormality (e.g., mitral valve prolapse, hypertrophic cardiomyopathy, aortic stenosis, myocarditis) or extracardiac conditions (esophageal dysmotility, cholecystitis), one must also consider the possibility of epicardial or microvascular coronary vasospastic disease (see below).

**Coronary Vasospasm**

Vasospasm of an epicardial coronary artery typically presents as variant (or Prinzmetal) angina in which episodes of rest pain occur despite well-preserved effort tolerance at other times. An electrocardiogram recorded during an episode of spontaneous pain usually shows ST elevation in the territory supplied by the vasospastic artery. Absence of a significant
coronary lesion in such a patient confirms the diagnosis of variant angina owing to focal coronary spasm (Figure 15.30). In these patients, coronary angiography is performed mainly to look at the extent of underlying atherosclerosis.® Provocative maneuvers to initiate spasm were once common to confirm the diagnosis and evaluate drug therapy.® It is now used mostly when the diagnosis of variant angina is uncertain and a patient with troublesome chest pain fails to manifest sufficient disease to explain its cause.

If provocative testing for coronary spasm is contemplated, the patient should be withdrawn from calcium channel blockers for at least 24 hours and long-acting nitrates for at least 12 hours before the study and should not be premedicated with either atropine or sublingual nitroglycerin. Ongoing therapy with any of these agents may render provocative tests falsely negative.® Although various provocative tests have been used (methacholine, epinephrine and propranolol, hyperventilation and tris-buffer, cold pressor), the most
commonly used provocative agent has been ergonovine or methylergonovine maleate \(^{100,103}\) (Methergine, Sandoz, East Hanover, NJ). These agents are stimulants of the \(\alpha\)-adrenergic and serotonin receptors in coronary vascular smooth muscle.

Testing for coronary spasm should be performed only after baseline angiographic evaluation of both the left and right coronary arteries. It should not be performed in patients with severe hypertension or severe anatomic cardiac pathology (left ventricular dysfunction, left main or multi-vessel disease, or aortic stenosis). As an example, a protocol for using methylergonovine calls for a total of 0.4 mg (400 mg equals 2 ampules) to be diluted to a total volume of 8 mL in an appropriately labeled 10-mL syringe. The provocative test consists of graded intravenous administration of 1 mL (0.05 mg), 2 mL (0.10 mg), and 5 mL (0.25 mg) of this mixture at 3- to 5-minute intervals. Parenteral nitroglycerin (100–200 mg/mL) must be premixed and loaded in a labeled syringe before the testing begins. It is also advisable to have an intracoronary calcium channel blocker (verapamil 100 \(\mu\)g/mL, diltiazem 250 \(\mu\)g/mL) or nitroprusside (100 \(\mu\)g/mL) close at hand in case nitroglycerin-refractory spasm develops. Temporary pacing and defibrillator equipment should also be available to treat the bradyarrhythmias or tachyarhythmias that sometimes accompany coronary spasm. At 1 minute before each ergonovine dose, the patient is interrogated about symptoms similar to those of his/her clinical complaint, and a 12-lead electrocardiogram is recorded. After each electrocardiogram, coronary angiography is performed, looking either at both arteries or only at the artery of highest clinical suspicion for vasospasm. In the absence of clinical symptoms, electrocardiographic changes, or focal coronary vasospasm, the next ergonovine dose is administered, and the cycle is repeated until the total dose of 0.4 mg has been given.

The provocative test should be considered positive only if focal spasm (>70% diameter stenosis) occurs and is associated with clinical symptoms and/or electrocardiographic changes. Even if there are no symptoms or electrocardiographic changes, both coronary arteries should be opacified at the end of the provocative test, and any generalized vasoconstrictor effect should be terminated by administration of
True coronary spasm. Intense focal vasospasm of the left anterior descending coronary artery is shown in right anterior oblique projection in a patient with variant angina. Note the absence of a significant underlying atherosclerotic stenosis in the top view, the absence of vasoconstriction of other vessel segments, and the marked ST elevation in the anterior leads during the spontaneous vasospastic episode. (From Baim DS, Harrison DC. Nonatherosclerotic coronary heart disease. In: Hurst JW, ed. The Heart, 5th ed. New York: McGraw-Hill; 1985, with permission.)

nitroglycerin before documenting the resolution of spasm and the extent of underlying atherosclerotic stenosis. It should be noted that coronary artery spasm may occur in two vessels simultaneously (Figure 15.31), and visualization of only one vessel may fail to adequately assess the magnitude of the vasospastic response.

Some operators have used an intracoronary methylergonovine administration protocol, in which a 4-minute intracoronary infusion (10 µg/minute in the right and 16 µg/minute in the left coronary) is performed. Alternatively, discrete doses of 5 to 10 µg may be administered into a coronary artery, waiting for 3 minutes and imaging between doses (maximal total dose 50 µg per vessel). These intracoronary protocols may be advantageous in that they produce less systemic effect (hypertension, esophageal spasm). The other intracoronary provocative test for coronary spasm uses acetylcholine (ACH) at serial doses of 20–50–100 µg injected into the left coronary, and 20–50–80 µg injected into the right coronary. Another ACH protocol uses incremental doses of 2, 20, 100, and 200 µg administered over periods of 3 minutes each into the left coronary artery, and 80 µg ACH over 3 minutes into the right coronary artery (RCA) in patients who do not develop symptoms or ischemic ECG changes. Heart rate, blood pressure, and the 12-lead-ECG must be continuously monitored during ACH testing. Some investigators have also used hyperventilation as a provocative test for spasm (Figure 15.31). The same caveats regarding ready availability of potent intracoronary vasodilators to treat spasm also apply to any of these provocational protocols.

Several additional comments about ergonovine are in order. Ergonovine testing should be avoided in patients with severe atherosclerotic stenosis (≥80%), in whom spasm is not required to explain the clinical symptoms. In these patients, however, we frequently do repeat coronary angiography of the stenotic vessel after the intracoronary administration of 200 mg of nitroglycerin to exclude the
possibility that spontaneous focal vasospasm is contributing to the appearance of severe atherosclerotic stenosis. Second, the operator should be aware that the positivity rate depends strongly on which patients are studied: the test is almost always positive in patients with known variant angina (if their disorder is active and medications have been withheld) and is positive in approximately one-third of patients with clinically suspected variant angina, but it is positive in \(<5\%\) of patients whose symptoms do not suggest variant angina.\textsuperscript{102,103} The Duke group\textsuperscript{106} reported ergonovine testing in 3,447 patients without significant coronary disease or variant angina, with an overall positivity rate of 4\% in such patients. There were two independent predictors of a positive test: mild to moderate disease on the angiogram (spasm often takes place at the point of such disease) and a history of smoking, the presence of which increased the positivity rate to 10\%.

Since finding spasm is so uncommon now that the syndrome is detected clinically in most patients and is treated so effectively by calcium channel blockers, the risk of ergonovine testing to evaluate patients with atypical symptoms and minimal fixed coronary disease is remarkably low. In the Duke study, significant complications occurred in only 11 patients (0.03\%), including myocardial infarction in 4 patients and ventricular tachycardia or fibrillation (VT or VF) in 7 patients.\textsuperscript{106} When provocative testing produces clinical symptoms but no angiographic evidence of vasospasm in either coronary artery, there may still be scintigraphic evidence of myocardial ischemia owing to microvascular spasm. Both multivessel epicardial and microvascular spasm have been implicated in tako-tsubo syndrome where extreme emotional stress is followed by chest pain, ST elevation, and a particular pattern of apical hypokinesis extending beyond the usual single coronary territory. If there are no signs of myocardial ischemia, an alternative diagnosis such as esophageal dysmotility,\textsuperscript{96} which can also be provoked by methylergogenous, should be considered.

It is also important to distinguish the intense focal spasm seen in patients with variant angina from the normal mild (15–20\%) diffuse coronary narrowing seen as a pharmacologic response to ergonovine in normal patients.\textsuperscript{107} True coronary spasm must also be distinguished from spasm induced by mechanical interventions such as rotational atherectomy (see Chapter 29) or catheter-tip spasm (Figure 15.32). Catheter-tip spasm is most common in the right coronary artery, is not associated with clinical symptoms or electrocardiographic changes, and does not indicate variant angina.\textsuperscript{108} It should be recognized as such, however, and treated by withdrawal of the catheter, administration of nitroglycerin, and nonselective or cautious repeat selective opacification of the involved vessel to avoid mistaking catheter-tip spasm for an atherosclerotic lesion. Spasm should also be distinguished from a “pleating” artifact that may occur when a curved artery is straightened out by a stiff guidewire (Figure 15.33), causing folds of the vessel wall to impinge on the lumen. Pleating is refractory to nitroglycerin but resolves immediately when the stiff guidewire is withdrawn.\textsuperscript{109}

Abnormal Coronary Vasodilator Reserve

Evidence has been accumulating to suggest that the patient group with angina and angiographically normal coronary arteries may contain a subgroup of patients who have myocardial ischemia on the basis of abnormal vasodilator reserve. Despite angiographic normality, intravascular ultrasound examination may show normal vessel wall architecture, intimal thickening, or atheromatous plaque,\textsuperscript{87} In these patients, coronary blood flow (as described in Chapter 24) may fail to rise normally with pacing tachycardia or exercise, and the coronary vascular resistance is increased abnormally.\textsuperscript{110} Also,
Vasomotor changes not representing true coronary spasm. During right coronary catheterization with a Judkins catheter (top left), this patient developed severe catheter-tip spasm. Recatheterization 24 hours later with an Amplatz catheter (top right) showed neither catheter-tip spasm nor an atherosclerotic stenosis. Following ergonovine 0.4 mg, marked diffuse coronary narrowing was observed (bottom left) without angina or electrocardiographic changes. After the intracoronary administration of nitroglycerin 200 μg (bottom right), there was marked diffuse vasodilation.

MISTAKES IN INTERPRETATION

An inexperienced operator often produces an incomplete or uninterpretable study, especially if he/she is using poor equipment. Such an operator is also likely to misinterpret the angiographic findings, with potentially serious clinical consequences. The following discussion summarizes some of the most common pitfalls that may lead the inexperienced coronary angiographer to mistaken conclusions.

Inadequate Number of Projections

There is no standard number of projections that will always provide complete information. Each major vessel must be viewed in an isolated fashion as if it stands apart from other vessels. Usually, the angulated views discussed earlier in this chapter are necessary to visualize clearly the anatomy of the proximal left anterior descending and circumflex arteries.

Inadequate Injection of Contrast Material

The inexperienced operator or assistant has a tendency to hold back on the volume and force of injection into the coronary circulation. This results in inadequate or intermittent, pulsatile opacification of the coronary arterial tree as contrast flow falls short of peak coronary flow during diastole. Because there is inadequate mixing of contrast agent and blood, pockets of nonradiopaque blood in such inadequate injections may even give the appearance of arterial narrowing.

Superselective Injection

It is not uncommon to catheterize the left anterior descending or circumflex coronary artery superselectively, especially when the left main coronary artery is short and its bifurcation occurs early. To the inexperienced operator, this may give the impression of total occlusion of the nonvisualized vessel (e.g., if only the circumflex artery is opacified, the operator may conclude that the left anterior descending artery is occluded). If adequate filling of the noncannulated vessel cannot be achieved by reflux, selective cannulation of the LAD may be obtained by counterclockwise rotation or use of the next-smaller Judkins catheter (e.g., JL3.5), whereas selection cannulation of the circumflex may be obtained by clockwise rotation or use of the next-larger Judkins catheter (e.g., JL5). With the right coronary artery, superselective injection

many of these patients show an abnormal rise in left ventricular end-diastolic pressure following pacing tachycardia and show less lactate consumption than shown by normal subjects in response to pacing tachycardia. A failure of small vessel coronary vasodilation, inappropriate vasoconstriction at the arteriolar level (Figure 15.34), and functional abnormalities of capillary endothelial cells in releasing endothelium-derived relaxing factor (EDRF) have been postulated to account for these findings. Many patients with the so-called syndrome X respond at least partially to treatment with a calcium channel blocker. Disordered small vessel vasoconstriction has also been implicated in the tako-tsubo syndrome where patients with angiographically normal epicardial arteries may present with chest pain, anterior ST elevation, and a unique pattern of apical akinesis.
Figure 15.33  Right coronary artery “pleating” artifact. **Left.** Baseline injection shows diffuse disease in this tortuous right coronary artery selected for rotational atherectomy. **Center.** Straightening of the proximal vessel by the stiff type C wire, creating three areas of infolding of the vessel wall (arrows) as well as the appearance of ostial stenosis (curved arrow). **Right.** Immediately on withdrawal of the guidewire, the artery returned to its baseline curvature and these defects were resolved (arrows).

Figure 15.34  Representative patients with abnormal acetylcholine response and no angiographic evidence of obstructive epicardial coronary artery disease. The upper panels show left coronary artery angiograms and electrocardiograms (ECGs) in a patient with epicardial spasm. Note the diffuse but distally accentuated narrowing of the left anterior descending coronary artery (wraps around the apex) during acetylcholine infusion together with ischemic ECG shifts in the inferior leads (A) and resolution of both findings after intracoronary nitroglycerin (B). The lower panels show an example of a patient with microvascular spasm. During acetylcholine infusion the patient had reproduction of chest pain and ischemic ECG changes but no epicardial vasoconstriction (C). After intracoronary nitroglycerin, chest pain and ECG changes resolved (D). (Reproduced with permission from Ong P, et al. High prevalence of a pathological response to acetylcholine testing in patients with stable angina pectoris and unobstructed coronary arteries: the ACOVA study (Abnormal COronary VAsmotion in patients with stable angina and unobstructed coronary arteries). *J Am Coll Cardiol* 2012;59:655–662.)
may occur if the catheter tip is too far down the vessel, leading to failure to visualize the conus and sinus node arteries. Because these are important sources of collateralization of the left coronary system, important information may be missed (see Figure 15.25 and 15.26). Adequate injection to give a continuous (nonpulsatile) reflux of contrast agent back into the sinus of Valsalva will help the operator to recognize vessels that originate proximally to the catheter tip and thus avoid the interpretation error of superselective injection.

Selective cannulation of a coronary artery may also fail to detect significant ostial stenosis, particularly if the catheter tip lies beyond the lesion and adequate contrast reflux is not produced. If ostial stenosis is suspected (e.g., if there is partial ventricularization or damping), we have found it helpful to perform a final injection during withdrawal of the catheter from the ostium (Figure 15.35).

Catheter-Induced Coronary Spasm

Coronary artery spasm may be related to the catheter itself, possibly caused by mechanical irritation and a myogenic reflex (see Figure 15.32). It is seen most commonly when the right coronary artery is engaged selectively, although it may occur rarely in the left anterior descending artery as well. Although catheter-tip spasm can occur with both the brachial and the femoral approach, it is probably more common with the right Judkins catheter, especially if the catheter tip enters the right coronary ostium at an angle and produces tenting of the proximal vessel. If coronary narrowing suggests the occurrence of spasm to the operator, sublingual, intravenous, or intracoronary nitroglycerin should be given and the injection repeated.

Congenital Variants of Coronary Origin and Distribution

This topic has been discussed earlier in this chapter and in Chapter 16, but it bears reemphasis. Variation in origin and distribution of the coronary artery branches may confuse the operator and cause him/her to mistakenly diagnose coronary occlusion. For example, a small right coronary artery that terminates in the AV groove well before the crux may be interpreted as an abnormal or occluded artery, whereas it is a normal finding in 7% to 10% of human hearts. Double ostia of the right coronary artery or origin of the circumflex artery from the right coronary artery may be similarly confusing and lead to misdiagnosis.

Myocardial Bridges

As discussed earlier, coronary arteries occasionally dip below the epicardial surface under small strips of myocardium. During systole, the segment of the artery surrounded by myocardium is narrowed and appears as a localized stenosis. These myocardial bridges occur most commonly in the distribution of the left anterior descending artery and its diagonal branches. The key to the recognition of these bridges is that the apparent localized stenosis returns to normal during diastole. Recent studies using the flow wire show clear derangement in phasic flow dynamics in muscle bridge segments and their normalization by stent placement. Although some severe muscle bridges can thus cause true myocardial ischemia under certain circumstances, they are seen in at least 5% of normal angiograms obtained in patients with no evidence of ischemia in the LAD territory.
Total Occlusion

If a coronary artery or a branch is totally occluded at its origin, it may not be visualized, and the occlusion may be missed. If the occlusion is flush with the parent vessel, no stump will be seen. Such occlusions are primarily recognized by visualization of the distal segment of the occluded vessel by means of collateral channels or by noting the absence of the usual vascularity seen in a particular portion of the heart.

REFERENCES

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The rich medical literature on coronary artery anomalies (CAA) suffers from many limitations, but the two main ones are:

1. the superficial, general infatuation with unusual anatomy (the “fascinomas” presented in many clinical sessions), which has led to thousands of case reports but also to a disorganized and tentative literature on the subject of CAA, and
2. the lack of a clear and widely accepted conceptual organization of the knowledge in this field. For an in-depth and comprehensive review of the subject, we would refer the interested reader to a book our group published in 1999.

In the current chapter, we briefly review contemporary information on CAA, particularly as it relates to the diagnostic and interventional activities performed in the catheterization laboratory.

DEFINITIONS

Given the great variability of coronary anatomy, a general definition of “normal” coronary arteries should be founded on the knowledge of the variations of each of the features used to describe coronary anatomy (e.g., the number and location of ostia, the diameter or cross-sectional area of coronary arteries). Generally, each descriptive feature should be considered anatomically normal when it is found in more than 1% of a general population or within 2 standard deviations of the mean value for Gaussian distribution continuous parameters. The most relevant clinical assessment of each anatomic variant should focus on the pathophysiological consequences of any given morphologic variation, and these consequences should be discussed separately from the variant’s anatomy.

Of the many coronary arteries, the “primary” (or elementary) ones are defined as the three main proximal arteries: one provides circulation to the anterior septum and anterior lateral wall (the left anterior descending or LAD), another provides blood flow to the obtuse marginal region of the left ventricle (the circumflex, or Cx), and the third provides circulation to the free wall of the right ventricle (the right coronary artery or RCA). The left main trunk may serve as a common stem that joins the LAD and Cx (a common left main stem is present in about 90% of cases and is not essential, but the LAD and Cx are essential). Normally, the LAD and Cx originate from an aortic area located above the upper or middle third of the left coronary sinus of Valsalva (also called the left posterior sinus). The right coronary artery originates from the upper or middle third of the right sinus of the Valsalva. Normally, the coronary ostia lead to an orthogonally oriented coronary proximal stem, off the aortic wall.

A popular classification of the coronary anomalies (Table 16.1) uses the basic features that describe each anatomic entity, especially the anomalies of origin, according to its course and destination. Figure 16.1 describes diagrammatically the normal distribution of the three primary coronary arteries in a coronal plane, and their multiple possible anomalies of origin and proximal course.

The prevalence of CAAs obviously depends on the definition of each CAA (which, unfortunately, is usually not mentioned in most reports of CAA studies). As a consequence of inadequate methodological discipline in this regard, the prevalence of CAA has been variably reported in the literature. Indeed, collecting meaningful and accurate prevalence data requires both the use of prospectively stated criteria for the diagnosis of CAA and the sampling of a general population, devoid of pretest bias. Because no such studies have been performed to date, we do not have yet credible, precise information about the prevalence of CAA in the general population; rather, most available prevalence data come from studies of
### A) Anomalies of origin and course
1. Absent left main trunk (split origin of LCA)
2. Anomalous location of coronary ostium within aortic root or near proper aortic sinus of Valsalva (for each artery)
   a. High
   b. Low
   c. Commissural
3. Anomalous location of coronary ostium outside normal “coronary” aortic sinuses
   a. Right posterior aortic sinus
   b. Ascending aorta, with anomalous course
      1. Intramural (ACAOS)
      2. Extramural
   c. Left ventricle
   d. Right ventricle
   e. Pulmonary artery. Variants:
      1. LCA arising from posterior-facing sinus (ALCAPA)
      2. Cx arising from posterior-facing sinus
      3. LAD arising from posterior-facing sinus
      4. RCA arising from anterior-right-facing sinus
      5. Ectopic location (outside facing sinuses) of any coronary artery from pulmonary artery
         1. From anterior left sinus
         2. From pulmonary trunk
         3. From pulmonary branch
   f. Aortic arch
   g. Innominate artery
   h. Right carotid artery
   i. Internal mammary artery
   j. Bronchial artery
   k. Subclavian artery
   l. Descending thoracic aorta
4. Anomalous origin of coronary ostium from opposite, facing “coronary” sinus (which may involve joint origin or adjacent double ostia). Variants:
   a. RCA arising from left anterior sinus, with anomalous course
      1. Posterior atrioventricular groove\(^a\) or retrocardiac
      2. Retroaortic\(^c\)
      3. Between aorta and pulmonary artery,\(^a\) preaortic, intramural (aortic), or ACAOS
      4. Intraseptal\(^a\)
      5. Anterior to pulmonary outflow\(^a\) or precardiac
      6. Posteroanterior interventricular groove\(^a\)
   b. LAD arising from right anterior sinus, with anomalous course
      1. Between aorta and pulmonary artery, preaortic, intramural (aortic), or ACAOS
      2. Intraseptal
      3. Anterior to pulmonary outflow or precardiac
      4. Posteroanterior interventricular groove
   c. Cx arising from right anterior sinus, with anomalous course
      1. Posterior atrioventricular groove
      2. Retroaortic
   d. LCA arising from right anterior sinus, with anomalous course
      1. Posterior atrioventricular groove\(^a\) or retrocardiac
      2. Retroaortic
      3. Between aorta and pulmonary artery,\(^a\) preaortic, intramural (aortic), or ACAOS
      4. Intraseptal
      5. Anterior to pulmonary outflow\(^a\) or precardiac
      6. Posteroanterior interventricular groove\(^a\)
   e. LCA arising from the “non-coronary” sinus, with anomalous course
      1. Intramural (ACAOS)
      2. Extramural
5. Single coronary artery

#### Table 16.1

**Classification of Coronary Anomalies**
Table 16.1 Continued

B) Anomalies of intrinsic coronary arterial anatomy
1) Congenital ostial stenosis or atresia (LCA, LAD, RCA, Cx)
2) Coronary ostial dimple
3) Coronary ectasia or aneurysm
4) Absent coronary artery
5) Coronary hypoplasia
6) Intramural coronary artery (myocardial bridge)
7) Subendocardial coronary course
8) Coronary crossing
9) Anomalous origination of posterior descending branch or septal penetrating branch
10) Absent PD or split RCA
   a) Proximal + distal PDs, arising from separate RCA sources
   b) Proximal PD arising from RCA, distal PD arising from LAD
   c) Proximal PD arising from RCA, distal PD arising from Cx
11) Absent or split LAD
    a) Large first septal branch and small distal LAD
    b) Double LAD
12) Ectopic origination of first septal branch

C) Anomalies of coronary termination
1) Decreased number of arteriolar/capillary ramifications (hypothetical)
2) Fistulas from RCA, LCA, or infundibular artery to
   a) Right ventricle
   b) Right atrium
   c) Coronary sinus
   d) Superior vena cava
   e) Pulmonary artery
   f) Pulmonary vein
   g) Left atrium
   h) Left ventricle
   i) Multiple microfistulas draining into one or both ventricles

D) Anomalous collateral vessels

"If a single, common ostium is present, the pattern is considered to represent “single” coronary artery.

ACAOS, anomalous origin of a coronary artery from an opposite sinus of Valsalva, with intramural course; ALCAPA, anomalous origin of the left coronary artery from the pulmonary artery; Cx, circumflex; LAD, left anterior descending coronary artery; LCA, left coronary artery; PD, posterior descending branch; RCA, right coronary artery.

patients seen in the catheterization laboratory. This type of study clearly has a referral bias but can still be important if correctly structured.1,2

Recently, our Center for Coronary Artery Anomalies at the Texas Heart Institute has spearheaded a comprehensive process of acquiring definitive data regarding the prevalence of CAA by collecting magnetic resonance imaging data in a large population of schoolchildren. In addition, our group has previously performed a prospective study of adult patients examined or treated in the cardiac catheterization laboratory. The findings indicated that the prevalence of CAA in our cohort was 5.64%.3 Most of the previous, uncontrolled studies produced a wide range of unreliable prevalence data.4

Of the 66 different types of CAA (Table 16.1), only one subgroup is considered to intrinsically pose any risk of causing coronary dysfunction (i.e., ischemia): the anomalous origin of a coronary artery from an “opposite” sinus of Valsalva, with an intramural course (ACAOS).7 Such anomalies are found in approximately 1% of adult cardiac catheterization laboratory patients; these anomalies are discussed in detail in the next section, which covers most of the important clinical issues in adult cases of CAA. Most of the other CAA variants are not known to cause ischemia by themselves (and these non-ACAOS CAA should not be included in a discussion of clinically important CAA in the adult), but they could have clinical consequences because of clinical uncertainty about their recognition and management and because of occasional complicating factors (the most frequent of which is associated coronary artery atherothrombotic disease). Hence, the primary responsibility of a cardiologist in the adult catheterization laboratory is to properly diagnose each form of CAA and then to establish the severity of each case.

Anomalous Origin of a Coronary Artery from an Opposite Sinus of Valsalva, with an Intramural Course

As confirmed by most autopsy-based studies on the subject,8,10 ACAOS is the only kind of CAA with a clear ischemic
potential. This anomaly is especially critical to recognize because of its mortality implications in the young, specifically in athletes and military recruits, as well as because of its potential to cause disabling angina, dyspnea, and syncope. Anatomists have long debated the mechanisms and specific anatomic features of ACAOS that may lead to critical ischemia. Initially, a slit-like orifice, tangential orientation of the origin, a passage between the aorta and the pulmonary artery, or ostial fibrous ridges were implicated in the causation of ischemia in ACAOS cases. More recently, accurate in vivo imaging of such anomalies by intravascular ultrasound (IVUS), as well as some anatomic evidence, has led to the clear conclusion that the intramural proximal course of the ectopic ACAOS coronary artery, inside the aortic wall, is the recurrent and quantifiable mechanism of ACAOS-related ischemia (Figures 16.2–16.6).

In the past, ACAOS was an uncertain diagnosis that was typically made when ectopic coronary origin was found incidentally in the catheterization laboratory. Currently, most patients with ACAOS are recognized because of an initial computerized tomographic angiography (CTA) study obtained for any reason (e.g., because of chest pain in the young, for screening purposes, or for associated acquired coronary artery disease). In the catheterization laboratory, selective coronary angiography in patients with ACAOS can be challenging because of the ectopic location of the coronary artery and its tangential origin from the aortic wall.

The R-ACAOS (ACAOS of the right coronary artery) cases frequently pose particular difficulties in locating and selectively cannulating the ectopic ostium at the left sinus of Valsalva if one is using routine diagnostic catheters. Such catheters are intended to be used for arteries that originate at a
Figure 16.3 Unselective (A) and selective (B) coronary angiographic frames in a typical case of R-ACAOS. Note that the proximal RCA appears mildly ectatic in the left anterior oblique projection but is not obstructed by this diagnostic technique. The RCA is dominant, with an ostium located next to that of the LCA. Computerized tomographic angiograms of R-ACAOS (C, sagittal plane; D, coronal plane). Figures 16.4 and 16.5 show the same case, imaged with different imaging techniques.

90° angle off the aortic sinuses. In R-ACAOS cases, the ostium is usually located somewhere between the left coronary ostium (which is usually normal) and the anterior commissure of the aortic valve. Also, the initial coronary course is tangential and located inside the aortic wall (“intramural”). The resulting operative frustration has led our group (which has developed a specific interest in such rare disorders) to design a dedicated catheter capable of consistently allowing for selective cannulation of the ectopic right ACAOS ostium. A coaxial approach and adequate support to ensure subselective catheterization (for selective angiography, but more importantly to facilitate IVUS, optical coherence tomography [OCT], and/or stent deployment) were realized by the use of this custom-made catheter featuring an anterior tilt of the most distal curve of an Amplatz-type catheter (custom-built by Cordis, Miami, FL, catalog number SM7600 AL3A). Adopting this catheter resulted in a success rate of almost 100% in quickly addressing 40 cases of R-ACAOS. In our extensive experience with IVUS in coronary anomalies, we have also found the intramural course in cases of “high origin” (even from the proper side of the aorta: see Figure 16.7) and cases of origin of the left coronary from the non-coronary sinus of Valsalva.12
Figure 16.4 IVUS images of the area close to the R-ACAOS ostium. A. Systolic frame. B. Diastolic frame. C. A distal RCA reference site (area of relative stenosis is about 60%). D through F. Optical coherence tomographic (OCT) images taken at the same sites. Note that the images are much more precise, allowing more accurate assessment of stenosis severity. D. Ostium during systole. E. Ostium during diastole. F. Distal reference; relative stenosis: 65% in systole, 60% in diastole.
Figure 16.5  OCT imaging in systole (A) and diastole (B) of a mild stenosis of the intramural segment in a case of R-ACAOS (of the lowest severity ever seen in our practice). The mean degree of stenosis was 30% (mild).

Figure 16.6  Angiographic images of L-ACAOS in systole (A) and diastole (B). The left main trunk seen in A shows the appearance of phasic narrowing relative to B. IVUS images showing the systolic (C) and diastolic (D) intramural segment and the distal reference (E) cross section of the left main trunk. Area of relative stenosis = 55%. F. CTA in the same case showing ectopic origin of the left coronary artery adjacent to the normally situated right coronary artery. G. Sagittal cross section of the aortic root, showing a compressed left main (arrows) between the aorta and the pulmonary artery.
Figure 16.6 (Continued)
Imaging in a 51-year-old patient with chest pain and dyspnea who was found to have high origin from the ascending aorta, above the left sinus. Ostial stenosis of both the right and left coronary arteries was found and was owing to hypoplasia and phasic lateral compression of both ostia. Nuclear stress testing had shown inferior ischemia. A. Selective angiogram of the right coronary artery, showing high origin of this artery above the left coronary artery, which is seen next to it, 1 cm above the sinotubular junction. B and C. IVUS of the right coronary artery at the ostium during systole (B) and diastole (C), showing 60% and 37% cross-sectional stenosis, respectively, relative to the distal reference vessel (D). E through G. Systolic (E) and diastolic (F) IVUS images of the ostium, showing 63% and 50% stenosis, respectively, relative to the distal reference area (G). The patient underwent surgical ostioplasty of both ostia.
Selective coronary angiography cannot reveal the severity of proximal R-ACAOS (or L-ACAOS) stenosis, but it can clearly indicate to the trained eye the presence of ACAOS. Specifically, angiography can definitely distinguish between the intramural (i.e., “between aorta and pulmonary artery” or preaortic) and the intraseptal (or infundibular) course, which is not a type of ACAOS (Figure 16.8). The criteria for differentiating the two forms by angiography are listed in Table 16.2.

Coronary angiography is also essential for establishing the important dominance patterns of the coronary arteries (or the origin of the posterior descending branch) and the coexistence of atherosclerotic, acquired coronary artery disease. Incidentally, it is remarkable that the proximal intramural coronary artery in ACAOS has consistently been found not to have atherosclerotic changes when studied by IVUS, even in cases featuring diffuse distal disease, as in diabetic patients.
Diagrammatic representation of the abnormal proximal courses of ectopic left coronary arteries in two similar cases: the intraseptal, infundibular variant (diagram in A, with typical angiogram in B), and the intramural, preaortic variant (diagram in A, typical angiograms in C, D). Only the intramural case (ACAOS) has intrinsic ischemic potential. In B (intraseptal) and C (intramural), the two variants are shown in the same right anterior oblique projection; note that the intramural variant features a course stuck to the anterior border of the aorta (the one on the right side of the aorta, AO, in this view), and it is tilted upward. In the opposite case, the intraseptal variant is directed inferiorly and anteriorly in this projection, as it provides a characteristic first branch that is clearly a septal branch (SPT) (B). In the intraseptal case, the distal left main reaches the epicardial surface of the heart at the proximal left anterior descending. D. The left anterior oblique projection, of the intramural variety, shows the same uphill course as in C, with a “halo” that suggests an intramural course, just below the sinotubular junction. MT: mixed, short common trunk, joining the origins of the RCA and the LCA. See text.
CTA is an excellent method of establishing confidently the specific type of abnormal courses that an ectopic artery takes (Figures 16.3C, D and 16.6F, G). Evidence suggestive of lateral compression can also be obtained by CTA, especially by using the equivalent view to the right anterior oblique projection, which reveals clearly the location of the abnormal proximal trunk “between aorta and pulmonary artery.” Unfortunately, this technique is not yet precise enough to detect and measure stenosis in ACAOS patients. Hence, the main reasons for performing IVUS (or, possibly, OCT) imaging in an ACAOS patient are based on the need to establish the severity of the individual case and the type of proximal coronary artery stenosis. Figures 16.4, 16.5, and 16.6C–E illustrate the typical and important findings that IVUS or OCT can reveal in cases of R-ACAOS and L-ACAOS, which we have come to consider the defining indicators of the severity of ACAOS in individual cases:

1. the length of the intramural segment;
2. the severity of circumferential hypoplasia with respect to the distal epicardial reference vessel;
3. the vessel asymmetry score (or the ratio of transverse to longitudinal diameter in cross-sectional images), which may be a simple marker of the severity of stenosis; and
4. the systolic versus diastolic cross-sectional area of stenosis during a cardiac cycle, measured at baseline and during a simulated exercise (the SAD test, which explores the changes of the same parameters during infusion of saline [500 mL bolus], atropine [0.5 mg], and dobutamine [40 μg/kg/minute]).

Our group has recently completed a large series of such studies and is in the process of publishing a comprehensive report that makes some preliminary recommendations. At present, the field is still in evolution and tentative, specifically with regard to operative recommendations. Table 16.3 shows a tentative algorithm that we empirically follow at the Center for Coronary Anomalies at the Texas Heart Institute.

At this time, we consider R-ACAOS to be severe if IVUS or OCT of the cross-sectional area of a dominant RCA intramural segment shows more than 55% stenosis at baseline, more than 60% stenosis with the SAD test, or both. Similarly, our group currently maintains that L-ACAOS is severe when the baseline stenosis is more than 50% in a young, physically active individual. In adults (age >35 years), the indication for intervention is less stringent in the absence of symptoms or evidence of ischemia on testing, but this point is not firmly established. In the young, especially if they are involved in competitive sports, intervention for R-ACAOS is generally favored in the presence of symptoms, but L-ACAOS (even without symptoms) usually indicates surgical intervention.

Table 16.2
Differential Angiographic Features in Cases of Preaortic (Intramural, L-ACAOS) and Infundibular (Intraseptal) Varieties of Ectopic Origin of the Left Coronary Artery from the Right Sinus of Valsalva

<table>
<thead>
<tr>
<th>Feature</th>
<th>Intramural</th>
<th>Intraseptal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retroaortic course in RAO projection</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Initial course in RAO projection</td>
<td>Preaortic/superior (around aortic root)</td>
<td>Anterior-inferior</td>
</tr>
<tr>
<td>First branch off left main</td>
<td>Distal LAD/Cx splitting</td>
<td>First septal branch off mid left main</td>
</tr>
<tr>
<td>Left main systolic narrowing</td>
<td>Not usually recognized by angiography; if present, it is at proximal 1 cm (lateral compression)</td>
<td>Frequent, at distal left main (mild concentric myocardial bridge effect)</td>
</tr>
<tr>
<td>Distal left main location</td>
<td>Normal (next to left sinus)</td>
<td>LM connects with mid-LAD</td>
</tr>
</tbody>
</table>

Cx, circumflex; LAD, left anterior descending coronary artery; RAO, right anterior oblique.
**Table 16.3** Algorithm Used Currently at the Center for Coronary Artery Anomalies at the Texas Heart Institute to Treat Coronary Artery Anomalies

1. **Asymptomatic patient** found to have a non-ACAOS coronary anomaly (benign).

   Recognition of the benign nature of the anomaly by adequate imaging, and reassurance of the patient and family.

2. **Asymptomatic patient** found to carry ACAOS at screening (performed for any reason).
   a. If R-ACAOS:
      - Nuclear or PET scan or echocardiographic stress testing for reproducible ischemia.
      - If negative: Clinical follow-up and reassurance.
      - If positive for reversible ischemia, scar, or myopathy: Catheter study with IVUS or OCT. If there is severe stenosis: Offer stent PCI or surgical repair in a qualified center, rather than clinical follow-up only.
   b. If L-ACAOS:
      - In patients younger than 35 years: Routine surgical repair (see text).
      - In patients older than 35 years: Surgical intervention if stress testing is positive.

3. Patients with R-ACAOS who are symptomatic (dyspnea, chest pain, dizziness, or syncopal spells, SCA) or have a positive stress test (preferably nuclear, echo, or PET): Offer IVUS or OCT imaging (to establish severity of stenosis). Intervention by stent PCI or surgery in an expert center if stenosis is severe. See text.

4. Patients with L-ACAOS who are symptomatic (dyspnea, chest pain, dizziness, or syncopal spells, SCA) or have a positive stress test (preferably nuclear, echo, or PET): Offer IVUS or OCT imaging (to establish severity of stenosis). Intervention by surgery in an expert center if stenosis is severe. See text.

ACAOS, anomalous origin of a coronary artery from an opposite sinus of Valsalva; IVUS, intravascular ultrasound; L-ACAOS, left ACAOS; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; PET, positron emission tomography; R-ACAOS, right ACAOS; SCA, sudden cardiac arrest.

At this time, surgical intervention in specialized centers for ACAOS tends to favor unroofing when feasible (especially in view of the possible involvement of the anterior commissure of the aortic valve). Reimplantation of the ectopic artery is also possible and is often successful in expert hands if the proximal intramural segment is removed. Bypass surgery with the use of internal mammary artery grafts is less likely to be successful because of competitive flow and the expected hypoplastic regression of the graft lumen if there is less than critical stenosis at baseline (the usual case). 12–21

In addition, we have recently spearheaded studies aimed at clarifying whether stent angioplasty could be considered an acceptable alternative to surgical repair with extracorporeal circulation for severe ACAOS. Technically, stent angioplasty has become a simple and reliable procedure since the introduction of adequate training and instrumentation, including the R-ACAOS custom-made guide catheter mentioned above. IVUS (or OCT) is the essential monitoring modality for the pre-procedure and postprocedure evaluation of stent deployment.

It is relevant to report that in our experience, intramural course of an ectopic coronary artery was observed with IVUS in cases of ectopic origin of one or both coronary arteries, high on the ascending aorta above the proper sinus (i.e., “high origin” from the ascending aorta). All such intramural courses can lead to various degrees of stenosis (Figure 16.7).

**Other Coronary Anomalies Frequently Encountered in the Adult Cath Lab: Coronary Fistulae and Myocardial Bridges**

Generally, the two conditions discussed below are encountered relatively frequently in the catheterization laboratory, but they are not intrinsic causes of coronary dysfunction. Still, they may become important if additional complicating factors arise.

**Coronary Fistulae**

Coronary fistulae are studied in the catheterization laboratory for various reasons. Here, we briefly summarize our understanding and approach to the treatment of coronary fistulae; for a more detailed description, we would again refer the interested reader to our comprehensive book on the subject. 7

Coronary fistulae are defined as consisting of abnormal connections between a coronary artery and a low-pressure vascular space, such as a systemic vein (e.g., the coronary sinus or the superior vena cava) or a cardiac cavity (both in the atrial and in the ventricular sections). The clinical importance of a coronary fistula is related to:
1. the amount of fistulous blood flow, which leads to progressive coronary fistulous tract enlargement and vascular wall degeneration, with secondary atherothrombotic changes that include aneurysmal dilatation;
2. the amount of right- and left-sided cardiac cavity overload, secondary to blood shunting;
3. coronary nutrient flow steal secondary to a parallel, competing, fistulous, low-pressure resistance path and the nutrient high-pressure path, with resulting possible ischemia of the dependent myocardial coronary territory;
4. aortic root distortion secondary to aneurysmal dilatation of the involved coronary artery and sinus of Valsalva, and any resulting regurgitation.

At present, most cases of large coronary fistulae are diagnosed initially by echocardiography or CTA. Later, they may become targets of diagnostic and therapeutic catheterization, in laboratory procedures.

In patients considered to require surgical repair, it is essential to ascertain preoperatively whether there is any associated fixed coronary artery disease, the exact course of the fistulous tract, and, especially, the site of origin of important nutrient branches that need to be protected during surgical or catheter-based interventions (Figures 16.9 and 16.10). In cases selected for catheter-based repair, the tortuosity and cross-sectional diameter of the fistulous tract are also fundamental aspects to consider when planning intervention with closure devices or coil embolization (Figure 16.10A–C).

Ideally, visualization of large fistulae should be performed with a guide catheter (generally size 6F to 8F), which can allow both stable selective positioning during angiography and adequate contrast medium injection, depending on blood flow regimens. As a guideline, one should consider that the normal, adult left coronary artery flow is in the range of 150 to 200 mL per minute, whereas the “surgical” (large) coronary fistulae have usually much more flow (depending on the diameter, degree of stenosis, and length of the fistulous tract, and final destination pressure regimen), typically in the range of 300 to 1,500 mL per minute. Oxygen saturation-based calculations of shunt are generally not reliable.

Although the indications for closing a coronary fistula are not well established, preventing aneurysmal dilatation is the main consideration. Indeed, even after successful repair, aneurysmal dilatation of the fistulous tract will remain, now in the presence of much reduced blood flow, thus increasing the patient’s risk of coronary mural thrombosis. Intervening before adult age is generally recommended, because negative postoperative remodeling of the fistulous artery (as indicated by the presence of mural calcifications) is not likely in the adult but is common in the young. Indeed, postoperative follow-up catheter-based or CTA is generally indicated to evaluate the patency of the nutrient coronary side branches and any residual coronary aneurysmal dilatation after blood flow has diminished.

Myocardial Bridges

Myocardial bridges are defined as coronary segments that undergo phasic systolic narrowing at sites of intramural course, generally within the left ventricular wall. Administering a vasodilator, such as intracoronary nitroglycerin, during coronary angiography enhances the angiographic appearance of the systolic narrowing. Usually, myocardial bridges are first identified in the catheterization laboratory either because of a chance association with other disease (especially left ventricular hypertrophy or coronary artery disease) or because a secondary study is performed in view of a positive stress test.

In patients with a history of acute myocardial infarction or angina-like chest pain, especially if it occurs at rest, evaluation of myocardial bridges should probably include a functional study of endothelial dysfunction, such as acetylcholine challenge (Figure 16.11). Figure 16.12 shows the angiographic and IVUS findings at a myocardial bridge in a patient with resting chest pain and hypertrophic cardiomyopathy. Endothelial dysfunction is particularly frequent in patients with myocardial bridges, and recent literature supports the notion that endothelial dysfunction may underlie the events of both myocardial infarction and resting angina. Intracoronary infusion of acetylcholine should be carried out according to existing protocols. In particular, progressive intracoronary doses of acetylcholine should be tested (25, 50, 75, and 100 μg administered over 30- to 120-second time intervals) with standby intracoronary infusion of nitroglycerin in case significant spasm or angina occurs. Significant stenosis is generally considered to be a reversible narrowing of more than 70% of the luminal diameter. Temporary right ventricular pacing is mandatory when acetylcholine is administered, because bradycardia is frequently induced.

Empirical indications for intervention on muscular bridges are not supported by any definitive studies at this time, so such interventions should be used prudently, if ever. Coronary stenting, in particular, should be used with caution, because it is associated with a clearly increased restenosis risk secondary to intimal growth, stent crushing, or both.

REFERENCES

Figure 16.9  Computerized tomographic angiograms (CTA) (A through C) of a case of a large coronary fistula from the left main to the posterior part of the right ventricle in a 27-year-old asymptomatic woman. This technique can show in great detail the luminal size, course, site of origin, and final termination of the fistula, as well as any mural aneurysms or clots. A. A 3D volume-rendering reconstruction shows clearly the luminal irregularities causing both stenosis and ectasia of different segments. B. Measurements of diameters at different levels by a volume-rendering image. The most relevant feature is the location of the branching of nutrient vessels, especially of the obtuse marginal, which is well shown by curved multiplane reformation (C). CTA is probably a better technique than catheter angiography for evaluating coronary fistulae and especially for gathering operational parameters for catheter-based closure. D. Coronary angiogram obtained at the time of a scheduled, elective coil embolization, 4 years after the CTA. The fistulous tract, distal to the origin of the OM, was found to be totally occluded by apparent but silent spontaneous thrombosis. Note that the LM and proximal Cx are significantly smaller in this image than on the CTA, suggesting that negative remodeling has occurred. Cx, circumflex; FT, fistulous termination; LAD, left anterior descending; OM, obtuse marginal branch; RV, right ventricle.
Figure 16.10 Imaging in the case of a 41-year-old woman with chest pain and dyspnea who was found to have a left coronary to coronary sinus fistula. A, B. Still frames of a cineangiogram of the left anterior oblique, cranial (A) and right anterior oblique (B) views of the left coronary. The large circumflex (Cx) is shown to separate from the short left main and the left anterior descending (LAD) arteries and to take a tortuous course to reach the coronary sinus and the right atrium (RA) after giving rise to OM-1 and OM-2. Note that any closure device should be deployed distal to the OM-2 to avoid causing perioperative infarct. C. The final result of successfully deploying five coils in the fistulous tract, distal to the origin of the OM-2. The 6F guiding catheter (GC) was used to support a deployment catheter (DC), the Tracker microcatheter (Boston Scientific, Natick, MA). Note that the first coil (the most distal) had the largest radius, to prevent embolism, while the others were packed behind the first until substantial interruption of the fistulous flow was achieved.
Figure 16.11 Angiographic frames obtained from a patient who presented with unusual, increased spastic tendency that manifested as takotsubo apical ballooning cardiomyopathy. An acetylcholine test revealed increased spasticity at the level of the proximal LAD segment, at the level of a myocardial bridge. After nitroglycerine infusion, diastolic images showed no diastolic narrowing (A), but there was systolic narrowing (B) typical of myocardial bridge; after acetylcholine was administered, diastolic (and systolic) stenosis appeared (C), and it was promptly resolved by repeated intracoronary nitroglycerine infusion (evidence of residual endothelial dysfunction at the site) (D).
Figure 16.12  A case of atypical chest pain in a patient with hypertrophic cardiomyopathy. The initial angiograms taken during systole (A) and diastole (B) revealed diffuse diastolic narrowing and systolic obliteration of the mid segment (4 cm long) of the left anterior descending; an IVUS study was used to establish the nature of the diastolic narrowing (intimal growth versus hypoplasia). IVUS images obtained after intracoronary nitroglycerine administration show that hypoplasia without intimal thickening was the mechanism of stenosis at the level of the myocardial bridge (C, proximal reference cross section; D, intramyocardial systolic and E, diastolic images). Unroofing of the myocardial bridge was suggested, in case medical treatment (with beta-blockers) was inadequate to relieve the symptoms. This procedure never became necessary.


19. Waller BF. Exercise-related sudden death in young (age less than or equal to 30 years) and old (age greater than 30 years) conditioned subjects. *Cardiovasc Clin* 1985;15:9–73.


Cardiac ventriculography is used to define the anatomy and function of the ventricles and related structures in patients with congenital, valvular, coronary, or myopathic heart disease. Specifically, left ventriculography may provide valuable information about global and segmental left ventricular function, mitral valvular regurgitation, and the presence, location, and severity of a number of other abnormalities such as ventricular septal defect and hypertrophic cardiomyopathy. As a result, left ventriculography is often included as part of the routine diagnostic cardiac catheterization protocol in a patient being evaluated for coronary artery disease, aortic or mitral valvular disease, unexplained left ventricular failure, or congenital heart disease. Similarly, right ventriculography may provide information about global and segmental right ventricular function and can be especially helpful in patients with congenital heart disease.

Pigtail Catheter

The pigtail catheter (developed by Judkins) has several advantages over an end-hole-only design for left and right ventriculography (Figure 17.1). Its end hole permits its insertion over a J-tipped guidewire so that the pigtail catheter can be advanced safely to the left ventricle from any arterial access site (see Chapter 6), even in the patient with brachiocephalic or iliac arterial tortuosity. The loop shape keeps the end hole away from direct contact with the endocardium, while the multiple side holes on the catheter shaft located up to several centimeters proximal to the pigtail loop provide numerous simultaneous exit paths for the contrast material. These offset jet directions help stabilize the catheter within the left ventricle during contrast injection and reduce the magnitude of catheter recoil. This virtually eliminates the possibility of endocardial staining, since the end hole usually is not positioned adjacent to ventricular trabeculae, and substantially reduces the occurrence of ventricular ectopic beats.

The pigtail usually passes easily across a normal aortic valve, either directly or by prolapsing across the valve leaflets. Passage across a stenotic aortic valve usually requires use of a straight leading guidewire (see Chapter 6). In patients with porcine aortic valve prosthesis, the pigtail generally passes across the bioprosthesis even more easily than do straight catheters such as the multipurpose, since the pigtail configuration seems to prevent the catheter from sliding down into the lateral sinuses outside the support struts. Pigtail catheters can also be passed retrograde across a ball valve prosthesis (Starr-Edwards), but the resulting interference of the catheter shaft with seating of the ball during diastole may cause significant aortic regurgitation. For this purpose, only the smallest-diameter (e.g., 4F) catheter should be used; dwell time across the valve should be kept to a minimum; and the patient should be monitored carefully for hemodynamic deterioration until the catheter is withdrawn from the left ventricle. Of course, no catheter should ever be passed across a tilting-disc aortic valve prosthesis (Bjork-Shiley,
Medtronic-Hall, or St. Jude) because of the risk that the catheter will be entrapped were it to pass through the smaller (minor) orifice of the valve.

The original Judkins pigtail design had a straight shaft leading up to the pigtail end. It was thus designed to sit directly under the aortic valve, and just in front of mitral inflow, relying on that inflow to distribute contrast to the apex of the left ventricle. In routine practice, this has been replaced by angled pigtail catheters, which have a 145° to 155° shaft angle at its distal end (just proximal to the side holes). This angle mimics the angle between the aortic root and the long axis of the left ventricle and helps the catheter achieve a central position within the left ventricle. This alignment may be further improved if the heart is pulled into a somewhat more vertical orientation by having the patient take and hold a deep breath during the left ventriculographic injection. Some authors have suggested that catheter manipulation and overall image quality are better with the angled catheter than with the straight pigtail catheter, but adequate ventriculography can be achieved with either shape.

**Straight Tip Left Ventriculographic Catheters**

The Sones catheter was widely used for left ventriculography when catheterization was performed from the brachial approach. The Sones catheter (80-cm Cordis SON-II, Sones Technique, Cordis Corporation, Miami, FL) is particularly suitable for left ventriculography because it has four side holes in addition to its end hole. This catheter comes in 5F, 6F, 7F, and 8F sizes; it tapers to a smaller external diameter near its tip. The catheter will accept a 0.035-inch guidewire, which can be useful in crossing severely stenotic aortic valves. Techniques for traversing a tortuous subclavian artery system and entering the left ventricle with the Sones catheter are discussed in Chapter 8. For left ventriculography, the Sones catheter should be positioned in an axial orientation (parallel to the ventricular long axis), with its tip midway between the aortic valve and left ventricular apex. Low injection rates (see below) usually minimize the extent and forcefulness of catheter recoil. Catheter recoil may still occur, however, with induction of multiple ventricular extrasystoles and potential danger of endocardial staining. Accordingly, the operator should hold the catheter during injection and be prepared to withdraw it if significant recoil develops.

The NIH and Eppendorf catheters have multiple side holes and no end hole (Figure 17.1). They are easily inserted through an arteriotomy (by the brachial approach) or percutaneously through a femoral arterial sheath. The Cordis NIH (polyurethane) and Cook NIH Torcon blue (polyethylene) catheters are relatively soft and unlikely to cause dissection or perforation. The NIH and Eppendorf can be gently prolapsed across the aortic valve, but of course cannot be aided by a leading guidewire because of the lack of an end hole. The Lehman ventriculographic catheter has a tapered closed tip that extends beyond the multiple side holes (Figure 17.1). The tapered tip may assist the operator in manipulating the
catheter through tortuous arteries and across a stenotic aortic valve. Once in the left ventricle, the tip lessens the likelihood of endocardial staining, but may increase the chance of ventricular ectopy during the injection of contrast material.

**Balloon Tip Ventriculographic Catheters**

The Berman angiographic catheter is a balloon tip catheter that is available in 4F, 5F, 6F, 7F, and 8F sizes (Arrow International). It is used for right ventriculography, pulmonary angiography, peripheral angiography, and in the reverse configuration for balloon occlusion angiography (Figure 17.2). The balloon tip provides the advantage of easier advancement in the right ventricle or in the pulmonary artery, and by keeping the catheter and side holes away from the endocardium, it can reduce the risk of myocardial staining and ventricular arrhythmias.

**INJECTION SITE**

Adequate opacification of either ventricle is accomplished only if a large amount of contrast material is delivered in a short period of time. Although satisfactory opacification of the left ventricle can sometimes be achieved by injection of contrast material into the left atrium, this requires trans-septal catheterization, does not allow evaluation of mitral valvular incompetence, and may obscure the basal portion of the left ventricle and the aortic valve. Similarly, the left ventricle may be opacified by aortography in patients with significant aortic regurgitation, and the right ventricle may be opacified by injecting contrast material into the venae cavae or right atrium. The best approach to ventriculography in the adult patient, however, is via injection of contrast material directly into the ventricular chamber in question.

In the left ventricle, the optimal catheter position is the midcavity, provided that ventricular ectopy is not a problem (Figure 17.3). The midcavitary position ensures (a) adequate delivery of contrast material to the chamber’s body and apex; (b) lack of interference with mitral valvular function, which would have otherwise produced factitious mitral regurgitation; and (c) positioning of the holes through which the contrast material is injected away from ventricular trabeculae (thereby avoiding a possible cause of endocardial staining). In some patients, however, the midcavitary position induces repetitive ventricular ectopy. In that case, the tip of the catheter is best repositioned in such a way that it lies in the left ventricular inflow tract immediately in front of the posterior leaflet of the mitral valve (Figure 17.4). This position is usually free of ventricular ectopy, but may produce mitral regurgitation if the catheter is too close to the mitral valve. In occasional patients with vigorous ventricular contraction, no stable midventricular position can be found for the catheter. The pigtail catheter can then be advanced to be in continuous contact with the left ventricular apex (assuming that there is no evidence of apical aneurysm of mural thrombus) to allow measurement of left ventricular pressure during stable rhythm and left ventriculography with the rate of contrast injection reduced to 10 mL/second (see below).

When the pigtail catheter is rotated in the left ventricle, it may pass under the chordae. This can be suspected if the catheter shaft passes close to the inferior wall or exhibits an abrupt kink, and can be confirmed if the loop of the pigtail opens up as the catheter is withdrawn back to the left ventricular outflow tract. Because the side holes on the catheter shaft are held in close proximity to the myocardial wall by the chordae, this position increases the risk of myocardial staining and should be corrected before ventriculography is
Figure 17.3  An example of midcavitary catheter position for 30° right anterior oblique left ventriculography using an angled pigtail catheter. A. Just before the injection of contrast material. B. At the end of rapid filling. C. At end-diastole (post A wave). D. At end-systole.

performed. If repositioning the catheter would be difficult (as in a patient whose stenotic aortic valve has just been crossed) and ventriculography is required, a reduced injection rate should be used as described above for the Sones catheter.

**INJECTION RATE AND VOLUME**

Rapid delivery of an adequate amount of contrast material requires the use of a power injector. Flow injectors (most commonly, the device manufactured by Medrad) allow one to select both the volume and the rate of delivery of contrast material. Sufficient pressure to deliver the selected volume of injectate in the selected time period is automatically developed, although a maximal pressure limit of roughly 1,000 psi is set to minimize the risk of catheter burst. Of course, this high pressure is not actually delivered to the catheter tip, but is dissipated as frictional losses in the shaft of the catheter. Some injectors permit synchronization of the injection of contrast material with the R wave of the electrocardiogram, so that a set flow rate is delivered in each of several successive diastolic intervals. Although this has been said to be a technique that lessens the incidence of ventricular ectopic beats and minimizes the volume of contrast material required for adequate ventricular opacification, our impression is that it offers no clear advantage over the nonsynchronized methods.

Cine left ventriculography is accomplished using an injection rate and volume that depend on (a) the type and size of catheter, (b) the size of the ventricular chamber to be opacified, (c) the approximate ventricular stroke volume, and (d) the pre-ventriculography hemodynamics. Different operators use different catheters and different injection parameters for left ventricular injection. In most cases performed with pigtail catheters, the injection parameters are chosen as 30 to 36 mL injected at the rate of 10 to 12 mL/second (i.e., a 3-second-long injection). Somewhat higher volume and rate may be used in patients with a high cardiac output or large ventricular chamber, and somewhat smaller volumes and rates may be used in smaller or irritable ventricles. When an end-hole (e.g., Sones or multipurpose) catheter is used for left ventriculography, the rate of injection of contrast material should not exceed 7 to 10 mL/second to minimize the chance of recoil and staining. Hand injection through the manifold cannot provide adequate volume and flow rate to fill the ventricle and should be avoided.
Low-osmolar contrast media have substantially improved the safety of left ventriculography in patients with depressed myocardial function, severe coronary artery disease, and/or aortic stenosis, as discussed in Chapter 2. Even so, in patients with hemodynamic evidence of severe left ventricular dysfunction and/or if filling pressures are markedly elevated (>25 mmHg), left ventriculography should be performed only after the elevated filling pressure has been reduced by the administration of intravenous nitroglycerin or sodium nitroprusside. With the current radiographic equipment, low-osmolar contrast agents, and techniques using smaller amounts of contrast material, it is a rare case that a patient cannot undergo left ventriculography safely. But failure to take a severely elevated pre-ventriculography pulmonary capillary wedge pressure or left ventricular end-diastolic pressure seriously can lead to disastrous consequences, including intractable pulmonary edema and even death. In any patient with increased risk (LV dysfunction, mural thrombus, renal insufficiency) one should always ask whether noninvasive means of assessing left ventricular function (see below) might not be preferable to contrast ventriculography.

Before performing a power injection of contrast material, one should take appropriate precautions in filling and firing the power injector to prevent air embolism. The injection syringe is made of siliconized plastic so that the contrast medium and any air may be easily visible. This syringe is usually loaded from a contrast bottle through a short U-shaped straw while the syringe barrel is pointed upward. With the injector still in the vertical position, 30-inch-long sterile roentgenography tubing is connected to the syringe, and all air is expelled from the syringe and tubing by holding the load switch in the forward position as the operator taps the syringe and its Luer-Lok connector to discharge all air bubbles. Alternatively, some laboratories fill the injector by connecting the sterile roentgenography tubing to the coronary manifold, drawing contrast from that supply (generally a slower process, more prone to bubble formation).

Only after all of the bubbles have been expelled in the nose-up position should the injector head be inverted. A fluid-to-fluid connection is accomplished by touching the meniscus of blood spurring from the hub of the catheter to the meniscus of contrast exiting the roentgenography tubing as the technician slowly advances the syringe plunger of the injector manually. When the connection is made, the injector operator stops advancing and begins retracting the plunger until the interface between contrast material and blood can be seen in the roentgenography tubing and verified to be free of air bubbles. Prior to the left ventriculographic run, a test injection of a small amount of contrast material is often performed under fluoroscopic visualization to enable the physician to assess catheter and patient position and confirm that ventricular ectopy does not occur. If the catheter is repositioned, another test injection is recommended before the definitive injection.

Prior to performing the angiogram, the physician should look closely at the injector syringe to confirm that it is filled.
with contrast medium, free of air, and oriented in the desired nose-down direction. He/she should grasp the catheter at its hub so that the catheter can be pulled back instantaneously if ventricular extrasystoles, myocardial staining, or other untoward events develop during injection. The technician or other individual firing the injector should be prepared to abort the injection on command from the physician operator in the event of an untoward occurrence. If extrasystoles develop, we withdraw the ventriculographic catheter a distance of approximately 2 to 3 cm after the first extrasystole, which usually results in a quiet position for the remainder of the 3- to 4-second contrast injection.

Instructions to the patient regarding respiration during contrast ventriculography vary from laboratory to laboratory. Earlier imaging systems were often inadequate to give good definition of the left ventricular silhouette unless ventriculography was performed during deep inspiration to move the diaphragm out of the radiographic field. With modern imaging systems, excellent definition of the ventricular silhouette can be achieved without the restriction that ventriculography be performed during held deep inspiration. Left ventriculography done during normal quiet breathing allows physiologic interpretation of left ventricular volumes, angiographic stroke volume, and calculated left ventricular regurgitant fraction in cases of valvular regurgitation.

**FILMING PROJECTION AND TECHNIQUE**

Projections should be used that provide maximal delineation of the structure of interest and minimal overlapping of other structures. The 30° right anterior oblique (RAO) projection eliminates overlap of the left ventricle and the vertebral column; allows one to assess anterior, apical, and inferior segmental wall motion; and places the mitral valve in profile to provide a reliable assessment of the presence and severity of mitral regurgitation. The 60° left anterior oblique (LAO) view allows one to assess ventricular septal integrity and motion, lateral and posterior segmental function, and aortic valvular anatomy. To prevent foreshortening of the left ventricle and visualize the entire length of the interventricular septum in profile, 15° to 30° cranial angulation should be added to the 60° LAO view, and the angiogram should be performed during a sustained deep inspiration to minimize obstruction by the diaphragm. This view allows visualization of ventricular septal defects and the associated left-to-right shunting, or the septal bulge and systolic anterior motion in hypertrophic obstructive cardiomyopathy, or isolated lateral wall motion abnormalities (Figures 17.5 and 17.6). For routine left or right ventriculography, 30 frames per second using the 9-inch field of view allows the best temporal and spatial imaging, but many laboratories now use 15 frames per second for both ventriculography and coronary angiography to reduce radiation exposure (see Chapter 2).

If both RAO and LAO ventriculograms are indicated, it requires two separate injections in a single-plane room. If available, biplane ventriculography is thus preferable to single-plane ventriculography because it allows one to obtain more information at essentially no additional risk to the patient. In the patient with coronary artery disease, biplane left ventriculography provides more information on the location and severity of segmental wall motion abnormalities than does single-plane ventriculography; in the patient with congenital heart disease biplane right ventriculography allows one to assess accurately the anatomy of the right ventricular outflow tract, the pulmonic valve, and the proximal portions of the pulmonary artery. But biplane ventriculography has several disadvantages, including (a) higher cost of the biplane cineangiographic equipment; (b) reduced

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**Figure 17.5** Mitral and tricuspid regurgitation. End-diastolic (A) and end-systolic (B) frames from a left ventriculogram performed in the 30° RAO projection in a patient with normal coronaries and presumptive AIDS cardiomyopathy, showing enlarged end-diastolic and end-systolic volumes, reduced ejection fraction of 38%, and 2+ mitral regurgitation. Note the dye movement to the enlarged left atrial volume; the contrast density method underestimates the severity of regurgitation, shown to be moderately severe by a regurgitant fraction of 36% and transesophageal echo. C. End-systolic frame from a right ventriculogram in the same patient performed in the 30° RAO projection showing 2+ tricuspid regurgitation. LA, left atrium; RA, right atrium; PA, pulmonary artery.
quality of cineangiographic imaging in each plane owing to radiation scatter caused by the opposite plane; (c) additional time required to position the biplane equipment appropriately, especially when the brachial approach is used; and (d) additional radiation exposure to personnel in the room. In reality, most laboratories have only one biplane laboratory in their imaging suite, so that almost all left ventriculograms are done single plane. Table 17.1 provides a list of preferred left and right ventriculographic views for various conditions. Additional information on preferred angiographic projections for congenital lesions is provided in Chapter 9 and in Table 9.5.

### RIGHT VENTRICULOGRAPHY

Although right ventriculography is rarely performed in the adult cardiac catheterization laboratory, it is important to be familiar with optimal views, injection catheters, and indications.

The anteroposterior (AP) view with cranial angulation and the lateral view are generally preferred for right ventriculography, as they elongate the right ventricular outflow tract and the central pulmonary arteries. The optimal catheter position is the midcavity, provided that repetitive ventricular ectopy does not occur (Figure 17.7). If ectopy is uncontrollable, the catheter may be positioned in the outflow tract, just below the pulmonic valve. Even here, however, repetitive ventricular ectopy may present a difficult problem. The use of a balloon tip catheter has the potential to reduce ventricular ectopy, and it is our preferred approach for right ventriculography (see above).

### ANALYSIS OF THE VENTRICULOGRAM

The left ventriculogram is analyzed both qualitatively and quantitatively on a normal sinus beat that follows a previous normal sinus beat in which the ventricle is well opacified; evaluation of ectopic or postectopic beats will give a false assessment of ventricular function. Overall, ventricular dysfunction is described as hyperdynamic (>70%), normal (50% to 69%), mildly hypokinetic (35% to 49%), moderately hypokinetic (20% to 24%), or severely hypokinetic (<20%). Regional wall motion can be graded qualitatively as normal, hypokinetic, akinetic, or dyskinetic for each of the segments seen in the right anterior oblique projection.
Table 17.1  Preferred Left and Right Ventriculographic Views for Specific Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Left Ventriculography</th>
<th>Right Ventriculography</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessment of LV and RV function</td>
<td>30° RAO 60° LAO</td>
<td>AP Cranial</td>
</tr>
<tr>
<td>Membranous VSD</td>
<td>70° LAO 30° Cranial RAO</td>
<td></td>
</tr>
<tr>
<td>Muscular VSD</td>
<td>4-chamber projection (45° LAO 45° Cranial) 70° LAO 30° Cranial RAO</td>
<td></td>
</tr>
<tr>
<td>Atrioventricular septal defects</td>
<td>4-chamber projection (45° LAO 45° Cranial) 45° RAO 45° Cranial</td>
<td>RAO Cranial Lateral</td>
</tr>
<tr>
<td>Pulmonic Stenosis</td>
<td></td>
<td>AP Cranial</td>
</tr>
<tr>
<td>Left ventricular outflow tract obstruction (including fibromuscular subaortic stenosis)</td>
<td>70° LAO 30° Cranial RAO</td>
<td>Lateral</td>
</tr>
<tr>
<td>Double outlet right ventricle</td>
<td>70° LAO 30° Cranial RAO</td>
<td>AP Lateral</td>
</tr>
<tr>
<td>L-transposition of the great arteries (Catheter in the morphologic left ventricle, antegrade)</td>
<td>RAO cranial/LAO Cranial</td>
<td></td>
</tr>
<tr>
<td>Transposition of the great arteries (Catheter antegrade, across the foramen ovale)</td>
<td>70° LAO 30° Cranial RAO</td>
<td></td>
</tr>
</tbody>
</table>

VSD, ventricular septal defect; AP, anteroposterior; LAO, left anterior oblique; RAO, right anterior oblique.

(antrolateral, apical, inferior, posterobasal segments) and in the left anterior oblique projection (basal septal, apical septal, apical lateral, basal lateral segments). Quantitative evaluation involves measurement of ejection fraction (the percent of end-diastolic volume that is ejected during systole), the absolute end-diastolic and end-systolic volumes (using the area-length method), and chord-by-chord local shortening (see Chapters 21 and 22).

The degree of mitral regurgitation can be estimated (on a scale of 1+ to 4+) by examining any systolic leakage of contrast from the left ventricle back into the left atrium, and the opacification of the left atrium relative to the left ventricle, in the right anterior oblique projection (see Chapter 40; Figure 17.6). In patients with a markedly enlarged left atrium from chronic mitral regurgitation, however, the dilution of the regurgitant contrast jet within this larger left atrial volume may lead to underestimation of regurgitation severity by the atrial density scale (Figure 17.7). A more quantitative method involves a comparison of the angiographic stroke volume (end-diastolic volume minus end-systolic volume) with the forward stroke volume (cardiac output divided by heart rate). These should be equal absent significant left-sided valvular regurgitation, but in patients with mitral (or aortic) regurgitation the angiographic stroke volume will be larger than the forward stroke volume (by an amount equal to the regurgitant volume). The severity of the regurgitant lesion can then be estimated by calculating the regurgitant fraction (the regurgitant volume divided by angiographic stroke volume), which indicates the percent of the volume ejected during each systole that goes backward into the left atrium rather than forward into the aorta. Mild (1+) mitral regurgitation is usually associated with a regurgitant fraction of <30%, moderate (2+) with a regurgitant fraction of 30 to 39%, moderately severe (3+) with a regurgitant fraction of 40% to 49%, and severe mitral regurgitation with a regurgitant fraction >50%. Qualitative review of the right and left ventriculogram can also identify congenital diseases such as RV dysplasia and left ventricular noncompaction (Figure 17.8), which should not be missed on a routine ventriculogram and which can be confirmed by MRI (Figure 17.9). In addition, in patients with acute myocardial infarction, the qualitative analysis of the left ventriculogram should focus on the identification of potential rare complications such as contained free wall ventricular rupture, ventricular septal defect, and papillary muscle rupture (Figure 17.7).
Figure 17.7 Various other pathologies seen on left ventriculography. A. Mitral valve prolapse, with prolapse of a thickened posterior leaflet behind the fornix (dotted arrow) and mitral regurgitation in the RAO projection. B. Ventricular septal defect 3 days post inferior myocardial infarction owing to single-vessel right coronary occlusion, with contrast crossing from the left to the right ventricles in the LAO-cranial projection. C, D. Papillary muscle rupture 5 days post inferior myocardial infarction (diastolic [C] and systolic [D] frames, showing dense contrast filling the left atrium and left atrial appendage (dotted arrow), respectively). E. Pseudoaneurysm (contained myocardial rupture, arrow) seen several weeks following a lateral wall myocardial infarction owing to single-vessel circumflex marginal disease.

INTERVENTION VENTRICULOGRAPHY—HISTORICAL PERSPECTIVE

Permanent segmental dysfunction of the left ventricular wall can be caused by frank infarction, but reversible segmental dysfunction can also be caused by ischemia. This can be transient with brief ischemia (Figure 17.10), more prolonged with stunning following a longer period of ischemia, or chronic with hibernation owing to sustained moderate ischemia, as with a collateralized chronic total occlusion.17

Before the introduction of newer and less invasive imaging modalities, left ventriculography was the only method available to assess left ventricular segmental function. Thus, several angiographic techniques were developed to help determine if an asynergic segment of the left ventricle is infarcted or just ischemic. Segments in which abnormal wall
motion is caused by ischemia generally show improvement in systolic motion, whereas segments in which abnormal wall motion is owing to infarction fail to improve, using these techniques.

For example, left ventricular segmental wall motion can be improved substantially by the administration of catecholamines. Two left ventriculograms are performed—the first in the resting (baseline) state and the second during a steady state infusion of epinephrine (1 to 4 mg/minute) or dobutamine (10 to 15 μg/kg per minute). Alternatively, left ventricular segmental wall dysfunction can often be improved by administration of nitroglycerin, either by improving collateral blood flow, reducing myocardial oxygen consumption to match available supply, or simply by reducing the afterload against which the left ventricle must eject. Left ventricular segmental wall motion can be influenced by postextrasystolic potentiation when a single ventricular premature beat is introduced during left ventriculography and is followed by a potentiated beat. Segmental wall motion during one of the preceding sinus beats is compared with that of the postextrasystolic beat and improvement on the potentiated beat as compared with the preceding sinus beat suggests ischemia rather than infarction. It is probably unwise, however, to attempt to induce the ventricular extrasystole by manipulating the left ventriculographic catheter during the injection of contrast material since such manipulation may cause endocardial staining. Segments in which wall motion improves with intervention generally maintain the same level

Figure 17.8 Left ventricular noncompaction and aneurysm in a patient with no significant coronary artery disease. A. LVG midsystolic frame in the RAO view. B. End-systolic frame in the LAO view. A large inferior aneurysm and extensive trabeculations of the anterior and lateral wall are seen. (Reproduced with permission from: Ionescu CN, Turcot D. Left ventricular non-compaction and aneurysm revealed by left ventriculography. Catheter Cardiovasc Interv 2012;80:109–111.)

Figure 17.9 Left ventricular noncompaction. Cardiac magnetic resonance images of a 26-year-old patient with heart failure. The images were obtained using steady state free precession and are displayed in the vertical long axis (left), axial (center), and short axis (right) planes, and demonstrate marked trabeculations (arrows) of the left ventricle, consistent with left ventricular noncompaction.
A 71-year-old woman under extreme emotional stress presented with anterior ST-segment elevation; elevated creatine phosphokinase isoenzymes, and diffuse akinesis of the left ventricular apex (including both anterior and inferior aspects), resembling the shape of a Japanese octopus trap (tako-tsubo; narrow neck and round bottom), despite angiographically normal coronary arteries. Within 3 weeks, left ventricular function had returned to near normal. The mechanism is believed to be intense sympathetic arteriolar vasoconstriction involving the apical myocardium. (Case provided by Alan Yeung, M.D., Stanford University. See also Wittstein IS, et al. Neurohumoral features of myocardial stunning due to sudden emotional stress, N Engl J Med 2005; 352:539–548.)

**COMPLICATIONS AND HAZARDS**

Although complications of cardiac catheterization and angiography are discussed in detail in Chapter 4, certain specific points relevant to ventriculography are presented here.

**Arrhythmias**

Ventricular extrasystoles occur frequently during ventriculography and are usually caused by mechanical stimulation of the ventricular endocardium by the catheter or a jet of contrast agent. Such extrasystoles can usually be eliminated or at least minimized by repositioning the catheter. Although short runs of ventricular tachycardia occur during an occasional ventriculogram, they almost always cease promptly when the catheter is removed from the ventricle. Rarely, the ventricular tachycardia caused by ventriculography is sustained even after catheter removal. It should be treated quickly with a bolus of intravenous lidocaine and, if necessary, direct current countershock. Ventricular fibrillation has been reported to be induced by an improperly grounded power injector.
Intramyocardial Injection (Endocardial Staining)

Deposition of contrast material within the endocardium and myocardium is usually caused by improper positioning of the ventriculographic catheter so that it passes under one of the papillary muscles or a side hole lies firmly against the endocardium. Although a small endocardial stain usually causes no problem, a large stain may lead to medically refractory ventricular tachyarrhythmias, including ventricular tachycardia or fibrillation. Rarely, the power injection of contrast material causes myocardial perforation, with resultant leakage of blood and contrast material into the pericardial space and development of cardiac tamponade. This must be treated by emergency pericardiocentesis and immediate consultation obtained from a cardiothoracic surgeon (see Chapters 38 and 44).

Fascicular Block

Because of the proximity of the anterior fascicle of the left bundle to the left ventricular outflow tract, transient left anterior fascicular block may occur during retrograde left heart catheterization. In the patient with underlying right bundle branch block and left posterior fascicular block, complete heart block may occur as the catheter is advanced into the left ventricle.23 Although temporary pacing is usually required, catheter-induced fascicular block usually resolves within 12 to 24 hours. Transient complete left bundle branch block is an extremely rare complication of retrograde left heart catheterization.24

Embolism

Inadvertent injection of air or thrombus probably poses the greatest risk associated with ventriculography. Nevertheless, the risk of air embolization should be avoidable by following good practices in filling the injector and confirming a bubble-free hookup as described above. The presence of thrombi on or within the ventriculographic catheter is minimized by frequent flushing of the catheter with a solution containing heparin when the ventriculographic catheter is first introduced and just prior to hooking up for the ventriculogram. If there is any suspicion (from noninvasive testing) of a thrombus in the left ventricular apex, great care should be taken to position the ventriculographic catheter in the left ventricular inflow tract, avoiding the apical portion completely, or ventriculography itself should be avoided, relying on noninvasive evaluation. Partially organized thrombi may also be dislodged from the left ventricular wall by the catheter tip or the force of a power injection. Accordingly, the ventricular angiographic catheter should not be advanced to the left ventricular apex except under exceptional circumstances (e.g., suspicion of idiopathic hypertrophic subaortic stenosis).

Complications of Contrast Media

With earlier ionic contrast agents, ventriculography produced a modest fall in systemic arterial pressure, a reflex increase in heart rate, and a transient depression of left ventricular contractility that resolved within 1 to 2 minutes. Patients used to experience a hot flash owing to the powerful vasodilation caused by the contrast material as it distributed throughout the arterial tree, and nausea or vomiting could occur in 20% to 30% of cases. With the current low-osmolar contrast agents, these complications are uncommon.

ALTERNATIVES TO CONTRAST VENTRICULOGRAPHY

2D and Real-Time 3D Echocardiographic Visualization of the Left Ventricle

Two-dimensional echocardiography may be used as an alternative to contrast ventriculography to assess global and regional left ventricular performance. Echocardiography is noninvasive, does not require exposure to radiation, and does not add to the contrast load of coronary angiography in patients at high risk for contrast-induced renal dysfunction. In a few subjects, echocardiography may fail to provide adequate images owing to extreme obesity or an increased anteroposterior chest dimension unless a transesophageal study is performed, or contrast is used. In most patients, however, adequate images of the left ventricle can be acquired in multiple short- and long-axis planes to evaluate segmental and global left ventricular function as well as the degree of mitral regurgitation. Two-dimensional echocardiographic imaging also allows determination of left ventricular volumes using a modification of Simpson’s rule based on analysis of orthogonal long-axis views. The left ventricular volumes provided by echocardiography tend to be somewhat smaller and the estimates of mitral regurgitation tend to be somewhat higher than those obtained with contrast ventriculography.14,25 Because two-dimensional echocardiography can be used to determine left ventricular wall thickness, it is an excellent method for quantitating left ventricular mass.

Real-time three-dimensional echocardiography (RT3DE) has emerged as a novel modality for the quantification of left ventricular volumes and function, for the evaluation of regional wall motion, myocardial mass and valvular function, and as a promising method to guide navigation within the cardiac chambers (see Chapter 3). RT3DE provides volumetric measurements that are highly reproducible and comparable to cardiac magnetic resonance (CMR) imaging, and overall more accurate and reproducible than 2D measurements.26
Radionuclide Imaging: First Pass, ERNA, and Gated SPECT

Noninvasive assessment of left ventricular systolic function may be performed with a variety of nuclear cardiology imaging techniques. The first such evaluation was performed with equilibrium radionuclide angiography (ERNA), also known as MUGA or gated blood pool imaging, a count-based technique not influenced by geometry and which is highly reproducible. Although this evaluation was traditionally performed as a planar technique, newer technology uses tomographic acquisition, which permits reorientation and allows for excellent visualization and quantitation of both right and left ventricular function. First pass imaging, a technically demanding method based on the transit of a rapid bolus of a radionuclide accompanied by high-temporal resolution image acquisition, may be performed at rest or with exercise and is perhaps the most accurate method for right ventricular functional determination.

A more contemporary nuclear cardiology technique, gated SPECT, is now frequently used to assess ventricular function, as well as to determine ventricular volumes, usually in conjunction with myocardial perfusion imaging. Based on a true three-dimensional approach, quantitative measures including LVEF are fully automatic, well validated, and highly reproducible with gated SPECT. Multiple commercial software packages are currently available, providing two- and three-dimensional images and allowing for accurate assessment of global and regional function (Figure 17.11). Ventricular dyssynchrony may also be assessed with novel gated SPECT software.

Magnetic Resonance Imaging and Computerized Tomographic Ventriculography

Perhaps the most accurate and reproducible method for measuring ventricular dimensions and evaluating regional wall motion is cardiac magnetic resonance (CMR) imaging. These images are acquired in a gated fashion throughout the cardiac cycle, and end-diastolic and end-systolic frames are identified. Because MRI images can be presented in any plane, a detailed assessment of regional wall motion can be accomplished in almost all subjects regardless of body shape or size, and this technique provides superior image quality. CMR is
felt by many to be the optimal method for volume and ejection fraction estimation as it is three-dimensioned and highly useful for nonsymmetric ventricles. Overall, CMR provides estimates of left ventricular volumes that are similar to those obtained with contrast ventriculography, and when compared with two-dimensional echocardiography, MRI may provide an accurate quantitation of left ventricular wall thickness, mass, perfusion, pericardial thickness, and partial information on valve function (Figure 17.12). Stroke volume, cardiac output, and other hemodynamic parameters may also be obtained. Myocardial tagging overlays a grid onto the myocardial walls and allows for clear visualization of deformities and wall motion abnormalities, with a warping of the grid pattern indicating how the myocardium twists and stretches as it contracts.

Retrospectively gated cardiac CT also provides useful LV functional assessment. Automated determination of myocardial surfaces in multiple axial images permits assessment of ventricular volume by the method of discs, similar to echocardiography, but with markedly improved spatial resolution. Very good to excellent correlation of CT volume and LVEF determination has been demonstrated when compared with echocardiography and with CMR or contrast ventriculography. Multidetector CT may provide better accuracy than contrast ventriculography or echocardiography, when compared with CMR as the reference standard for LV function.

Electromechanical Mapping

Originally developed for electrophysiology, the Biosense electromagnetic mapping catheter uses tip sensors to measure the relative strengths of the electromagnetic fields emitted by three coils positioned under the patient support, and thereby to calculate the exact position of the catheter tip in three dimensions. When the catheter is placed in contact with the left ventricular endocardium, the unipolar electrogram can be recorded from multiple locations within the left ventricle. Recording the motion of the catheter over the cardiac cycle allows calculation of cardiac volumes (including those at end-diastole and end-systole), local wall motion, and wall shortening. Areas of myocardial infarction show poor local shortening with low unipolar voltage. In contrast, areas with severe ischemia show reduced local shortening with retained unipolar voltage. Although more time-consuming than contrast ventriculography, electromechanical mapping may provide more detailed assessment of ventricular function, the potential for recovery after revascularization, and a highly accurate way to deliver local therapies (local drug injection, myocardial or cell replacement therapy) to ischemic areas of the left ventricle. Electromechanical mapping is currently used in ongoing clinical trials to direct intramyocardial injections of cell therapies (see Chapter 36).

Electrical Conductance Catheter

If a multielectrode catheter is positioned along the long axis of the left ventricle (from the aortic valve to the apex) and current is passed between the proximal and distal most electrodes, the voltage difference between pairs of interposed electrodes will reflect the local conductance and thus the regional blood volume (Figure 17.13; see also Chapter 21). In actuality, this needs to be corrected for the parallel conductance of the surrounding myocardium by subtracting a correction volume determined by comparing the conductance-calculated stroke volume to the actual stroke volume. A second correction factor to the slope of the relationship between calculated conductance and actual volume is determined by monitoring the signal as 5 mL of 10% saline is injected into the pulmonary artery and passes through the left ventricle. The main application of conductance volume measurements consists in monitoring of instantaneous pressure–volume loops in response to various drugs or interventions. Recording of serial pressure–volume
loops during balloon occlusion of the inferior vena cava allows a clinical definition of the end-systolic pressure–volume relationship as a measure of left ventricular function. This technique can also be used in the right ventricle or aorta to measure serial volume changes and compares favorably with echocardiographic, magnetic resonance, or nuclear methods.

REFERENCES

Although right heart catheterization was first described in 1929, angiographic visualization of the pulmonary arteries was not performed until 1938. Initially, pulmonary angiography was performed using a nonselective technique (by intravenous injection of contrast material), to avoid venous cutdown, catheter manipulation, and fluoroscopy. Selective pulmonary arteriography recorded on serial cut films was then introduced by Sasahara and colleagues in 1964. The basic objective remains visualization of the lumen of the main and branch pulmonary arteries. Current practice reflects advances in catheter design, the development of rapid digital subtraction imaging equipment, and the availability of safer low-osmolar contrast agents.

Since the introduction of newer imaging modalities including computed tomography angiography (CTA) and magnetic resonance angiography (MRA), catheter-based pulmonary angiography has been in use less frequently in the diagnosis of acute pulmonary embolism. However, it remains the gold standard technique for diagnosing pulmonary embolism and is also indicated for evaluating a variety of congenital and acquired diseases, such as pulmonary arteriovenous malformations (PAVMs), pulmonary artery stenosis and aneurysm, pulmonary vein stenosis, anomalous pulmonary venous return, and pulmonary artery neoplasm, inflammation and hemorrhage. Although the frequency of use of diagnostic pulmonary angiography has declined over the past decade as contemporary noninvasive imaging techniques, including multislice CTA and MRA imaging, have reached competitive diagnostic accuracy for diseases involving the pulmonary vasculature, there has been a recent resurgence of this technique as various transcatheter interventions on the pulmonary circulation, including balloon angioplasty with or without stent placement, mechanical embolectomy, embolization, and foreign body retrieval have been introduced. Although this procedure still largely remains the province of vascular radiologists in many centers, interventional and general cardiologists should have a basic understanding of its technical aspects. Pulmonary angiography is usually performed to visualize the pulmonary circulation after right heart catheterization with hemodynamic measurements. This chapter reviews the vascular anatomy, techniques and role of pulmonary angiography in the diagnosis and treatment of pulmonary embolism, and a variety of congenital and acquired diseases of the pulmonary vasculature.

The main pulmonary artery arises from the conus of the right ventricle, first anterior to and then to the left of the aorta. It progresses 4 to 5 cm in a posteromedial direction before it bifurcates into the right and left pulmonary arteries.

The right pulmonary artery courses horizontally in the mediastinum, passing anterior to the right main stem bronchus and posterior to the ascending aorta and superior vena cava. The right upper-lobe branch (truncus anterior) arises within the mediastinum before reaching the right hilum and divides further into the three segmental upper lobe arteries (Figure 18.1). The remainder of the right pulmonary artery continues as pars interlobaris till the origin of the middle-lobe (two arteries) and upper-lobe segmental arteries. From this point, the artery continues as pars basalis and gives rise to four segmental arteries of the lower lobe.

The left pulmonary artery is a direct posterior continuation of the main pulmonary artery, crossing over the left main stem bronchus before passing posterior to the bronchus as the pars superior. Thus, the proximal portion of the left pulmonary artery is foreshortened in a frontal view and is best seen in a left anterior oblique (LAO) or lateral view. There is no large upper lobe branch, but a variable number of small segmental arteries supplying the left upper lobe originate from the outer aspect of the pars superior. The pars interlobaris and basalis give rise to two lingular and four lower lobe segmental arteries.

The lobar and segmental branching is remarkably variable, and there are many supernumerary branches, which outnumber the conventional branches and penetrate the lung directly. Each segmental artery supplies a pulmonary

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**ANATOMY**

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The lobar and segmental branching is remarkably variable, and there are many supernumerary branches, which outnumber the conventional branches and penetrate the lung directly. Each segmental artery supplies a pulmonary
Figure 18.1 Segmental pulmonary arterial anatomy. Right lung, right anterior oblique view (1) and left anterior oblique view (2). A. Right middle lobe medial segmental artery; B. Right lower lobe anterior basal segmental artery; C. Right lower lobe lateral basal segmental artery; D. Right lower lobe posterior basal segmental artery; E. Right lower lobe medial basal segmental artery; F. Right middle lobe lateral segmental artery; G. Right lower lobe superior segmental artery; H. Right upper lobe posterior segmental artery; I. Right apical segmental artery; J. Right upper lobe anterior segmental artery. Left lung, right anterior oblique view (3) and left anterior oblique view (4). A. Lingula, inferior segmental artery; B. Left lower lobe anteromedial basal segmental artery; C. Left lower lobe lateral basal segmental artery; D. Left lower lobe posterior basal segmental artery; E. Left upper lobe anterior segmental artery; F. Lingula, superior segmental artery; G. Left lower lobe superior segmental artery; H. Left upper lobe apical-posterior segmental artery. (Reprinted with permission from Kandarpa K, ed. Handbook of Cardiovascular and Interventional Radiology, Little Brown and Company, 1988.)

perfusion segment (Figure 18.2), as resolved by conventional nuclear pulmonary scans.

The segmental pulmonary veins are variable within the lung parenchyma. Ultimately, however, they form a superior and an inferior vein on each side before they enter the left atrium. The left veins, however, may merge to form a common vein within the pericardium.5

TECHNICAL CONSIDERATIONS

Hemodynamic Monitoring

Patients who need pulmonary angiography are often acutely ill and may require continuous blood pressure measurements and electrocardiographic monitoring. Sinus bradycardia or heart block may occur as vascular access is gained. Complete heart block during right heart catheterization can also occur owing to impact of the right bundle branch in patients with underlying left bundle branch block, rarely necessitating temporary pacing. Transient supraventricular and ventricular arrhythmias are also common during catheter advancement through the right heart chambers, and sustained tachyarrhythmias with hemodynamic impairment may necessitate electrical cardioversion.

An important part of the procedure is formal hemodynamic measurements (both pressures and oxygen saturation) during catheter advancement. The coronary sinus is occasionally entered while trying to access the right ventricular outflow tract (particularly from subclavian, jugular,
or brachial access route). To minimize the risk of perforation, catheter advancement should be halted if a right atrial pressure waveform continues to be present as the catheter is advanced across the spine into what should fluoroscopically be the right ventricle. Catheter position in the coronary sinus can be confirmed or excluded by a hand injection of a contrast medium under fluoroscopy. Damping of the pressure in the main pulmonary artery may indicate the presence of massive pulmonary embolism (PE), with the catheter holes embedded in the embolus. In that situation, a hand injection of contrast can confirm the diagnosis.

The formal hemodynamics prior to angiography (Table 18.1) may also suggest the presence of congestive heart failure, valvular disease, intracardiac shunts, pulmonary hypertension, or pericardial disease. Severe hemodynamic embarrassment may also require modification of the angiographic procedure, including catheter placement, injection rates, and image recording modes. In particular, complications of pulmonary angiography are more common in patients with pulmonary hypertension (particularly in the presence of right ventricular dysfunction), mandating special precautions such as supplemental oxygen, reduced amounts of contrast agent, or superselective rather than mainstream pulmonary artery injections.6

Percutaneous Venous Catheterization

Pulmonary angiography is performed using the technique described by Seldinger in 1953.7 The veins used for catheterization of the pulmonary artery are the femoral, jugular and upper extremity vein. Of these, the right femoral vein is preferable because it provides a relatively straight course to the inferior vena cava and right heart. In patients with suspected proximal deep vein thrombosis (DVT), ultrasound examination may be considered prior to vascular entry. The procedure is performed with mild conscious sedation. It is important
Table 18.1 Hemodynamic Measurements (Normal Ranges)

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>8–10</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Right Atrial Pressure, mmHg</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A wave</td>
<td>2–10</td>
<td></td>
</tr>
<tr>
<td>V wave</td>
<td>2–10</td>
<td></td>
</tr>
<tr>
<td><strong>Right ventricular pressure, mmHg</strong></td>
<td>Systolic 15–30</td>
<td></td>
</tr>
<tr>
<td></td>
<td>End-diastolic 0–8</td>
<td></td>
</tr>
<tr>
<td><strong>Pulmonary artery pressure, mmHg</strong></td>
<td>Mean 10–20</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Systolic 15–30</td>
<td></td>
</tr>
<tr>
<td></td>
<td>End-diastolic 3–12</td>
<td></td>
</tr>
<tr>
<td><strong>Pulmonary capillary wedge pressure, mmHg</strong></td>
<td>Mean 5–12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A wave 3–15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>V wave 3–12</td>
<td></td>
</tr>
<tr>
<td><strong>Arteriovenous oxygen difference, mL/L</strong></td>
<td>30–50</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac output, L/min</strong></td>
<td></td>
<td>4.0–8.0</td>
</tr>
<tr>
<td><strong>Cardiac index, L/min/m²</strong></td>
<td></td>
<td>2.6–4.6</td>
</tr>
<tr>
<td><strong>Pulmonary vascular resistance, Wood units</strong></td>
<td>0.7–1.1</td>
<td></td>
</tr>
</tbody>
</table>

*(Mean pulmonary artery pressure–pulmonary capillary wedge pressure)/cardiac output.*

that the patient be alert during the procedure so that he can cooperate with breath holding during imaging. In case heparin has been administered for suspected pulmonary embolism, it should be continued during the examination.

The technique for arterial and venous vascular access has been described in detail in Chapter 6, and the reader is referred to that discussion. To minimize the risk of dislodging thrombi during catheter advancement, manual injection of 10 to 15 mL of contrast into the femoral vein may help to exclude massive iliac vein or cava thrombosis prior to advancing the catheter to the right heart.

Occasionally, because of femoral or iliac vein thrombosis, inferior vena cava occlusion, or groin infection, the femoral vein cannot be used. The vein of choice then becomes the jugular or an upper extremity vein. The right heart may be approached easily with a balloon-directed catheter when gaining vascular access via the internal jugular vein.

Of the upper extremity veins, the basilic vein in the antecubital fossa is preferable, while the cephalic vein is not suitable since it enters the axillary vein at an abrupt angle. If the basilic vein cannot be accessed, the brachial vein can also provide access.

**Pulmonary Artery Catheterization**

Most catheters used for diagnostic pulmonary angiography are between 5F and 7F to provide a lumen that will accommodate contrast injection rates of 20 to 25 mL/second. A 4F nylon pulmonary catheter allows flow rates of 20 mL/second at 1,050 psi and may reduce access site complications. The three common approaches for pulmonary artery catheterization are shown in Figure 18.3. The presence of a properly placed IVC filter does not necessarily preclude a transfemoral approach. Safe transfemoral angiography has been reported by passing straight or J-tipped guide wires followed by catheters through stainless steel Greenfield, Vena Tech, and Bird’s Nest filters. After the guide wire is passed through the IVC filter, a long sheath is placed across the filter with its leading tip beyond the filter to prevent filter dislodgment.

Catheters used for pulmonary angiography are of two basic designs: the pigtail type and balloon-tipped type. The pigtail type catheters have multiple side holes whereas the curled catheter tip allows safe passage through the right heart. While being removed from the pulmonary arteries, all pigtail catheters must be straightened with a floppy-tip guide wire or a J-tipped guide wire under fluoroscopic observation, since the catheter tip may otherwise engage a papillary muscle, chordae tendineae, or tricuspid valve leaflet during withdrawal. The balloon-tipped catheters are assisted by blood flow through the right heart chambers and into the pulmonary arteries. Side holes in the catheter shaft allow power injection into the main branches, whereas the catheter end-hole makes balloon occlusion angiography possible with the same catheter (Figure 18.4).
Figure 18.3 Techniques for pulmonary artery catheterization. A. Straight body pigtail catheter and tip-deflecting wire. The pigtail catheter is placed in the right atrium (1). The wire is deflected to point toward the right ventricle (2). The wire is fixed, and the catheter is advanced over it into the right ventricle (3). The tip deflection is released (4). Counterclockwise rotation of the catheter swings the pigtail anteriorly (5). Simultaneous advancement of the catheter places it into the main pulmonary artery. Advancing the catheter farther usually takes it into the left main pulmonary artery. The tip-deflecting wire is used to direct the catheter downward and to the right for right main pulmonary artery catheterization. B. Grollman pulmonary artery catheter. The pigtail catheter is placed in the right atrium (1). The anteromedial portion of the right atrium is probed to facilitate catheter entry into the right ventricle (2). The catheter is then slightly withdrawn and rotated counterclockwise to allow entry into the right ventricular outflow tract and main pulmonary artery (3). C. Balloon-tipped catheter. The balloon is inflated under fluoroscopic guidance in the common iliac vein, and the catheter is advanced under observation into the right atrium (1). The catheter is then rotated anteromedially to facilitate direct entry into the right ventricle (2). As soon as the tricuspid valve is passed, documented by a right ventricular pressure waveform, the catheter is rotated to point the balloon tip cranially toward the right ventricular outflow tract before advancing it further (3). Deep inspiration of the patient may facilitate flow-directed entry of the balloon tip from the outflow tract into the main pulmonary artery, with a preference to enter the left pulmonary artery.

Balloon catheters are first deflated and can then be removed without fluoroscopy.

The most common pigtail catheter is the Grollman pulmonary artery catheter (Cook Inc. Bloomington, IN). This 6.7F polyethylene catheter has a 90° reversed secondary curve 3 cm proximal to the pigtail (Figure 18.4). If the catheter tip becomes lodged in the right ventricular outflow tract, use of a soft-tipped J guide wire may facilitate catheter entry into the main pulmonary artery. In challenging cases, the pulmonary artery can be catheterized using a conventional large-lumen balloon flotation catheter with placement of an exchange-length J-tipped guide wire in the pulmonary artery, and subsequent advancement of the angiographic pigtail over the wire.

In patients with right atrial enlargement, the right ventricle may be difficult to probe with the standard Grollman catheter because the distal end of the catheter may be too short to allow direct passage. In such cases, the 90° angle of the distal tip may be enlarged by introducing a manually bent proximal end of a guide wire. The Van Aman (7 Fr APC, Cook Inc. Bloomington, IN) catheter is a 7F polyurethane modified Grollman catheter with a 90° reversed secondary curve 6 cm (rather than 3 cm) proximal to the pigtail and has been successfully used for pulmonary artery catheterization in patients with right heart enlargement.

The 7F Berman balloon catheter (Critikon Inc. Tampa, FL), which has no end hole, cannot be used with a guide wire, and requires introduction through a venous sheath. From the jugular or brachial approach, the catheter follows a continuous curve through the outflow tract and into the right pulmonary artery. The right pulmonary artery may be catheterized from below by using a reverse curve in which the Berman catheter is curved against the lateral right atrial wall before crossing the tricuspid valve, so that it enters the right ventricle pointing up as though it were coming from above. This approach is particularly helpful in the presence of tricuspid regurgitation, since the right atrial catheter loop provides more backup when advancing the catheter than seen.
Figure 18.4 Catheters for pulmonary angiography. Left to right. The Nyman, Grollman, and straight pigtail catheters (Eppendorf type), and the balloon occlusion catheter with side holes distal to the balloon (Berman type).

with direct transit of the tricuspid valve from below. Catheterization of the left pulmonary artery is often more difficult, and may require the use of deflection guide wires into the angiographic catheter if standard attempts at catheter manipulation are unsuccessful.

Preferred catheters for the brachial approach include a 5F nonreversed Grollman catheter and a 5F multiple-bend pigtail catheter15,16 (Cordis Corp., Miami, FL). Direct catheter entry into the right ventricle may be difficult using the brachial approach. Looping the catheter around the right atrial free wall, counterclockwise rotation, and gentle retraction are necessary to probe the right ventricle.

The two catheters used for pulmonary angiography at the author’s institution are 7F curved pigtail catheter (7F APC, flow rate 32 cc/second at 1,200 psi) and 7F Mont-1 Torcon NB Advantage Catheter (flow rate 29 cc/second at 1,200 psi; Cook Medical Inc., Bloomington, IN). The 7F catheter can be introduced from a femoral or jugular vein without placing a 7F sheath in the vein. The tip of the catheter is turned toward the right ventricle just above the diaphragm. The catheter is advanced through the tricuspid valve until it enters the right ventricle, where the catheter is turned clockwise while advancing it toward the pulmonary outflow tract. Although pulmonary artery catheterization with the curved pigtail catheter is generally easy, it may become difficult in patients with large right atrium and ventricle; in these patients, the curved catheter tip may not negotiate the tricuspid valve. In such patients, the tip-deflecting wire technique is used to advance the catheter into the right ventricle. The deflecting wire is positioned in the catheter just proximal to the pigtail. The wire is deflected, directing the catheter toward the tricuspid valve, and then the manipulator instrument is held stable. The catheter is advanced off the manipulator wire into the right ventricle. When the catheter tip is in the right ventricle, the manipulator wire is withdrawn, and then the catheter is advanced into the right ventricular outflow tract and pulmonary artery while rotating it clockwise. Alternatively, a guide wire can be advanced through the catheter into the right ventricle and pulmonary artery. If the catheter tip is being advanced toward the right ventricular apex, causing ventricular arrhythmias, it should be retracted immediately toward the tricuspid valve, and then a J-tipped guide wire should be advanced into the pulmonary artery. The catheter is then advanced into the pulmonary artery over the guide wire. When the catheter tip is advanced from the cephalic portion of the right atrium, occasionally it will pass through a patent foramen ovale or an atrial septal defect into the left atrium and even into the pulmonary vein. In such a situation, the injection of contrast medium into the pulmonary vein will fill the left atrium without filling the pulmonary vasculature. When this occurs, the catheter tip is withdrawn to the right atrium and re-advanced from the caudal portion of the right atrium into the right ventricle and then into the pulmonary artery. Occasionally, the catheter tip will enter the coronary sinus without entering the right ventricle. When this occurs, the tip of the catheter will not advance. The catheter tip should then be withdrawn into the right atrium, and re-advanced into the right ventricle.

Once the catheter is positioned in the left pulmonary artery, it can be connected to a pressure transducer and the pulmonary artery pressure can be measured. After the pressure is obtained, selective pulmonary angiography is performed in two oblique projections. The catheter is then turned toward the right pulmonary artery while retracting it to the main pulmonary artery. If this maneuver fails to reposition the catheter in the right pulmonary artery, a standard guide wire or a tip-deflecting wire technique can be used to turn the catheter tip from the left pulmonary artery to the right pulmonary artery.

Catheter Exchange

The curved pigtail catheter can be easily advanced into the right or left descending pulmonary artery for selective and superselective angiograms of the right middle lobe, left
lingular segment, and lower lobes. When superselective catheterization of the segmental or subsegmental pulmonary arteries is required for evaluation of the peripheral pulmonary vasculature or to perform therapeutic embolization, the catheter exchange method is used to exchange the pigtail catheter for a sheath, a guiding catheter, or an end-hole selective catheter. A long guide wire (at least 180 cm) is introduced into the catheter and gently advanced through the pigtail as far into the pulmonary artery branch as possible. Then, while the guide wire is held stationary, the catheter is slowly withdrawn over the guide wire until it exits from the puncture site. A new catheter or introducer is then advanced over the guide wire. When the catheter has been advanced the desired distance, the guide wire can be removed and the catheter tip is further manipulated into the desired branch using a steerable guide wire such as the angle tipped Glide wire (Terumo Interventional Systems, Somerset, NJ).

Contrast Agents and Injection Rates

Low-osmolar contrast agents with an iodine concentration of at least 300 mg/mL are recommended for pulmonary angiography. The achieved reduction in side effects such as cough reflex, flushing, hypotension, and nausea with these nonionic agents promotes motion-free image acquisition. In vitro activation of platelets has been reported with the low-osmolar agents iohexol (Omnipaque, GE Healthcare Inc.) and iopamidol (Isovue, Bracco Diagnostics). One study found increased plasma levels of plasminogen activator inhibitor-1 in patients following pulmonary angiography with iohexol and increased thrombin–antithrombin III complexes with iohexol and ioxaglate (Hexabrix, Guerbet LLL). Newer isosmolar nonionic agents have not been tested in patients undergoing pulmonary angiography, but the isosmolar nonionic dimer iodixanol (Visipaque, GE Healthcare) appears to reduce major adverse cardiovascular events, as compared with low-osmolar ionic contrast agents, in patients with acute coronary syndromes who undergo percutaneous coronary intervention, and also to reduce contrast-induced nephropathy, as compared with iohexol.

The contrast injection rate is determined by the rate of blood flow in the selected vessel, pulmonary artery pressure, imaging modes, and the catheter used for angiography. Contrast medium should be injected at a rate that approximates as closely as possible the rate of blood flow in the artery being opacified. Injecting too slowly results in poor opacification of the pulmonary arterial trees. Too rapid an injection, on the other hand, results in reflux of the contrast medium into the contralateral pulmonary artery. The left and right pulmonary arteries have a blood flow of 25 cc per second in most patients. The injection rates are adjusted according to the flow rate estimated at test injections and the disease being investigated. The usual injection rates in patients with normal pulmonary artery pressure are 25 cc per second for a total volume of 50 cc. In general, the rate of injection for superselective pulmonary angiograms should be slightly more than the expected blood flow of the artery being injected to, to ensure complete filling of the vascular bed. Depending on the size of the pulmonary artery being injected to, the injection rate for superselective angiograms is 5 to 10 cc per second for a total volume of 15 to 20 cc (Table 18.2). In the presence of pulmonary hypertension, the amount of contrast medium should be reduced to minimize the adverse hemodynamic impact of a full contrast injection under such circumstances. The rate of injection in this condition should be reduced to 15 to 20 cc per second for a total volume of 30 to 40 cc. Even though the rate of injection is reduced, the total volume of contrast should be at least 30 cc to ensure complete filling of the central pulmonary arteries for the evaluation of pulmonary thromboembolic disease. With the use of low-osmolar contrast agents, tailored pulmonary angiography with lower flow rates and more distal injections has proved to be safe even in the presence of severe pulmonary hypertension. Contrast injection should be performed using an automated injector system at a pressure of at least 600 psi (42 kg/cm²). For balloon occlusion angiography of segmental vessels, a hand injection of 5 to 10 mL is used.

Imaging Modes

Digital techniques have virtually replaced conventional cut films. Hagspiel et al. found digital subtraction angiography

### Table 18.2 Injection Factors for Pulmonary Angiography

<table>
<thead>
<tr>
<th>Artery</th>
<th>Injection Rate (cc/sec)</th>
<th>Quantity of Contrast Medium (cc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right/left pulmonary artery</td>
<td>25</td>
<td>50</td>
</tr>
<tr>
<td>Right/left pulmonary artery (pulmonary hypertension)</td>
<td>15–20</td>
<td>30–40</td>
</tr>
<tr>
<td>Lobar pulmonary arteries</td>
<td>15–20</td>
<td>30–40</td>
</tr>
<tr>
<td>Segmental pulmonary arteries</td>
<td>5–10</td>
<td>15–20</td>
</tr>
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</table>
(DSA) with selective pulmonary arterial injections equivalent to conventional cut-film angiography in diagnostic performance and image quality. In 80 patients, DSA allowed more accurate detection of pulmonary emboli with better interobserver agreement than allowed by conventional cut film. In 54 patients with suspected PE but a negative digital angiogram, none suffered a thromboembolic event after a mean of 12 months.

The major advantage of DSA over cut film is that high-resolution images can be obtained with lesser amount of contrast agent. This is particularly important for evaluation of patients with pulmonary hypertension and renal insufficiency. Other advantages include rapid image acquisition and flexible display format. Images can be viewed individually or in cine format on the monitor, in either the subtracted or the un subtracted mode. Masks can be selected image by image and their pixels shifted to best match the anatomy. In addition, DSA may even allow satisfactory opacification of pulmonary arteries when contrast is injected into the superior vena cava or right atrium. The major disadvantage of DSA is that it requires motionless image acquisition. This may be especially difficult in evaluation of patients with severe cardiopulmonary symptoms, who may not be able to hold their breath during image acquisition. Mask shifting helps minimize cardiac motion artifacts but is less helpful in reducing respiratory motion artifacts. However, although serial cut film still offers higher spatial resolution than that achieved by cineradiography or DSA, there is no evidence that DSA is inferior to serial cut film in the detection of subsegmental PE.

Filming rates are based on the normal transit rate of contrast through the lung. Injected contrast reaches the capillaries in 2 to 3 seconds while the left atrium fills in 4 to 6 seconds. With cut film, a total of 12 images are usually obtained: 3 images per second in 3 seconds, and 1 image per second for an additional 6 seconds. With digital systems, a full second of mask images are obtained before injection (about 1 second for an additional 6 seconds). Higher rates may be used in uncooperative patients, in large individuals, or in situations where high flow is expected (for example in PAVMs). Slower acquisition rates are recommended for patients with low cardiac output.

A minimum of two radiographic series are required for each lung to exclude pulmonary embolism. The two standard views are the frontal and the 45° ipsilateral posterior oblique. These views have been validated for pulmonary embolism in a large clinical trial. If it is available, biplane filming is preferred over monoplane filming to reduce the total amount of contrast. Although the lateral is the true orthogonal view to the frontal projection, it is not desirable for most cases of pulmonary angiography, since even selective right or left injections frequently cause reflux into the opposite lung, which may confuse interpretation. If a sufficient amount of contrast (40 to 50 mL) is injected and prolonged filming is carried out, the lateral and oblique views may also be used to evaluate left ventricular size and function as well as the anatomy of the ascending aorta or proximal coronary arteries.

At the author's institution, pulmonary angiograms are obtained with contrast injection in the right or left pulmonary artery. Left pulmonary angiography is performed in 50° right anterior oblique (RAO) and 40° LAO views. Right pulmonary angiography is performed in 30° RAO and 40° LAO views (Figure 18.5). The DSA matrix should be the highest, at 1,024 × 1,024, whenever possible. For the field size, maximum magnification that allows visualization of the entire lung on both views should be used for obtaining the best images.

Complications and Contraindications

Major complications can be defined as those that are life-threatening or require intervention or intensive monitoring. Minor complications can be defined as those that regress spontaneously without long-term morbidity, even if patients require prolonged monitoring. The complications observed during the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study were tabulated according to these definitions (Table 18.3). It is noteworthy that the study involved injecting high-osmolar ionic contrast through pigtail catheters with images recorded on cut films.

Three of the five deaths reported by Stein and colleagues may have occurred owing to severe baseline cardiopulmonary compromise rather than catheterization or angiography. In one study, three deaths occurred in the presence of a right ventricular end-diastolic pressure of >20 mmHg.

Unlike in previous large series studies, no myocardial perforations occurred in PIOPED, which can be attributed to the exclusive use of pigtail type rather than straight catheters, such as the Eppendorf. Renal failure and insufficiency occurred in the PIOPED group in 0.3% and 1.0%, respectively, more often in elderly patients.

There are no absolute contraindications to pulmonary angiography, although risk clearly increases with severe pulmonary hypertension, allergy to iodine contrast, renal insufficiency, left bundle branch block, or severe congestive heart failure. With the use of nonionic, low-osmolar contrast and prophylactic oxygen administration, the risks in these conditions may be reduced.

In patients with a history of anaphylactoid reaction to intravenous contrast, the author advises the use of preprocedural corticosteroids and nonionic low-osmolar contrast agents.

PULMONARY EMBOLISM

The annual incidence of venous thromboembolism—DVT and pulmonary embolism (PE)—exceeds 1 per 1,000. The main cause of early death is acute right ventricular failure, although most deaths beyond 30 days are owing to underlying disease (e.g., cancer, congestive heart failure, or chronic lung disease). The overall 3-month mortality is approximately 15%.
Diagnosis

PE may not be suspected, because it can mimic a wide spectrum of medical diseases. Common differential diagnoses thus include chronic lung disease, congestive heart failure, pneumonia, acute myocardial infarction, aortic dissection, pericarditis, cancer, pneumothorax, musculoskeletal pain, and anxiety states. The most common symptoms include dyspnea, chest pain, cough, and hemoptysis. Pleuritic pain is more often present in patients with segmental PE. The presence of syncope and severe painless dyspnea usually indicates a hemodynamically significant PE, particularly when accompanied by tachycardia and tachypnea. Clinical signs of right ventricular dysfunction may include distended neck veins, an accentuated pulmonic component of the second heart sound, or a right ventricular heave. Occasionally, the murmur of tricuspid regurgitation may be present.

Assessment of the clinical pretest probability helps improve the diagnostic accuracy of any test in patients with suspected PE. Wells and coworkers32 have prospectively tested a bedside assessment to estimate this probability based on the following: signs or symptoms of DVT (3 score points); no alternative diagnosis is more likely than PE (3 score points); heart rate of >100 beats per minute (1.5 score points); immobilization or surgery within 4 weeks prior to the assessment (1.5 score points); a history of DVT or PE (1.5 score points); hemoptysis (1.0 score points); and cancer (1.0 score point). A score of \( \geq 4.0 \) using this schema makes the presence of PE unlikely.
Table 18.3 Complications of Pulmonary Angiography in the PIOPED Study (N = 1,111)

<table>
<thead>
<tr>
<th>Major</th>
<th></th>
</tr>
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<tbody>
<tr>
<td>Death</td>
<td>5 (0.5%)</td>
</tr>
<tr>
<td>CPR, ventilation</td>
<td>4 (0.4%)</td>
</tr>
<tr>
<td>Renal failure (dialysis)</td>
<td>3 (0.3%)</td>
</tr>
<tr>
<td>Hematoma (2-unit transfusion)</td>
<td>2 (0.2%)</td>
</tr>
<tr>
<td>Total</td>
<td>14 (1.3%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Minor</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory distress</td>
<td>4 (0.4%)</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>10 (0.9%)</td>
</tr>
<tr>
<td>Angina</td>
<td>2 (0.2%)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>2 (0.2%)</td>
</tr>
<tr>
<td>Pulmonary congestion</td>
<td>4 (0.4%)</td>
</tr>
<tr>
<td>Urticaria, itching, or periorbital edema</td>
<td>16 (1.4%)</td>
</tr>
<tr>
<td>Hematoma</td>
<td>9 (0.81%)</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>6 (0.54%)</td>
</tr>
<tr>
<td>Subintimal contrast (dissection)</td>
<td>4 (0.4%)</td>
</tr>
<tr>
<td>Narcotic overdose</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Right bundle branch block</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Total</td>
<td>60 (5.4%)</td>
</tr>
</tbody>
</table>

Nonimaging Tests

Electrocardiography

The ECG will exclude acute ST-segment elevation myocardial infarction and may help establish the diagnosis of PE in the presence of a classic S1Q3T3 pattern, incomplete or complete right bundle branch block, right axis deviation, or clockwise rotation in the precordial leads. The Qr pattern in V1 and inverted T waves in the anterior precordial leads indicate hemodynamically significant PE with an increased risk for adverse clinical events.33

D-Dimer

D-dimer is a product of specific proteolytic degradation of cross-linked fibrin via endogenous fibrinolysis. In a pulmonary angiography study (performed with quantitative enzyme-linked immunosorbent assay [ELISA]) a plasma D-dimer of <500 ng/m had a >90% negative predictive value for excluding PE.34 In another study, the negative predictive value was 99.6%, whereas in an overview the ELISA D-dimer test had a sensitivity of 94%, suggesting that fewer imaging studies may be required in patients with negative D-dimer measurements.35 The specificity of the D-dimer test, however, was only 43% in outpatients with suspected PE.36 Owing to this very low specificity, the D-dimer measurement is not very useful in hospitalized patients with suspected PE, being best suited for the emergency department or office setting. A prospective study has demonstrated that the use of a screening D-dimer measurement of ≤1.0 μg/mL can preclude pulmonary CT angiography in patients suspected of having acute PE.37

Arterial Blood Gas Analysis

Arterial blood gases38 and alveolar–arterial oxygen gradients39 are not helpful in differentiating patients with confirmed or excluded PE by pulmonary angiography. Therefore, arterial blood gases should not be used as a screening test.

Noninvasive Imaging Tests

Ventilation Perfusion Scanning

Lung scanning has been the principal imaging test for suspected PE. However, an increasing number of hospitals obtain lung scans only in patients with clinical situations such as allergy to radiographic contrast agents, severe renal insufficiency, or pregnancy. Normal and high-probability lung scans are themselves diagnostic. However, most patients with suspected PE have ventilation perfusion scan results that are nondiagnostic (low or intermediate or indeterminate probability scans). The diagnostic accuracy may be improved when scans are interpreted in conjunction with clinical pretest probability, but additional imaging studies are usually required. Ventilation/perfusion SPECT (single photon emission computed tomography) may be employed in the following clinical situations, including in patients with normal chest X-Ray: renal dysfunction, contrast allergy, pregnancy, all cases of follow-up, patients with long life expectancy, and cases with disagreement between clinical and imaging findings and suboptimal imaging findings.41

Contrast-Enhanced Chest Computed Tomography

Chest CT has virtually replaced lung scanning as the initial imaging test for PE.42 The latest generation of multidetector CT scanners (Figure 18.6) permits image acquisition of the entire chest with 1 mm resolution and a single breath hold of <10 seconds, enabling accurate imaging of the complete pulmonary vasculature. At the same time, the deep veins can be examined for proximal DVT by obtaining additional images from the pelvic and femoropopliteal regions. Chest CT also helps detect alternative diagnoses, such as aortic dissection, pneumonia, or pericardial tamponade. As compared with first-generation single-slice scanners, the sensitivity of multishow detector CT increases from about 70% to >90%.43 The
ongoing PIOPED II study compares various imaging strategies, including lung scanning, venous ultrasound, digital subtraction pulmonary angiography, and contrast venography, against multirow detector chest CT.45

In patients with confirmed PE, chest CT may also provide prognostic information in the presence of right ventricular enlargement if identified in a reconstructed CT four-chamber view. In a study of 63 patients with PE, a ratio of right to left ventricular dimension of >0.9 identified patients at risk for adverse clinical events.46

Magnetic Resonance Angiography
MR imaging avoids ionizing radiation and iodinated contrast agents, and also allows assessment of left and right ventricular function and size, potentially important for risk stratification. Under specialized study circumstances, MR may be nearly as sensitive and as specific as pulmonary angiography for PE.47 Limitations include restricted spatial resolution for evaluation of peripheral pulmonary arteries, limited round-the-clock availability, prolonged examination time, and difficulties in monitoring severely ill patients in the scanner.

A multicenter prospective study (PIOPED III) evaluated the accuracy of magnetic resonance pulmonary angiography and MR venography in diagnosing pulmonary embolism.48 It was found that MR angiography was technically inadequate in 25% of patients (range, 11% to 52%). However, technically adequate MR angiography and venography had a sensitivity of 92% with a specificity of 96%.

Venous Ultrasonography
Compression ultrasound study of the deep veins is noninvasive and accurate in diagnosing symptomatic proximal DVT. If it confirms DVT in patients with symptoms suggestive of PE, the diagnosis can be made without further workup. However, more than half of the PE patients have no ultrasound evidence of DVT because the entire clot has already embolized to the lungs. Therefore, patients suspected of PE who have no evidence of DVT still require further investigation for PE.

Contrast Venography
Contrast venography is highly accurate for proximal and distal DVT but may provoke phlebitis (uncommon with use of nonionic contrast media) or hypersensitivity reactions. Although contrast venography is the gold standard for DVT diagnosis, it is rarely performed in patients with suspected
PE. Venography is required for catheter-directed thrombolysis, catheter embolectomy, percutaneous angioplasty with or without stent placement, and insertion of an inferior vena cava (IVC) filter. Inferior vena cavography with iodinated contrast medium or medical grade carbon dioxide (30 to 40 cc CO₂) is performed to evaluate patency of the IVC, and exclude cava duplication or renal vein anomaly prior to filter placement. CO₂ has no nephrotoxicity or allergic reaction and is safe in both the arterial (below the diaphragm) and the venous circulations if air contamination can be prevented.⁴⁹

In critically ill or pregnant patients, and in patients with renal failure, IVC filters such as the Günther Tulip Filter (Cook Medical Inc., Bloomington, IN) can be accurately deployed in the infrarenal IVC, at the bedside, under intravascular ultrasound (IVUS) guidance. This can eliminate the need for contrast medium, fluoroscopy, and transport of critically ill patients. The procedure employed at the author’s institution involves accessing the right femoral vein using the micropuncture technique under ultrasound guidance, introduction of the introducer sheath over a guide wire, and advancement of the same over the J-tipped guide wire. After completing IVUS examination of the entire IVC from the right atrium to the iliac vein and identifying the right atrium, hepatic and renal veins, aorta, and IVC bifurcation, the sheath and IVUS transducer are positioned just below the lowest renal vein, and the guide wire and IVUS catheter are withdrawn. The preloaded filter introducer is then advanced to the distal end of the introducer sheath, and the filter is exposed into the IVC by retracting the sheath toward the operator. The filter is then released into the IVC. The IVUS catheter is then reintroduced to confirm the filter position.

Echocardiography

Transthoracic echocardiography has emerged as an important tool for risk stratification of patients with acute PE. The presence of right ventricular dysfunction on the echocardiogram is an independent predictor of early death,³¹ but echocardiography cannot be recommended to diagnose or exclude PE routinely because about half of the patients with confirmed PE have normal echocardiogram.⁵⁰ However, bedside echocardiography facilitates discrimination of patients suspected of having either PE or cardiogenic shock. Potentially life-saving therapy, including thrombolysis, catheter intervention, or surgical embolectomy, can be initiated based on echocardiographic evidence of right ventricular dysfunction without necessarily performing time-consuming PE imaging tests.⁵³ Transesophageal echocardiography helps visualize clots within the left and right main pulmonary arteries and is an alternative to the transthoracic approach for patients with poor image quality.⁵²

Overall Diagnostic Strategy

The initial assessment includes clinical pretest probability, physical examination, and an ECG. A plasma ELISA D-dimer should be obtained in all outpatients (Figure 18.7). If the D-dimer is normal, PE is essentially excluded.⁵³ If D-dimer levels are elevated, the author recommends a chest CT as the initial imaging test (Figure 18.7). In patients with conditions such as renal insufficiency, pregnancy, or allergy to contrast agents, ventilation perfusion scanning may be used instead of chest CT. If the clinical suspicion remains high after a negative or indeterminate chest CT or lung scan, the author recommends obtaining a venous ultrasound study. If the ultrasound study is negative or equivocal, the author recommends proceeding to pulmonary angiography. This strategy is safe and only rarely requires pulmonary angiography.⁵³

Interpretation and Validity of Pulmonary Angiograms

Large cut-film angiographic studies have validated the angiographic criteria for acute PE.²⁷,⁵⁴,⁵⁵ Primary angiographic criteria for PE are persistent central or marginal intraluminal radiolucenty and the trailing edge of an intraluminal radiolucency obstructive to contrast flow (Figure 18.8). Complete obstruction showing abrupt vessel cutoff with a concave border of the contrast column is also considered primary evidence of acute PE (Figure 18.9). These criteria have also been validated for DSA (Figure 18.10).³¹,⁵⁶ Secondary signs include oligemic or avascular regions, focal prolonged arterial phase, abruptly tapered peripheral vessels, and focal diminished venous flow. The latter signs have not been validated for PE and should be interpreted with caution.

Of the PIOPED population,²⁷ 35% had positive and 61% had negative pulmonary angiograms for PE. Angiography was nondiagnostic in 3% of the patients and was not
completed in 1% because of complications. Two angiographic readers agreed that PE was present or could not be diagnosed with certainty in 92% of cases. The readers agreed that PE was absent or could not be excluded with certainty in 82% of cases. Interobserver agreement for cut-film pulmonary angiography decreases with diminishing pulmonary artery caliber. It was 98% for lobar PE, 90% for segmental PE, but only 66% for subsegmental PE. Subsegmental PE was diagnosed in 6% of patients. In another angiographic study, the proportion of patients with subsegmental PE was 30%.

Interobserver agreement of DSA appears to be superior to that of cut-film angiography. In 140 patients with suspected PE, the kappa values ranged between 0.28 and 0.59 for cut-film angiography and between 0.66 and 0.89 for DSA.

Because pulmonary angiography is the diagnostic gold standard for PE, sensitivity, specificity, and predictive values cannot be directly calculated. The sensitivity and specificity are estimated as 98% and 95% to 98%, respectively. The validity of pulmonary angiography was assessed with follow-up studies of patients with negative angiograms in whom anticoagulation was withheld. In five studies, 840 patients had at least 3 months of follow-up. Recurrent venous thromboembolism was documented in 1.9% of these patients. Therefore, it is almost always safe to withhold anticoagulants in patients with suspected PE and a negative pulmonary angiogram.

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**Figure 18.9**

A. Right lower lobe balloon occlusion pulmonary cineangiogram demonstrates multiple vessels “cut off” (arrows). B. Balloon deflation facilitated distal contrast distribution, with a visible trailing edge of a thrombus (arrows).
Hemodynamic Characteristics

Many PE patients without cardiopulmonary disease have normal hemodynamics. Systolic right ventricular pressure rarely exceeds 50 mmHg in patients without pre-existing cardiopulmonary disease (Figures 18.11, 18.12, and 18.13). Instead, an acute increase in right ventricular afterload with a systolic pressure above 50 to 60 mmHg will result in acute right ventricular dilatation and systolic failure. Patients with recurrent PE may tolerate higher systolic pressure values prior to the development of right ventricular failure. As a result of right ventricular diastolic dysfunction, the right ventricular diastolic pressure approximates pulmonary artery diastolic pressure and typically shows a prominent dip and rapid rise. Right atrial pressure is elevated, with a prominent A wave and a steep x-descent. As right ventricular dilatation and dysfunction evolve, reduced right ventricular output impairs left ventricular filling. Left ventricular distensibility may be further compromised owing to a shift of the interventricular septum toward the left ventricle. Left ventricular cardiac output is decreased, with the systemic arterial waveform showing a sharp upstroke owing to compensatory increase in systemic vascular resistance.

In PE patients, increased myocardial shear stress can be quantified with brain natriuretic peptide levels; elevated troponin levels indicate myocardial ischemia and microinfarction. Myocardial ischemia and microinfarction are probably caused by increased oxygen demand of the failing right ventricle and reduced coronary perfusion as a consequence of decreased systemic cardiac output.
Endovascular Therapy for Acute Pulmonary Embolism

In patients with massive PE, catheter intervention with or without embolectomy is an alternative to systemic thrombolysis or surgical embolectomy (Figures 18.14 and 18.15). If the bleeding risk is not increased, catheter intervention may be combined with local or systemic thrombolysis. Most of the devices appear to be effective, safe, and potentially life-saving in the presence of large fresh clots (Table 18.4), but none has been investigated in a controlled clinical trial. The Greenfield transvenous embolectomy catheter has been available the longest, but it has limited efficacy in the presence of chronic clots and does not address the risk of re-embolization. This device is no longer available.

The endovascular technique proceeds as follows: the right femoral vein or right internal jugular vein (if the femoral vein approach is not available due to DVT) is accessed using the micropuncture technique under ultrasound guidance. A 7F sheath is inserted in the femoral vein, and a 7F APC or MONT-1 catheter is advanced into the right atrium and manipulated through the tricuspid valve and right ventricle into the pulmonary artery. Contrast medium is injected under fluoroscopy to assess pulmonary artery blood flow and the severity of pulmonary emboli. Right and left pulmonary arteriograms are then obtained at reduced contrast injection rates and quantities. The pulmonary artery with the largest central embolus is cannulated, and a 7F-long sheath is placed over a heavy-duty guide wire or an Amplatz superstiff guide wire. Catheter-directed mechanical thrombofragmentation and aspiration with intrathrombic injection of 10 mg tPA is performed to debulk central clot and achieve restoration of pulmonary artery blood flow. Any mechanical thrombectomy device can be used to remove clots. This initial intervention may be followed by catheter-directed thrombolysis with central infusion of tPA at 20 mg per hour for 2 to 7 hours. An inferior vena cava filter is put in place at the end of the intervention.

OTHER INDICATIONS FOR PULMONARY ANGIOGRAPHY

Pulmonary Hypertension

Chronic Thromboembolic Pulmonary Hypertension

Most patients with chronic thromboembolic pulmonary hypertension have neither documented history of DVT or PE nor any identifiable coagulopathy. Dyspnea with exertion and fatigue are the most common complaints. The nonspecific nature of these findings may substantially delay diagnosis. The chest radiograph usually reveals right ventricular enlargement and enlarged main pulmonary arteries. ECG changes are consistent with pulmonary hypertension. Arterial blood gases often reveal resting hypoxemia with a widened A-a gradient. Echocardiography documents pulmonary hypertension and right ventricular dilation and dysfunction.
**Primary Pulmonary Hypertension**

Primary pulmonary hypertension (PPH) is a rare disease of unknown etiology, distinguished by characteristic arterial, capillary, and venular lesions. The term “primary” is used in the absence of congenital or acquired pulmonary, cardiac, or collagen vascular disease. There is a genetic predisposition in about 10% of patients. The human herpes virus 8 may play a role in the pathogenesis. If this condition is left untreated, pulmonary artery pressure and pulmonary vascular resistance will increase steadily until the right ventricle fails.

Echocardiography usually first documents the presence of pulmonary hypertension in patients with unexplained dyspnea or fatigue. Chest CT helps exclude secondary forms of pulmonary hypertension. Right heart catheterization is the gold standard for establishing the presence of pulmonary hypertension and is particularly important in excluding pulmonary venous hypertension in the presence of a normal left ventricular filling pressure.

Angiography reveals nonspecific dilatation of the proximal pulmonary arteries with smooth, rapid tapering of distal vessels (Figure 18.17). A distal corkscrew appearance of the arteries may also be seen.

Acute drug challenge with a short-acting, titratable vasodilator during continuous monitoring of the hemodynamic profile is recommended in patients in whom calcium channel blockers are considered. Patients in whom a reduction in pulmonary vascular resistance of ≥20% is associated with a decrease in mean pulmonary artery pressure of ≥20% are considered responders. Symptomatic intolerance includes a decrease of >40% in mean systemic arterial pressure, an increase of >40% in heart rate, or signs and symptoms leading to discontinuation of drug. Acute drug challenge is also recommended in patients with end-stage congestive heart failure to prove that high pulmonary vascular resistance is not fixed and to ensure eligibility for heart transplantation.
Catheter fragmentation in combination with a continuous systemic infusion of 100 mg alteplase over 2 hours in a 64-year-old female with massive pulmonary embolism and cardiogenic shock. A. Frontal view demonstrating subtotal filling defects in both main pulmonary arteries. B. Catheter thrombus fragmentation in the left pulmonary artery (pars superior) using a pigtail rotational catheter. C. Following catheter fragmentation, improved flow in the left upper lobe pulmonary arteries (arrow) was accompanied by a prompt increase in systemic arterial pressure from 70 mmHg to 95 mmHg. D. Lateral view demonstrating a significant proximal stenosis of the right coronary artery approximately 7 seconds after nonselective injection of 40 mL contrast into the main pulmonary artery (arrow).

However, acute drug challenge is optional in PPH patients in whom bosentan is being considered. An increasing number of vasodilator drugs for chronic use are available to treat PPH (see Chapter 42).

Intravenous epoprostenol (Flolan) is most commonly used to test acute vasodilator response (Table 18.6). The dose is up-titrated until systemic effects (headache, flushing, or nausea) occur. Caution is warranted in patients with coexisting congestive heart failure.

Adenosine is a potent pulmonary vasodilator and has a half-life of <5 seconds. Adverse effects include dyspnea and chest discomfort. It should not be administered in patients on theophylline or with acute asthma.

In contrast to epoprostenol or adenosine, nitric oxide has no inotropic properties and does not increase cardiac output. It is inhaled via a face mask.

**Rare Indications**

**Pulmonary Arteriovenous Malformation**

This entity is probably the result of an embryologic defect in the terminal capillary loop. Polycythemia and reduced arterial PO₂ are manifestations of an extracardiac right-to-left shunt. Most patients with PAVMs are asymptomatic, although dyspnea, cyanosis, digital clubbing, and hemoptysis may be present. Paradoxical emboli via PAVMs can result in cerebrovascular accident or abscess. PAVMs are classified into two types: simple and complex PVA. Simple PAVMs are usually a complex branching mass, supplied by one to three subsegmental arteries, all arising from the same segmental artery. Complex PAVMs are supplied by two or more different segmental arteries. Complex PAVMs are more frequent in the right middle lobe or lingula.
The walls of PAVMs are quite thin. Multiple PAVMs are present in one-third of cases. From 40% to 65% of PAVMs are associated with hereditary hemorrhagic telangiectasia (the Rendu-Osler-Weber syndrome). PAVMs are rarely seen with Fanconi syndrome (pancytopenia, radial deformities, and brown skin pigmentation).

Screening for PAVMs can be done noninvasively with contrast echocardiography. Multidetector CT helps establish the diagnosis (Figure 18.18). When intervention is planned, selective pulmonary angiography is necessary, with frontal and both oblique views of each lung.

PAVMs can be percutaneously embolized with coils such as the Nester coils (Cook Medical Inc., Bloomington, IN) or Amplatzer Vascular Plugs (AVP, St. Jude Medical, Inc., St. Paul, MN) (Figure 18.19). With the potential for direct systemic emboli, extreme caution must be exercised and angiographic procedure must be meticulously followed to avoid air embolism, catheter thrombosis, or embolism of occlusion devices. The coils and AVP should be oversized by 30% to 50% of the diameter of the feeding artery to prevent migration of the occluding devices. Follow-up CT scanning with contrast should be performed 1 year after embolization or when the initial symptoms recur. When the previously embolized arteries have recanalized, repeat embolization should be performed with coils or AVP.

Acquired pulmonary arteriovenous shunts can be secondary to trauma, infection, or hepatogenic angiodysplasia. Infection-related shunts are seen in bronchiectasis, invasive aspergillosis, tuberculosis, and schistosomiasis.

Pulmonary Artery or Vein Stenosis

An increasing number of patients with repaired congenital heart disease now survive into adulthood and may present with pulmonary vascular stenoses and occlusions. Most pulmonary arterial and venous stenoses occur in association
Table 18.5

<table>
<thead>
<tr>
<th>Finding</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pouching</td>
<td>Contrast filling concave pouches in organized thrombus, with delayed</td>
</tr>
<tr>
<td></td>
<td>opacification or obstruction of the distal artery</td>
</tr>
<tr>
<td>Webs/bands</td>
<td>Persistent thin or thick linear radiolucencies in lobar or segmental</td>
</tr>
<tr>
<td></td>
<td>vessels causing stenosis with or without poststenotic dilatation</td>
</tr>
<tr>
<td>Luminal</td>
<td>Scalloped arterial margins</td>
</tr>
<tr>
<td>irregularity</td>
<td></td>
</tr>
<tr>
<td>Vessel tapering</td>
<td>Abrupt narrowing of major pulmonary arteries</td>
</tr>
<tr>
<td>Vessel</td>
<td>Obstruction of lobar arteries,</td>
</tr>
<tr>
<td>obstruction</td>
<td>usually at their origin</td>
</tr>
</tbody>
</table>


Figure 18.16

Chronic pulmonary thromboembolism. Frontal view of right pulmonary angiogram in a 42-year-old female still dyspneic after an acute pulmonary embolus was documented 6 months earlier and treated. The proximal pulmonary arteries are dilated. The distal vessels taper rapidly and are irregular (arrows). Eccentric stenoses are present (arrowheads), as are intraluminal webs (open arrow).

Figure 18.17

Primary pulmonary hypertension. A 45° right anterior oblique view of the left pulmonary angiogram of a 30-year-old male with primary pulmonary hypertension. The rapid tapering of segmental vessels may be noted.

with congenital cardiac disease such as tetralogy of Fallot, truncus arteriosus, pulmonary valvular stenosis, patent ductus arteriosus, aortic stenosis, ventricular septal defects, or transposition of the great vessels. Pulmonary blood flow is often maintained by surgical shunts or systemic-to-pulmonary collaterals. Isolated stenoses may present following pulmonary artery banding after systemic to pulmonary artery shunts such as Blalock-Taussig, Waterston-Cooley, or Glenn anastomosis. In patients with congenital heart disease, pulmonary angiography may be required to evaluate the indication for reoperation, including assessment of the size of pulmonary vessels and collaterals, and documentation of intracardiac or extracardiac shunt patency.

Stenosis may also be secondary to rubella, chronic infections (such as histoplasmosis), or infestations (such as schistosomiasis). Stenoses are associated with idiopathic hypercalcemia. Lung transplant pulmonary arterial stenoses
Dose Regimens: Acute Vasodilator Testing

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Dose</th>
<th>Dose Increments</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous epoprostenol</td>
<td>2 ng/kg/min</td>
<td>2 ng/kg/min every 15 min</td>
<td>16 ng/kg/min</td>
</tr>
<tr>
<td>Intravenous adenosine</td>
<td>50 μg/kg/min</td>
<td>50 μg/kg/min every 15 min</td>
<td>350 μg/kg/min</td>
</tr>
<tr>
<td>Inhaled nitric oxide</td>
<td>20 ppm</td>
<td>20 ppm every h</td>
<td>80 ppm</td>
</tr>
</tbody>
</table>

are not common and carry a poor prognosis. Congenital single or multiple stenoses may be present without cardiac anomalies (Figure 18.20). Angioplasty and stent placement for treatment of pulmonary artery stenoses have been used primarily for treatment of congenital stenoses. Pressure recordings are helpful in establishing hemodynamic significance of pulmonary branch stenoses.

Pulmonary vein stenosis is increasingly seen in patients who undergo radiofrequency ablation of the pulmonary venous ostia for treatment of atrial fibrillation. Balloon angioplasty with or without stent placement has been used successfully to treat symptomatic patients.

Pulmonary Artery Aneurysms

Pulmonary artery aneurysms may appear as a perihilar mass on chest radiographs. Spiral chest CT or MR is useful to confirm the diagnosis. Most aneurysms occur centrally, usually secondary to pulmonary hypertension or following surgical correction of congenital heart disease. Degenerative pulmonary aneurysms can be seen in the Marfan syndrome. Tuberculosis results in pulmonary artery aneurysms known as the Rasmussen aneurysms. Other infectious causes of pulmonary artery aneurysms include syphilis and septic emboli. Rupture of pulmonary artery aneurysms may cause fatal hemorrhage. Multiple pulmonary artery aneurysms may be seen in the Behçet disease and are associated with poor prognosis. Peripheral pulmonary arterial pseudoaneurysms may be caused by blunt or penetrating trauma (Figure 18.21), primary or metastatic lung neoplasm (Figure 18.22), bronchiectasis, abscess, and acute or chronic inflammatory lung disease. Pulmonary artery pseudoaneurysms must be excluded using multidetector CT pulmonary angiography in patients with recurrent bleeding following embolization of bronchial and nonbronchial systemic collateral arteries. Technical and clinical success has been reported for percutaneous embolization with coils and covered stents such as iCAST (Atrium Med. Corp, Hudson, NH; Advanta V12-nonUS). If bleeding continues after selective embolization of pulmonary artery pseudoaneurysm, embolization of the bronchial and nonbronchial systemic arteries supplying pulmonary arteries is indicated.
Pulmonary arteriovenous malformations treated with percutaneous transcatheter embolization in a 47-year-old man with a family history of hereditary hemorrhagic telangiectasia. 

A. Chest computed tomography demonstrates an arteriovenous malformation with a feeding artery (longer arrow) and a draining vein (shorter arrow). 

B. Right pulmonary DSA in LAO projection (arterial phase) showing the feeding artery (3.6 mm diameter) and an aneurysm (arrow). 

C. Late arterial phase of “B” showing a draining vein (arrow). 

D. Post AVM embolization with two 6 mm diameter Amplatzer Vascular Plugs 1 showing occlusion of the feeding artery with no filling of the AVM.
**Pulmonary Artery–Bronchial Fistula**

Pulmonary artery–bronchial fistula is rare but can cause massive hemoptysis. The etiology includes lung transplantation, lobectomy, lung resection, Swan-Ganz catheterization, and expandable bronchial stent placement. In patients with massive hemoptysis, fiberoptic bronchoscopy should be performed to determine the causes so that appropriate endovascular intervention can be performed. At the same time, the airway must be protected before specific interventions can be initiated. When a pulmonary artery–bronchial fistula is suspected, a Fogarty balloon-tipped catheter should be inflated to occlude the bleeding bronchus. After percutaneous placement of a 12F sheath in the femoral vein, a pulmonary artery catheter is introduced into the pulmonary artery and a DSA is obtained. If contrast extravasation or a pseudoaneurysm is not observed, a repeat angiogram is performed after deflation of the balloon. If the contrast medium extravasates, the balloon catheter is reinflated, and a stent graft of appropriate size is put in place. The self-expanding covered stents in current use are GORE Viabahn Endoprosthesis (W.L. Gore Associate Inc., Flagstaff, AZ, available in 5 to 13 mm diameter), Fluency Plus (Bard Peripheral Vascular, Tempe, AZ, available in 6 to 10 mm diameter), and Wallgraft (Boston Scientific, Inc., Watertown, MA, available in 6 to 14 mm diameter). The balloon-expanding covered stent available for use is Atrium iCAST covered stent (Atrium, Hudson, NH, available in 5 to 10 mm diameter).

**Figure 18.20** Left interlobar pulmonary artery stenosis. Left pulmonary angiogram of isolated pulmonary arterial stenosis in an adolescent male.

**Figure 18.21** Massive hemoptysis following Swan–Ganz catheter placement in a 69-year-old man with a history of MI and placement of aortic balloon pump. **A.** Right pulmonary DSA in LAO projection showing a peripheral pulmonary artery pseudoaneurysm (arrow). **B.** Selective catheterization and contrast injection into the feeding artery of the pseudoaneurysm (arrow). **C.** After coil embolization (arrow), the feeding artery and pseudoaneurysm are occluded. Hemoptysis has ceased after the embolization.
Pulmonary Venous Aneurysm

Pulmonary venous aneurysms are rare. The condition may occur congenitally, posttraumatically or in association with mitral regurgitation.\textsuperscript{93,95} The pulmonary venous aneurysm can be demonstrated by CT scan, pulmonary DSA, or systemic arterial injection in the presence of systemic artery-pulmonary artery communication. Because no direct access to the pulmonary vein is available, percutaneous direct puncture embolization can be used. With the use of CT guidance or angiographic visualization of the aneurysm, a 22 gauge skinny needle is introduced into the pulmonary venous aneurysm, and 0.018 inch microcoils are deposited.\textsuperscript{96}

Partial Anomalous Pulmonary Vein Return

This entity may be observed in isolation or more often in combination with an atrial septal defect. Anomalous veins commonly enter the right atrium directly. Transesophageal echocardiography is accurate in delineating the cardiac abnormalities. Pulmonary angiography with delayed filming is useful for diagnosis and quantification of the left-to-right shunt. An oxygen saturation run should include a sample from the high superior vena cava to exclude the rare possibility of solitary left anomalous pulmonary vein return.\textsuperscript{97}

Meandering Pulmonary Vein

Meandering pulmonary vein is a rare congenital venous anomaly in which the pulmonary vein takes a tortuous course through the lung before entering the left atrium.\textsuperscript{98} Rarely an anomalous right pulmonary vein may drain into both the inferior vena cava and left atrium. Both pulmonary CTA and MR imaging can delineate the meandering course of this anomalous vein. Pulmonary angiography can be definitive in diagnosing such meandering vein (Figure 18.23).

Pulmonary Artery Neoplasms

Leiomyosarcoma of the pulmonary artery is a rare neoplasm. It typically is seen in the main pulmonary artery in relation to the pulmonary valve (Figure 18.24). The tumor is entirely intraluminal in half the reported cases and spreads along the lumen. Pulmonary angiography with hemodynamic assessment may be required preoperatively (Figure 18.25). It is important to evaluate the venous phase for any pulmonary venous involvement. Arterial or venous obstruction, encasement, displacement, or rarely intraluminal invasion may be identified.

Inflammation

Inflammatory diseases of the lung manifest a spectrum of findings at pulmonary arteriography. In Takayasu arteritis, the degree of pulmonary involvement correlates with the severity of brachiocephalic disease.\textsuperscript{99} Findings include stenosis, occlusion, and, rarely, dilatation of pulmonary arteries. CT angiography best demonstrates the wall thickening and enhancement of involved arteries.\textsuperscript{100} Systemic-to-pulmonary artery communications may exist, with bronchial arteries serving as collaterals to the occluded pulmonary arteries. The Behçet disease involves pulmonary arteries with a nonspecific vasculitis in about 5% of patients. Angiographic findings are predominantly aneurysms, with occlusion noted less frequently. Severe mediastinitis from histoplasmosis can compress and occlude the pulmonary arteries and veins as they traverse the mediastinum. Lymph node involvement can compress adjacent arteries and veins.

Foreign Bodies

The pulmonary arterial system is the final destination for the devices placed in the venous system in case they get fractured or embolized. Pulmonary angiography is performed in right and LAO projections to determine the size and orientation of the vessel containing the foreign body. Percutaneous retrieval using a nitinol snare (Amplatz Gooseneck Snare, ev3, Plymouth, MN) or grasping forceps has simplified the approach to foreign body removal. Balloons are well suited to engage lost stents and either to redeploy the stent in a safer location or to remove it. Right femoral vein is used for access, and a 12F to 14F sheath is introduced into the femoral vein for retrieval of foreign bodies from the pulmonary artery (Figure 18.26).
Multiple peripheral pulmonary artery aneurysms in an 11-year-old male with metastatic spindle-cell sarcoma. A. CTA showing a metastatic lung mass with pseudoaneurysm in the right lower lobe (arrow). There were multiple lung metastases with intratumoral contrast collection in the left lung (not shown). B. Venous phase of right pulmonary DSA showing a faint contrast collection (arrow) in the right lower lobe. C. Selective contrast injection showing multilobulated pseudoaneurysm (arrow). D. After coil embolization, the feeding artery and pseudoaneurysm are occluded (arrow).
Figure 18.23 Meandering pulmonary vein in a 28-year-old woman with a history of respiratory tract infection. Chest X-Ray and CT showed a right upper lobe vascular lesion suggestive of pulmonary AVM. A. Right upper lobe DSA showing normal right upper lobe arteries. B. Venous phase of “A” showing a meandering right upper lobe pulmonary vein (arrow) draining into the left atrium.

Figure 18.24 Nonselective cut-film pulmonary angiogram in a 62-year-old male with progressive dyspnea and elevated jugular venous pressure. An irregular intraluminal mass (leiomyosarcoma) is seen in the left main pulmonary artery. Severe reduction in distal flow indicates a hemodynamically significant stenosis. (Courtesy of Richard Baum, MD, Department of Radiology, Brigham and Women's Hospital, Boston, MA.)
Figure 18.25  Pulmonary artery pressure tracing from the patient presented in Figure 18.24. During catheter withdrawal from the left into the main pulmonary artery trunk, hemodynamic significance of the stenosis was confirmed. (Courtesy of Richard Baum, MD, Department of Radiology, Brigham and Women’s Hospital, Boston, MA.)

Figure 18.26  Retrieval of a catheter fragment from left pulmonary artery. The left-sided Port-A- Catheter had fractured at the entry level into the subclavian vein and the distal catheter fragment had embolized into left pulmonary artery. A. Axial CT scan showing the central end of the fractured catheter (arrow). B. Transfemoral left pulmonary DSA (LAO) showing the fractured catheter fragment in left pulmonary artery (arrow) without thrombus. C. The fractured catheter was snared by a Goose Neck Snare and removed. D. Photograph of the Goose Neck Snare (ev3, Plymouth, MN).
REFERENCES


Atherosclerosis is a systemic disease that afflicts millions of patients annually in the United States. Historically, most of the clinical focus has been on its coronary artery manifestations, given their frequency and the potentially grave consequences. Although specialists in vascular medicine and vascular surgery have long recognized that peripheral (i.e., extracardiac) arterial occlusive disease may contribute significantly to morbidity and mortality, it is only recently that invasive and interventional cardiologists have become actively involved in its diagnosis and management. To support that involvement, this chapter includes atherosclerotic manifestations in all major arterial territories. It reviews the natural history, clinical presentation, noninvasive diagnostic modalities, and angiographic techniques used in patients with peripheral vascular disease, including aneurysmal disease of the thoracic and abdominal aorta, and atherosclerotic disease of the extracranial carotid arteries, renal arteries, and lower-extremity arteries.

PERIPHERAL IMAGING TECHNIQUES

Aortography and peripheral angiography have a history as long as that of cardiac catheterization. Shortly after W. Forssmann reported the passage of a catheter from his own arm vein into his right atrium in 1929,1 dos Santos and colleagues described their experience in performing abdominal aortography by direct needle puncture.2 Seven years later, Nuvoli performed aortography via direct needle puncture of the ascending aorta.3 Fortunately, these direct access techniques have now been virtually replaced by the percutaneous and direct (see Chapters 6 and 8) techniques for catheter introduction, which form the foundation of modern angiography. In the past decade, major improvements have also been made in noninvasive imaging techniques, so that modalities such as duplex ultrasound, computed tomography (CT), and magnetic resonance angiography (MRA) are now frequently the initial investigations for diagnosis and monitoring of peripheral vascular disease. These noninvasive imaging techniques augment the traditional techniques of catheter-based angiography, facilitating detection of subclinical disease, stratification for interventional procedures, and safe and reliable methods for continued surveillance.

CROSS-SECTIONAL ARTERIAL IMAGING

Contemporary cross-sectional techniques for computed tomographic angiography (CTA) and MRA produce high-resolution and reproducibly validated angiographic displays of nearly all peripheral circulatory beds. The use of high magnetic flux imaging as well as regionally specialized algorithms optimizes imaging performance for specific anatomic and pathologic conditions. Unlike traditional catheter-based angiography, CTA and MRA produce multiplanar (orthogonal) images through embedded data acquisition; this allows angiographic evaluation using dedicated workstations to produce images in projections (e.g., axial, sagittal, and curved planar reconstructions) that cannot be obtained by catheter methods (curved planar reformation, or CPR pictures). An evaluation of cross-sectional data sets, often referred to as “raw data,” permits a unique and highly detailed perspective of both vascular and the adjacent structures, which contributes to pathologic diagnosis.4 (Figure 19.1).

While noninvasive imaging modalities avoid many of the potential complications of catheter-based angiography, some limitations still exist. CTA is associated with relatively high levels of exposure to ionizing radiation, often exceeding the dose in conventional angiography.5 Consequently, repeated
use of CTA imaging in younger patients may be associated with a mildly increased hazard of subsequent malignancy. CTA also requires the administration of iodinated contrast, which allows potential harm in patients with contrast hypersensitivity or impaired renal function. MRA avoids radiation exposure, but is a longer examination, and is thus susceptible to image degradation related to motion artifact. Respiratory and cardiac gated techniques have been applied with some promise for thoracic vascular imaging. Patients with permanently implanted ferromagnetic medical devices (e.g., pacemakers or implantable defibrillators) or shrapnel have absolute contraindications for MRA. Notably, most metallic stents are nonferromagnetic or have sufficient implant stability to not preclude MRA; however, the magnetic susceptibility artifact produced by stents obscures evaluation of the stented vascular segment (Figure 19.2). Finally, the gadolinium chelates administered intravenously in most MRA techniques have been associated with the potential for nephrogenic systemic fibrosis in renally impaired patients (glomerular filtration rate <30 mg/minute). Newer MRA protocols are being refined to allow accurate arterial imaging without the administration of gadolinium. These techniques utilize three-dimensional fast spin-echo acquisition with cardiac gating, with digital subtraction of systolic phase images from the diastolic ones to eliminate venous and background signals; k-space optimization facilitates rapid scanning and enhances contrast resolution.

For patients in whom the principal goal is identification of a distal target vessel for bypass or endovascular treatment, two-dimensional time-of-flight (2D-TOF) MRA has an established value and does not require the administration of gadolinium chelates.

There are numerous MRA sequences with many still evolving. Historically, time-of-flight MRA (TOF-MRA) was the initial approach. Two-dimensional TOF detects the inflow of unsaturated protons in the flowing vascular pool against the background tissue, which has been suppressed by the rapid sequences of radiofrequency signals. Although still
used on occasion, 2D-TOF has limited spatial resolution and a tendency to overestimate stenosis severity. Phase contrast MRA (PC-MRA) represents another bright blood imaging sequence. PC-MRA allows determination of flow direction, although images are substantially degraded by in-line, sluggish, or turbulent flow (and dephasing of spins), with resulting loss of vascular signal.

Contrast-enhanced MRA (CE-MRA), utilizing timed intravenous bolus injections of gadolinium chelates, is the predominant MRA imaging sequence. CE-MRA improves the signal-to-noise ratio (SNR), is independent of flow, and has validated excellent correlation with catheter angiography. Since gadolinium is a blood-pool agent, CE-MRA is acquired as steady state images rather than as dynamic sequences. Consequently, contamination by overlying vascular structures and veins may degrade image quality (Figure 19.3). To allow dynamic CE-MRA imaging over large vascular fields, multistation MRA or moving-table MRA has been utilized. Multistation MRA requires multiple injections, masking of the venous and parenchymal signal from the initial injection, and the use of high volumes of contrast. Moving-table MRA with bolus chasing overcomes some of these limitations by maximizing the data obtained from a single bolus. The rapid transit time from the aorta to the lower limbs is such that venous filling cannot be completely negated, although the preliminary application of saturation pulses and the use of venous tourniquets are effective in suppressing venous signal in most instances. The physics of advanced imaging sequences and Fourier transformation techniques are beyond the scope of this chapter. Nevertheless, it can be stated that higher field strength magnets, fat saturation, and improved bolus timing maximize the SNR. Enhanced imaging techniques now allow high-resolution single-breathhold images of the chest and great vessels without the need for gating, and techniques such as time resolved imaging of contrast kinetics (TRICKS) reliably provide sequential flow images comparable to those from conventional angiography.

Since it was first reported in 1992, CTA has seen several improvements, which have resulted in rapid image acquisition and improved image resolution. In particular, the development of multidetector CT (MDCT) has allowed shorter image acquisition time, thinner sections, and improved longitudinal coverage (Figure 19.4). Like in MRA, manually or automatically triggered bolus timing algorithms allow optimal image timing and contrast opacification of the target vascular bed. In comparison to MRA and duplex sonography, CTA for the initial imaging evaluation of peripheral artery disease (PAD) is associated with reduced costs owing to a lesser need for additional imaging. Dedicated software or third-party workstations allow detailed image rendering in multiple projections, although an evaluation of the source axial data remains a critical component of image interpretation. Images are generally reconstructed to render longitudinal vessel displays similar to those in conventional angiograms and can
be viewed in multiple projections from a single acquisition. The two major reconstruction protocols produce surface rendered (SR) and maximum intensity pixel (MIP) displays (Figure 19.5). SR images provide a three-dimensional shaded appearance of the arteries with or without background skeletal or soft tissue details. To produce this effect, thresholding is applied wherein only structures with a Hounsfield density above a certain value (i.e., iodinated contrast density) are included in the final image, in a gated fashion; soft tissues and other lower-density images are excluded from the final picture. MIP images display all contiguous uniform density pixels, as in an opacified blood vessel, in a two-dimensional representation. MIP images may also be viewed in any projection, and can in addition be paged through to provide a better evaluation of internal vessel structure. CTA has some notable limitations, predominantly due to its dependency on contrast resolution between opacified vessels and the surrounding tissue. To achieve this contrast differentiation, a high volume (80 to 150 cc) of iodinated contrast delivered through a larger-bore IV at a rate of 3 cc/sec is required. Consequently, CTA has an associated risk of contrast hypersensitivity and contrast-induced nephropathy (CIN), and is precluded in patients with stage 4 or worse chronic kidney disease. In patients with congestive heart failure, impaired venous or arterial transit times, poor peripheral intravenous access, or marked asymmetry in limb flow, inadequate opacification and image degradation may occur. While CTA is highly correlated with conventional angiography for aortoiliac disease, reliability is less in the case of femoropopliteal disease and even more impaired for infrapopliteal disease. In these distributions, the presence of medial calcification reduces accurate visualization of the arterial lumen, and the thresholding effect of SR-CTA prevents differentiation between calcium and contrast. As a result, a densely calcified and highly stenotic vessel may appear to have a normal caliber on SR-CTA. Newer reconstruction techniques have been developed to overcome the problem associated with evaluating calcified vessels. Most notably, curved planar reconstructions (CPR) produce midline images from the composite arterial dataset, thus improving lumen imaging and stenosis evaluation (Figure 19.5). Even though this technique improves the outcomes, inaccurate assessment of calcified arteries still remains a major drawback of CTA. The strengths and weakness of each technique are listed in Table 19.1.
Catheter-based angiography has equally undergone a new level of complexity and sophistication and, at this writing, remains the gold standard for diagnosis of arterial disease. As with cardiac angiography (Chapter 2), the techniques of vascular angiography are predicated on maximizing benefit for the patient while minimizing the associated risk. These principles are summarized in the recently updated consensus conference guidelines regarding the clinical competency required for the diagnosis and management of peripheral vascular diseases.25

Principles of vascular angiography may be divided into general considerations common to all vascular territories and specific considerations relating to individual vascular beds. General considerations include techniques of arterial access, radiographic equipment, catheter design and use, anticoagulation, and contrast selection. Specific principles, discussed in their relevant sections, include the choice of arterial access,
Table 19.1  Relative Advantages and Disadvantages of CTA and MRA

<table>
<thead>
<tr>
<th></th>
<th>CTA</th>
<th>MRA</th>
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<tbody>
<tr>
<td>Cost burden</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Speed and availability</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>Claustrophobia</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Bone separation</td>
<td>+</td>
<td>++</td>
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<tr>
<td>Less motion artifact</td>
<td>+++</td>
<td>+</td>
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<tr>
<td>Calcified vessel imaging (especially tibial arteries)</td>
<td>+</td>
<td>+++ (TRICKS imaging)</td>
</tr>
<tr>
<td>Ionizing radiation</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Nephrotoxic contrast</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Nephrogenic systemic fibrosis</td>
<td>++</td>
<td>- (in advanced CKD)</td>
</tr>
<tr>
<td>Visualize stent lumina</td>
<td>++ (CPR imaging)</td>
<td>- (artifact)</td>
</tr>
</tbody>
</table>

+ denotes a favorable characteristic; – denotes an unfavorable characteristic.

TRICKS, time resolved imaging of contrast kinetics; CPR, curved planar reconstructions; CKD, chronic kidney disease.

VASCULAR ACCESS

Although arterial access has been discussed previously (Chapters 6, 7, and 8), its importance in achieving a safe, complication-free procedure cannot be overstated, particularly in patients with known peripheral vascular disease. Deciding on the appropriate site of access for peripheral arteriography is a preprocedural decision of utmost importance, analogous to planning a surgical incision. Optimal access reduces the likelihood of complications and shortens the duration of the procedure. The most favorable site of access is determined based on the clinical history, physical examination, and noninvasive studies (e.g., duplex ultrasonography, MRA, or CTA). The most commonly used sites remain the common femoral and brachial arteries. If the femoral pulse is diminished or absent (e.g., owing to occlusion more proximally), one of several methods may be used to facilitate successful entry of the artery.\(^{26,27}\) We strongly recommend confirming the site of femoral access by fluoroscopy in all patients, particularly in those with ambiguous surface landmarks (see Chapter 6). For retrograde femoral access, a skin mark at the lower end of the femoral head is generally selected to allow entry into the femoral artery in the middle of the femoral head; this facilitates counter-pressure for successful manual hemostasis after catheter removal and assures that puncture remains below the inguinal ligament. In situations in which an initial high puncture is noted (above an imaginary line connecting the anterior inferior iliac spine and pubic symphysis, denoting the position of the inguinal ligament), removal of the needle and repuncture is recommended. Arterial calcification, which is frequently present in diseased arteries, can also aid as a fluoroscopic target. Ultrasound guidance, and road mapping of a contrast injection performed via a catheter positioned in the distal aorta from the contralateral groin, may also be helpful.

Although many operators use crossover techniques from the contralateral femoral artery, antegrade puncture of the ipsilateral common femoral artery (CFA) is widely used to approach femoral, popliteal, or infrapopliteal disease. Antegrade access is considered more challenging technically and limits angiography to the ipsilateral leg, but it offers a more stable platform for intervention. The patient’s orientation is reversed in such a way that the feet are placed at the head of the gantry, allowing maximal mobility of the image intensifier around the lower limbs. As in retrograde access, the desired site of entry is in the middle of the CFA below the inguinal ligament, but given the different angulation, the skin puncture is made at or above the top of the femoral head\(^ {26} \) (Figure 19.6). A 9 cm needle is frequently required, as compared with the standard 7 cm needle used for retrograde access. A less acute needle angle, generally <45°, facilitates catheter and sheath insertion by avoiding the kinking associated with a steeper-angled entry. Arterial puncture should be performed under fluoroscopic guidance aiming for the mid or upper portion of the femoral head.
Aids to antegrade access include arterial calcification or prior studies (angio, CTA, or MRA) that define the bifurcation of the CFA in relation to the femoral head. In cases with a known high CFA bifurcation, the antegrade stick should be modified accordingly.

Having achieved arterial puncture, a 0.035 inch wire is advanced under fluoroscopic guidance into the proximal SFA or PFA. The wires that we recommend include a Bentson wire (with a 15 cm floppy atraumatic tip), a Wholey wire (which provides a gentle steerable tip) or an angled Glidewire (which gives easy passage into the femoral circulation but must be used with care as it may track subintimally or be skeletonized by the sharp edge of the access needle). For scarred groins from prior surgery, the use of nitinol core wires can be useful to prevent kinking. We recommend use of a 5F sheath until the site of arteriotomy and procedural requirement have been confirmed. To confirm the site of antegrade access, angiography with 30° to 50° of ipsilateral oblique angulation will define the arteriotomy site in relation to the common femoral bifurcation. Anticoagulation agent should be administered once the correct position of the access point has been confirmed and if intervention is anticipated; anticoagulation is not routinely used in purely diagnostic angiography. Extra care should be taken to remove the antegrade sheath promptly following the procedure to minimize complications. It is our practice to consider reversing anticoagulation to facilitate immediate sheath removal in the catheterization laboratory, although the availability of closure devices has reduced the need to reverse anticoagulation.

Great care should be exercised while advancing and manipulating catheters and guidewires in the severely diseased peripheral circulation to reduce the chance of embolization related to the traumatic disruption of cholesterol-rich atherosclerotic plaque. This rare but devastating complication of arteriography may lead to livedo reticularis, hypertension, renal failure, stroke, or potential death (see Chapter 4). Although there are no proven therapies effective in the management of this dreadful complication, prostanooids (e.g., PGE1, PGI2) may serve a palliative role in those cases in which it occurs.\textsuperscript{29,30}

\section*{Radiologic Equipment}

As in cardiac catheterization, optimal imaging requires a radiographic gantry capable of axial and sagittal orientation with sufficient mobility to allow imaging of all vascular beds. To capture the larger regions of interest (e.g., the entire aortic arch, the pelvic vasculature, or both legs) a large-field (14 inch or 36 cm) image intensifier is recommended. Widespread application of digital imaging has facilitated contrast enhancement and noise reduction, providing superior angiographic results. Digital subtraction angiography (DSA) and road mapping are two techniques commonly used in peripheral angiography and intervention. In DSA, subtraction of a precontrast mask suppresses interfering structures from subsequent projections, thereby enhancing arterial filling and masking fixed structures (bone, calcifications, soft tissue, and air densities). This allows the use of lower doses of iodinated contrast or use of noniodinated contrast including carbon dioxide or gadolinium.\textsuperscript{31,32} (Figure 19.7A, B).

Further postprocessing features include contrast inversion (changing white arterial structures to appear black), magnification, pixel shifting, picture integration (landmarking), contour enhancement, image stacking, and three-dimensional reconstruction of the subtracted image.\textsuperscript{33-37} Quantitative analysis may be used to assess vessel diameters and lengths, degree of luminal narrowing, and blood flow velocity.\textsuperscript{38} Another useful technique used in DSA is road mapping. This technique is used for selective catheterization and is a useful aid for visualization of a moving catheter. Prior to moving the catheter, a small amount of contrast medium is injected. The image with filled vessels is stored in memory as a mask (a road map along which the catheter is to be moved). This mask is then subtracted from the fluoroscopic images that follow, which will display both the vessels and the catheter with its tip. Some newer angiographic equipment allows the creation of a “smart mask” from prior angiograms which can be used to generate a roadmap image. Although it is not used in cardiac work (where cardiac motion precludes acquiring a suitable “mask” image), DSA is of great value in peripheral angiography as it reduces contrast volume, procedure time, and radiation exposure.
Figure 19.7  A. Normal abdominal aortogram using iodinated contrast material obtained by digital imaging technique. B. Same imaging data, but with enhancement of contrast-filled vessels obtained by the subtraction of all background densities (bones, soft tissue, gas) as recorded on a mask immediately prior to contrast injection.

CATHETERS AND GUIDEWIRES

Just as there are a wide range of cardiac catheters and guidewires, vascular angiography and intervention have a wide range of tools available to meet different anatomic challenges. In addition to standard, thin-walled 18 gauge needles that will accommodate a 0.038 inch wire, micropuncture (e.g., 21 gauge) needle sets are available that allow conversion to a nonstandard (e.g., 0.035 inch) guidewire in situations where there is a high risk of bleeding or after unsuccessful needle puncture attempts.

Most peripheral guidewires are made of a stainless steel coil surrounding a tapered inner core that runs the length of the wire for additional strength. A central safety wire filament is incorporated to prevent separation if ever the wire coil were to fracture. Standard wires vary in diameter from 0.012 to 0.052 inch, with 0.035 and 0.038 inch being the most commonly used sizes. The length of most standard wires is between 100 and 180 cm; longer exchange-length guidewires (measuring 260 to 300 cm) permit keeping the tip of the wire at a selected position during catheter exchange. Tip configurations include straight tip, angled tip, and J-shaped tip. Special features may include the ability to move the wire’s inner core to vary the length of the floppy tip, deflect the wire tip, or transmit torque from the shaft to the tip so that it can be steered within the vascular tree. Varying degrees of shaft stiffness (e.g., extra-support wires) allow advancement of stiff devices through tortuous vessels. Low-friction wires with a hydrophilic coating (glide wires) have revolutionized peripheral work and made it possible to perform superselective catheterization and traverse complex stenoses and long occlusions.

Peripheral angiographic catheters are constructed of polyurethane, polyethylene, Teflon, or nylon with a wire braid in the wall of the catheter to impart torque ability. An ideal catheter has good memory, is nonthrombogenic, has sufficient torque control to facilitate rotational positions, can accommodate high-pressure injection, and tracks well (frequently aided by hydrophilic polymer coating). Catheters vary in French size, length, and hole pattern—a single end hole for selective injections, both end and side holes, or a blocked end with only side holes. For catheters designed to be positioned in the abdominal aorta, a length of 60 to 80 cm is sufficient; in the thoracic or carotid areas, a length of 100 to 120 cm (similar to those of left heart catheters) may be required. The most common diagnostic catheter sizes are 4F to 7F.

Several catheter shapes have been designed, and each ultimately determines a specific function (Figure 19.8). They fall into the following general types:

- Straight catheters with multiple side ports that are used for rapid injection into large vessels and for exchange.
- Pigtail or tennis-racket catheters that are used for nonselective angiography in large vessels (i.e., aorta, pulmonary artery, or cardiac chambers). Multiple side holes along the distal shaft allow rapid delivery of contrast instead of a single forceful jet that could cause catheter whipping or subintimal dissection as might be seen with contrast exiting the end-hole alone.
- Simple curved catheters (e.g., Berenstein, Cobra, Headhunter) that are used for vessel selection.
- Complex reverse-curve catheters (e.g., Simmons, side-winder, SOS-OMNI) that are used for selective catheterization of certain aortic branches.
Preventative methods for CIN have focused on the development of non-nephrotoxic contrast agents. Two such agents have now emerged as alternatives in patients with renal dysfunction or a history of contrast allergy. Carbon dioxide ($\text{CO}_2$) as a contrast agent has been used extensively in many vascular beds. Its primary advantage is that it obviates any risk of allergic reaction or nephrotoxicity. Its application is limited to arteries below the diaphragm to minimize the risk of cerebral embolization, and digital subtraction equipment is required. Another agent gadolinium (gadopentetate dimeglumine) has traditionallly been used with magnetic resonance imaging, but can also be applied to catheter-based imaging. Like $\text{CO}_2$, it is relatively non-toxic, although the maximal dose is limited to 0.4 mmol/kg (approximately 60 mL). Gadolinium should not be used in patients with grade 4 chronic kidney disease owing to the risk of nephrogenic systemic fibrosis.

In patients with renal insufficiency, several strategies have been deployed with varying degree of success to reduce the risk of CIN. The primary preventive measures include limiting the contrast dose and vigorous preprocedural hydration. The addition of bicarbonate saline solutions to the hydration regimen has been demonstrated to help prevent CIN in multiple observational studies, although this has been disputed in one, more recent, trial in which bicarbonate infusions increased risk. As mentioned above, owing to the inconsistency in results, the use of oral or intravenous N-acetylcysteine prior to angiography is no longer recommended. Finally, targeted renal therapy using direct intrarenal infusion of fenoldopan via a specialized two-prong catheter (Benephit, Angiodynamics) holds promise for lowering CIN but requires enlargement of the femoral access sheath or a second arterial puncture.

Beyond these general peripheral imaging techniques, there are a number of important considerations relating to each portion of the arterial tree. In this and subsequent chapters relating to peripheral circulation, we will review the territories in a head-to-foot sequence.

**Thoracic Aorta**

The aortic valve is composed of three leaflets that form the three sinuses of Valsalva: right, left, and posterior. The ascending aorta itself begins just beyond the sinus segment, and courses in a mostly anterior–posterior direction. The diameter of the ascending aorta varies between 2.2 and 3.8 cm in middle-aged adults and increases slightly with advancing age. After it passes over the main pulmonary artery and left mainstem bronchus, the aorta gives rise to the brachiocephalic trunk and then courses posteriorly and leftward in front of the trachea. It then gives rise to the remaining arch vessels—the left common carotid, and left subclavian arteries—from its upper surface. (Figure 19.9A)
Distal to the origin of the left subclavian artery, the aorta narrows slightly at the site of the isthmus where the ligamentum arteriosum (the remnant of the fetal ductus arteriosus) tethers the aorta to the left pulmonary artery. Just distally to this point, a fusiform dilatation, called the aortic spindle, may occur. The descending aorta then continues anterior to the spine, with a diameter of approximately 2.5 cm. Vessels deriving from the descending portion of the aorta are nine pairs of posterior intercostal arteries (levels T3 to T11). The first and second posterior intercostal arteries are supplied by the superior intercostal artery, which is a branch of the subclavian artery. At the level of the fourth to sixth thoracic vertebrae, anteriorly directed bronchial arteries come off to supply each lung.
Disorders of the Thoracic Aorta

Aortic Coarctation

Coarctation of the aorta (see also Chapter 35) occurs in 0.02% to 0.06% of the population and may be associated with bicuspid aortic valve (33% of cases), patent ductus arteriosus, ventricular septal defect, or the Turner syndrome. To bypass the resulting bandlike narrowing of the aorta, collateral flow occurs retrograde into the posterior intercostal branches of the descending aorta. The resultant enlargement and tortuosity of these intercostal arteries are responsible for the “rib notching” seen in chest radiographs.

The classical findings by aortography or MRA are of a high-grade, discrete narrowing of the aorta at the level of the isthmus, with associated dilatation of the ascending aorta and enlargement of the internal thoracic and intercostal arteries. Aortography assumes a significant role in differentiating the wide variety of abnormal patterns, including complete aortic interruption, hypoplastic aorta, and the most common type—a stenosis at the site of the isthmus, distal to the origin of the left subclavian artery. Both AP and lateral (right anterior oblique [RAO]/left anterior oblique [LAO]) aortography should be initially undertaken, with contrast injection performed proximal to the presumed site of coarctation using either large-film or cineangiographic technique. When attempting to traverse the site of narrowing in retrograde fashion, care must be taken to avoid inadvertent perforation of the thin-walled poststenotic segment. Entry to the poststenotic aorta from the brachial or axillary arteries may hence be preferred.

Patent Ductus Arteriosus

The prevalence of patent ductus arteriosus is 1/5,500 in children below 14 years of age. Selective aortic angiography is sensitive in demonstrating small shunts and surpasses the sensitivity of right heart catheterization with stepwise oximetry (see also Chapters 12, 35, and 45).

Aortic Aneurysms

Thoracic aortic aneurysms (TAAs) and pseudoaneurysms may have various causes, including those that are degenerative, atherosclerosis-related, or congenital (aneurysms of the Valsalva sinus); other causes include trauma, infection (syphilitic, bacterial), cystic medial degeneration, connective tissue disorders, and vasculitic and chronic dissection. Degenerative aneurysms involving the descending aorta account for approximately 75% of TAAs. Cystic medial degeneration (as seen in the Marfan syndrome) may also result in aneurysms of the ascending aorta (Figure 19.9B). Aneurysms caused by blunt or penetrating trauma often involve the proximal descending thoracic aorta where the mobile arch segment joins the descending segment fixed to the spine. These may present as pseudoaneurysms—contained ruptures that lack intimal and medial components and are contained only by adventitia and periaortic tissue.

The natural history of TAAs is poorly understood as compared with the extensive data available on untreated infrarenal abdominal aortic aneurysms (AAA). Many patients with TAAs are asymptomatic at the time of diagnosis, with the aneurysm incidentally detected during testing for an unrelated disorder. Thoracic aneurysms appear to enlarge at a more rapid rate than that observed in abdominal aneurysms (0.42 versus 0.28 cm/year), and aneurysms larger than 5 to 6 cm in diameter enlarge even faster and have a higher likelihood of rupture. The cumulative 5-year risk of rupture is increased fivefold in aneurysms ≥6 cm in diameter. Symptoms tend to develop late in the course of the enlargement of the aorta and are usually related to impingement on adjacent structures. In addition to presenting with catastrophic rupture, patients with TAA may report dyspnea, hoarseness, dysphagia, stridor, and plethora with edema from superior vena cava compression. Neck or jaw pain may also be present in patients with aneurysms of the aortic arch. Dilatation of the aortic valve annulus and aortic valve may produce aortic regurgitation and congestive heart failure. Aneurysms of the descending thoracic aorta may produce pleuritic left-sided or interscapular pain, whereas thoracoabdominal aortic aneurysms may induce complaints of abdominal pain and left shoulder discomfort from irritation of the left hemidiaphragm.

The primary treatment for TAAs is surgical repair when the diameter reaches more than 5 to 6 cm or symptoms develop. The standard procedure is to use a Dacron graft to replace the diseased segment. In most patients undergoing elective thoracic aorta surgical repair, aortography is required to provide information about the location of the aneurysm and its relationship to major aortic branches in the chest and abdomen. Optimal surgical approaches, as well as operative risks, are best defined by imaging the coronary, brachiocephalic, visceral, and renal arteries during injections. Stent graft devices have been successfully used as an alternative to surgical grafting for both thoracic and aortic degenerative TAAs and posttraumatic descending TAAs. Although early experience has been plagued by incomplete aneurysm thrombosis, graft leak, and failure, advances in the technology have rapidly expanded the role of endovascular stent grafts for TAAs (Chapter 37).

Aortic Dissection

Aortic dissection is a longitudinal cleavage of the aortic media by a dissecting column of blood. An intimal tear allows the passage of blood into the aortic wall, separating the inner and outer layers of the aortic wall and creating a “double-barrel lumen.” Men are affected about twice as frequently as women. Most patients are between 50 and 70 years of age and have arterial hypertension. Other risk factors include cystic medial degeneration, Marfan syndrome, bicuspid aortic valve, aortic coarctation, blunt trauma, pregnancy, connective tissue disorders, and thoracic aorta operative procedures. The dissection may extend proximally from its origin to the aortic annulus, or distally to involve the entire...
length of the aorta and any or all of its major branches, until terminated by an aortic branch or atherosclerotic plaque. Associated peripheral and visceral patterns of arterial obstructions may be owing to direct extension of the dissection plane into the affected arterial orifice (static dissection) or compromise of the visceral artery origin by the expanded false lumen (dynamic dissection).\(^{92}\)

Dissection is usually heralded by the sudden onset of excruciating pain described as tearing, throbbing, lacerating, ripping, or burning in the anterior chest, neck, or intrascapular region.\(^{93}\) Similar pain may occur with rupture or sudden expansion of a chronic dissection. If the acute dissection results in compression of aortic branches, symptoms and signs of acute myocardial infarction,\(^{94\text{-}95}\) stroke or TIA, paraparesis,\(^{96}\) mesenteric ischemia, renal failure,\(^{97}\) paraplegia, and extremity ischemia\(^{98}\) may result. Most patients with ascending aortic extension who are treated medically die within 3 months, usually from dissection into the pericardium, mediastinum, or pleural cavity.

Once considered the gold standard for diagnosis of aortic dissection, aortography (which has a sensitivity of 80% and specificity of 95%) has largely been replaced by CT, MRA, and transesophageal echocardiography\(^{99}\) (TEE). Visualization of an intimal flap is the only direct aortographic sign that is pathognomonic of dissection. This occurs frequently in association with delayed or sluggish filling of a second lumen, although about 20% of patients with aortic dissection have only one visible aortic channel. The presence of a false lumen may still be suspected, however, if that single channel shows evidence of diminished caliber and absent branching owing either to extrinsic compression by a hematoma in the false lumen or to intrinsic luminal collapse consequent to loss of wall elastin.\(^{92}\) The false lumen of an aortic dissection is distinguished angiographically by its anterolateral ascending and posterolateral descending position, differential reduced flow, and a generally larger caliber than that of the true lumen. Beyond documenting the dissection, aortography provides information about aortic insufficiency and branch vessel or coronary artery involvement, particularly in cases where CT or MRI findings are equivocal and there is a strong clinical suspicion of aortic dissection.\(^{100}\)

Two classification systems of aortic dissection are widely used: The De Bakey classification and the Stanford classification. The De Bakey classification is based on the anatomical extent of the dissection.\(^{86\text{-}103}\) In type I, the tear originates in the ascending aorta and extends distally. Type II dissections are confined to the ascending aorta. In type III, the dissection may be confined to the descending aorta (type IIIa) or extend into the abdominal aorta and iliac arteries (type IIIb). The Stanford classification is based solely on the location of the origin of the dissection.\(^{102}\) Type A includes all cases where the ascending aorta is involved, and type B includes those where the ascending aorta is not involved.

When approaching a patient with suspected aortic dissection, the preferred entry point is the femoral artery with the best pulse. An atraumatic diagnostic catheter (e.g., pigtail or tennis racket) with a soft J-tipped or 15 cm floppy tipped guidewire should be advanced under fluoroscopic guidance with frequent test injections. Since the entry to the false lumen is commonly on the greater (outer) curve of the aorta, the catheter may be used to direct the wire toward the inner curve to maximize the chance of remaining in the true lumen. If this is performed successfully, structures like the aortic leaflets and coronary arteries will be visible, and it will be possible to enter the left ventricle. It is not uncommon, though, to enter the false lumen during initial catheter advancement. When this becomes apparent on test injections, care should be taken to avoid extending the false lumen, pulling the catheter back and using the techniques discussed above to reenter the true lumen.

Surgical repair of Stanford type A aortic dissections entails Dacron graft placement of the ascending aorta.\(^{103}\) If the aortic valve is abnormal, it is replaced.\(^{94}\) In contrast, most patients with type B acute aortic dissections can be initially treated with medical therapy, reserving surgical intervention for those with signs of impending rupture (persistent pain and hypotension), ischemia of legs or mesentery, renal failure, paraparesis, or paraplegia.\(^{95}\) In cases of chronic dissection, operative treatment should be considered if the diameter of the descending aorta exceeds 5 to 6 cm or symptoms develop. Endovascular stents and balloon fenestration have been successfully used in treating the ischemic complications associated with aortic dissection.\(^{104\text{-}106}\)

**Vasculitides**

Vasculitis, highlighted by inflammation of the vessel wall, has two forms that commonly affect the aorta and its branches. These produce dilation of the proximal aorta, narrowing or exclusion of large aortic branches, or both. Takayasu arteritis is characterized by irregularity of the ascending aorta, narrowing of the descending aorta, obstructions of arch vessels, and aortic insufficiency or dissection.\(^{107\text{-}109}\) There may also be associated stenoses in the pulmonary arterial bed as a distinguishing feature. Therapeutic options include surgical bypass or balloon angioplasty demonstrating adjunctive stenting in patients with end organ ischemia.\(^{110,111}\) Intervention should generally be reserved until acute inflammation has subsided.

Giant cell or temporal arteritis is a vasculitis of large and medium arteries. Angiographic evidence of aortic branch involvement shows long, smooth stenoses alternating with relatively normal segments. The intracranial carotid artery and its branches, or the distal subclavian arteries, are usually involved, with aortic disease being relatively uncommon.\(^{112}\)

**Connective Tissue Disorders**

Several inherited diseases, including Marfan syndrome, Ehlers-Danlos syndrome, and heredity annuloaortic ectasia, may be responsible for noninflammatory degeneration of the aortic wall. These may lead to aneurysm formation, rupture, or dissection.
Marfan syndrome is a rare autosomal dominant disorder that may affect the aorta, heart, eye, and skeleton. Cardiovascular complications occur in >50% of patients. Cystic medial degeneration accounts for the resultant changes in aortic root dilation with aortic ectasia, aortic insufficiency, aneurysm formation, or dissection. In Marfan syndrome, the aortic dilatation is primarily confined to the aortic root. Asymptomatic aortic dissection may be seen in approximately 10% of patients. Treatment for patients with the Marfan syndrome and cystic medial degenerative disease should include elective replacement of the ascending aorta and the aortic sinuses when the largest diameter of the aorta is 5.0 to 5.5 cm. The most commonly performed procedure is replacement of the ascending aorta and the aortic valve with a composite graft containing a Dacron graft and a mechanical valve prosthesis. The coronary arteries are reimplanted in the Dacron graft.

Ehlers-Danlos syndrome is a rare set of genetic disorders of collagen production. The literature describes more than nine types of this syndrome with features of hyperextensibility of joints and thick skin. Vascular complications include vessel thrombosis, rupture, and embolization from aneurysms.

**Thoracic Aortography**

Arch aortography has historically been used to examine the aorta for aortic valve or root disease; suspected aneurysms or dissections; congenital anomalies such as vascular rings, coarctation, or patent ductus arteriosus; for evaluation of vascular injuries associated with blunt or penetrating chest trauma; and for examination of stenoses at the origin of the great vessels. Although TEE, CT, and magnetic resonance arteriography (MRA) have been applied in many of these clinical settings, aortography remains the gold standard for aortic imaging.

Thoracic aortography is usually performed via the femoral approach. In cases of suspected aortic dissection with diminished or absent femoral pulses or a history of catheter-related cholesterol embolization, angiography may also be performed safely via a brachial access. A high-flow multi-side-hole (pig-tail) catheter is positioned in the ascending aorta, just above the sinus of Valsalva. Contrast (40 to 60 mL injected at 20 mL/second) is injected using a power injector. For cine imaging, 30 frames per second may be used; for digital imaging 4 to 6 frames per second should be used with breath-holding to minimize motion artifact. The LAO projection optimally delineates the aortic arch. In the RAO projection, the ascending and descending aorta are often superimposed and the origin of the great vessels tends to be obscured. Use of DSA allows a lower concentration of contrast to be used (20 mL/second for a total of 30 mL at 4 to 6 frames per second). The aortogram should be centered and angulated to provide the maximum amount of information on the clinical setting. For example, aortography used to evaluate blunt injury should include sufficient imaging of the descending thoracic aorta, whereas aortography for ascending aortic dissection should also enable detection of regurgitation into the left ventricle.

**ABDOMINAL AORTA**

**Anatomy**

The abdominal aorta starts at the level of the diaphragm (T12) and proceeds anterior to the spine and to the left of the inferior vena cava until it bifurcates into the common iliac arteries (CIAs) at the level of the fourth lumbar vertebra (Figure 19.10A). The normal diameter of the midabdominal aorta varies between 1.50 and 2.15 cm, with a slight increase in size with age and for the male gender. Three main branches of the aorta originate from its ventral surface. The first is the celiac artery at the level of T12–L1. The second branch is the superior mesenteric artery (SMA), which takes

**Figure 19.10**

A. Normal abdominal aortogram in anteroposterior projection. B. Aortogram demonstrating an infrarenal abdominal aortic aneurysm (4.7 cm) that underestimates the accurate size owing to the presence of mural thrombus (arrows). C. Distal aortic occlusion below the renal arteries.
Clinical Manifestations of Abdominal Aortic Disease

In patients with AAA, the goals of preoperative imaging are detection, staging, surveillance, and diagnosis of rupture.\(^{120,121}\) Important information in planning a management strategy includes the size and length of the AAA; proximal and distal margins; number, location, and patency of renal and mesenteric arteries; and presence of lower-extremity occlusive disease and any associated aneurysmal disease (e.g., iliac, hypogastric, femoral, or other intra-abdominal vessels) (Figure 19.10B). The role of abdominal aortography in the preoperative assessment of patients with AAA has diminished with the advent of CT, MRI, and sonography. Preoperative angiography may be useful in cases of suspected suprarenal or juxtarenal aortic aneurysm involvement, renal or mesenteric artery stenosis, horseshoe kidney, and iliofemoral occlusive disease.

Atherosclerotic occlusive disease, or PAD, may warrant arteriographic examination of the aorta. PAD may result in complete occlusion of the aorta (Figure 19.10C). The cause usually is a chronic thrombotic occlusion superimposed on severe atherosclerosis of the distal aorta and iliac arteries. Leriche syndrome is a chronic aortic occlusion and consists of buttock and thigh claudication, impotence, and the absence of femoral pulses.\(^ {122}\) Congenital coarctation syndromes, which include Williams syndrome,\(^ {123}\) neurofibromatosis,\(^ {124}\) congenital rubella,\(^ {123}\) and tuberous sclerosis,\(^ {126}\) may also involve the abdominal aorta and its branches. Aortography reveals a smooth tapered proximal and midabdominal aorta with proximal renal artery involvement and narrowing of the superior mesenteric or celiac arteries. Middle aortic syndrome (abdominal aortic coarctation) produces stenoses of the midaorta and its associated major branches.\(^ {127}\) Treatment options include surgical bypass or percutaneous transluminal angioplasty with endovascular stenting in certain cases, although experience is limited and the exact role of the latter is controversial.\(^ {128}\)

Abdominal Aortography

Abdominal aortography is typically performed via the femoral approach, using a 4F to 6F multi-hole pigtail or an Omni Flush diagnostic catheter. If the femoral pulse is not palpable on either side, alternative options include translumbar, axillary, brachial, or radial approaches. The tip of the catheter should be positioned at the T12 or L1 level, thus placing the side holes adjacent to the first and second lumbar vertebrae. Contrast medium should be injected at a rate of 15 mL/second for a total volume of 30 to 50 mL. At least four frames per second should be obtained when evaluating the mesenteric or renal arteries. When performing arteriography in an aorta with suspected or known aneurysmal disease or severe atherosclerotic involvement, meticulous care should be taken to avoid dislodging of mural thrombus or plaque resulting in distal embolization.

Ideally, two views of the aorta—anteroposterior and lateral—are obtained, particularly if the origins of the mesenteric vessels are being evaluated. Assessment of a transcatheter pressure gradient can also be used to augment angiographically assessed severity of an aortic narrowing. This is most easily performed by measuring the pressure gradient between a 4F or 5F catheter placed above the lesion and the side port of a long femoral sheath placed at the level of the aortic bifurcation. For aortic lesions, a gradient of 10 mmHg is considered significant. Further augmentation of the gradient using vasodilators (200 µg of intra-arterial nitroglycerin) delivered into the lower aorta can also be useful. IVUS provides additional information, and is a useful adjunct for aortic intervention, providing accurate lesion measurements. Although a 15 MHz transducer provides superior imaging of the aorta, it requires a larger sheath for access (8F). A 30 MHz (2.4F) transducer allows superior far-field imaging, as compared with a 40 MHz coronary transducer, without the need for up-sizing the arterial sheath.

SUBCLAVIAN AND VERTEBRAL ARTERIES

Anatomy

The brachiocephalic, left common carotid, and left subclavian arteries arise from the aortic arch after it passes over the main pulmonary artery and left main stem bronchus.\(^ {24}\) Whereas the right subclavian and right common carotid arteries originate as branches of the brachiocephalic trunk (also known as the innominate artery), the left common carotid and left subclavian arteries usually originate separately from the aortic arch. An aortic arch variant in which the brachiocephalic and left common carotid arteries may have a common origin (i.e., bovine arch) is present in about 10% of the population.\(^ {129}\) The major branches of the subclavian artery that deserve special attention are the internal mammary and vertebral arteries; the latter originate from the superior aspect of the vessel (opposite the internal mammary) and proceed into the skull through the cervical transverse processes.

Manifestations of Subclavian Disease

Atherosclerosis of the proximal subclavian artery may manifest clinically as arm claudication, subclavian steal, or (in patients with previous internal mammary grafting) coronary
ischemia. In classic subclavian steal, stenosis or occlusion of the proximal subclavian artery causes blood from the contralateral vertebral artery to flow antegrade across the basilar system and then retrograde down the ipsilateral vertebral artery to fill the subclavian artery distal to the lesion (Figure 19.11A). In rare cases, this may cause cerebral ischemia during upper extremity exercise. In patients who have undergone internal mammary artery bypass grafting to a coronary artery, a proximal subclavian obstruction may cause retrograde flow in the graft during arm exercise and lead to coronary ischemia (coronary-subclavian steal) (Figure 19.11B, C). Stenosis of the vertebral origin is relatively common, particularly at its origin from the subclavian artery; however, cerebral symptoms are unusual, given the dual blood supply (from both vertebrales and from the carotid arteries by way of the posterior communicating artery) unless both vertebrales are diseased.

**Subclavian and Vertebral Arteriography**

An aortic arch arteriogram with a 5F pigtail catheter can visualize the origin of the great vessels to evaluate for atherosclerotic occlusive disease. (See the section entitled “Thoracic Aortography”.) The optimum catheter for selective catheterization of the innominate or subclavian artery depends on the configuration of the great vessels of the neck. For the simple origin takeoff, arteriography can generally be performed with a 5F Davies, Berenstein, JR4, hockey stick, or VTK catheter. If the arch aortogram demonstrates an elongated arch, a reverse-curve catheter such as a 5F VTK or Simmons may be required. A 30° to 45° LAO projection is useful for selecting each of the branches, with the catheters formed and oriented in the ascending aorta and withdrawn sequentially from the innominate through the left common carotid to the left subclavian artery. Angiography of the innominate is usually best performed with 30° to 40° RAO and mild caudal angulation to open out the innominate–subclavian bifurcation. Subclavian and vertebral angiography can generally be performed in the anteroposterior view, with the addition of an oblique view (RAO or LAO) if there is suspicion of an eccentric lesion. The origins of the internal mammary arteries are often clearly defined in the RAO cranial angulation, a point of particular importance in subclavian intervention.

If a proximal vertebral artery stenosis is expected, selective injection of the ipsilateral subclavian artery in the anteroposterior projection is usually diagnostic. Modest angulation may sometimes be necessary. Translesional gradients across innominate or subclavian lesions can be obtained with either

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**Figure 19.11**

A. Selective left subclavian arteriogram depicting severe ostial stenosis (arrow) and retrograde flow through left vertebral artery (white). B. Arteriogram of subclavian artery in patient status post-CABG with a LIMA graft and a high-grade ostial stenosis (double arrow) resulting in poor visualization of the graft (arrow). C. Arteriogram following successful stenting of the subclavian artery stenosis and restoration of antegrade flow into the LIMA graft.
a 0.014 inch pressure wire or simultaneous pressures measured between a 4F or 5F catheter placed beyond the lesion and the side port of a long 6F sheath placed in the distal aorta. Injection of vasodilators into the distal subclavian circulation can be used to simulate exercise and augment the gradient. A gradient of 15 mmHg is considered significant for subclavian or innominate stenosis.

**CAROTID ARTERIES**

**Anatomy**

The brachiocephalic artery bifurcates into the right subclavian and right common carotid arteries as the first main branch off the aorta. The left common carotid is typically the second main branch of the aorta. Each common carotid runs within a fascial (carotid) sheath, lateral to the vertebrae, and bifurcates into an external and internal carotid artery branch at the fourth cervical vertebra. Although the internal carotid artery normally has no main branches prior to entering the skull, it forms a tortuous portion known as the carotid siphon within the cavernous and supraclinoid segments, after which it divides into the anterior and posterior cerebral arteries. The external carotid artery has several major branches named after their territory of supply.

**Extracranial Carotid Atherosclerosis**

Approximately 700,000 strokes occur annually in the United States, of which 25% to 30% are owing to extracranial carotid artery disease. In the Minneapolis-St. Paul, Minnesota, metropolitan area during 1985, there were 1,792 hospital discharges with the diagnosis of acute stroke, representing an event rate of 828/100,000 population in men and 551/100,000 in women. Patients with carotid disease frequently have severe coronary artery disease. In a population of 506 patients undergoing evaluation for potential carotid revascularization, 16% of patients without clinical clues suggestive of coronary heart disease were found to have severe, surgically correctable coronary artery disease. Even patients with asymptomatic carotid artery stenosis have an increased risk of coronary events. In one study of 444 male patients, the 4-year mortality rate was 37%, with 61% of the deaths owing to coronary artery disease. Multivariate analysis showed diabetes mellitus, an abnormal electrocardiogram, and the presence of intermittent claudication to be associated with an increased mortality risk (two or three risk factors revealed annual mortality rates of 11.3% and 13%, respectively). Just the finding of increased carotid intima media thickness on duplex ultrasonographic images predicts a higher risk of myocardial infarction or stroke, as much as 3.87 times that observed in patients with minimal thickness.

Most patients with extracranial carotid artery disease are identified by the presence of a carotid bruit on physical examination, with no referable symptoms. Estimates of the prevalence of asymptomatic carotid bruits in adults range from 1% to 2.3% in patients in the age group of 45 to 54 years and 8.2% in patients older than 75 years. Among patients scheduled to undergo other vascular surgical procedures, however, the incidence of cervical bruits ranged from 6% to 16% with a mean prevalence of 10%. An asymptomatic carotid bruit carries a 1.5% annual incidence of stroke and a 3-year stroke risk of 2.1% (as demonstrated by the European Carotid Surgery Trialists). Among patients with an asymptomatic bruit and with severe (70% to 99%) carotid stenosis, the 3-year risk of stroke was 5.7%.

Absence of a bruit, however, does not imply absence of significant carotid disease. In a study of the North American Symptomatic Carotid Endarterectomy Trial (NASCET), 1,268 patients with recent transient cerebral ischemia or nondisabling stroke were examined for the presence of a carotid bruit. Fifty-eight percent of patients had a bruit localized to the ipsilateral carotid artery; 31% had a carotid bruit involving the contralateral vessel; and 24% had bilateral carotid bruits. The sensitivity and specificity of a focal bruit for predicting high-grade ipsilateral carotid stenosis was 63% and 61%, respectively. In this patient subgroup, absence of a bruit lowered the pretest 70% to 99% probability of a carotid stenosis from 52% only to 40%. Recently, in a meta-analysis of 22 studies involving over 17,200 patients, the odds ratio for myocardial infarction in those patients with cervical bruits as compared to those without was 2.15 and that for cardiovascular death was 2.27.

Once established, extracranial carotid artery stenosis progresses in approximately 20% to 40% of cases. In one prospective natural history study of 232 patients with mild (<50%) or moderate (50% to 79%) carotid stenosis followed up with annual carotid duplex ultrasonography for a mean of 7 years, 23% demonstrated disease progression. One-third of these patients developed severe stenosis (80% to 99%) or occlusion. Progression to either 80% to 99% stenosis or occlusion was more likely in patients whose initial stenosis was 50% to 79% rather than <50%. More recent data in 425 asymptomatic patients with 50% to 79% carotid stenosis followed for a mean of 38 months demonstrated progression of stenosis in 17% of 282 arteries with at least two serial carotid duplex examinations. In general, this carried a moderately low incidence of ipsilateral stroke (0.85% at 1 year, 3.6% at 3 years, 5.4% at 5 years), but patients with 80% to 99% carotid stenosis had an annual neurologic event rate of 20.6%.

Many carotid lesions are discovered only after the patient begins to experience symptoms, which may vary from transient monocular blindness (amaurosis fugax) to expressive or receptive aphasia, hemiparesis/hemiplegia, and mental status changes. Although these episodic symptoms last a few minutes to a few hours and then completely resolve, they are harbingers of recurrent and potentially nonreversible events, and thus warrant urgent evaluation and therapy in an attempt to prevent a catastrophic
stroke. The first study in this evaluation is carotid duplex ultrasonography, which provides two-dimensional images of the extracranial carotid arteries and may provide information about plaque morphology (Figure 19.12A). Color-coded images can detect increased velocities of blood flow, which correlate to higher degrees of stenosis, while Doppler waveforms and velocities can also be measured to evaluate stenosis severity when performed by skilled vascular ultrasonographers\textsuperscript{149} (Figure 19.12B). Once a significant stenosis is identified, contrast or MRA can be performed to corroborate the ultrasound study findings (Figure 19.12C). A strategy of duplex ultrasonography followed by CTA yielded a sensitivity of 100\% and specificity of 84\%.\textsuperscript{150} In cases in which there is discordance between duplex ultrasonography and cross-sectional imaging techniques, catheter angiography is warranted.

Publication of a randomized trial comparing carotid endarterectomy to carotid artery stent placement in standard surgical risk patients demonstrated equivalence of the endovascular procedure\textsuperscript{151} (Figure 19.12D).

**Carotid Arteriography**

Carotid arteriography remains the gold standard for detecting the presence of and assessing quantitative narrowing of the carotid and intracerebral vasculature. Despite the advances made with noninvasive techniques such as duplex ultrasonography, MRA, and spiral CTA, selective carotid catheterization may be indicated to more accurately delineate the degree of stenosis involving the distal common and internal carotid arteries and the extent of disease at the bifurcation, as well as providing information about the intracranial circulation, including collateral flow patterns.

To completely evaluate cerebral circulation, carotid angiography should be performed in conjunction with arch aortography and selective vertebral angiography. Arch aortography is a crucial first step because it allows characterization of the arch configuration and optimal catheter selection. Anatomical variations of the typical aortic arch include origin of the left common carotid from the innominate (bovine arch) seen in 25\%, origin of the left vertebral from the aorta in 3\%, and origin of the right subclavian as the distalmost

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**Figure 19.12**

A. Color duplex image of severely stenotic right internal carotid artery (ICA). B. Corresponding spectral waveform of ICA showing increased peak systolic and end-diastolic velocities. C. Carotid arteriogram confirming severe stenosis involving the right ICA. D. Arteriogram of carotid bifurcation following successful stenting of stenotic right ICA.
vessel in 1%. For normal arch anatomy, a 5F Davies, Berenstein, or Headhunter catheter can be used. For elongated arch anatomy, a retroflexed catheter such as a VTK or Simmons may be required to selectively engage the great vessels. Having engaged the carotid ostium, the catheter can be advanced over a 0.035 inch glide wire.

Once the catheter is beyond the aortic arch, careful double-flushing is mandatory to minimize risk of embolization. Injections of diluted low-osmolar contrast are typically performed with digital subtraction at 4 to 6 mL/second for a total of 8 mL in the common carotid artery with DSA at 4 or 6 frames per second, and at 3 to 4 mL/second for a total of 5 to 6 mL in the vertebral artery (Figure 19.12C, D). In general, we begin with lower rates and volumes of contrast in the cerebral circulation and make adjustments as needed for subsequent images. Angiography should be extended into the venous filling phase to rule out any venous abnormality. Parenchymal images provide a reference for cortical perfusion that can serve as a basis for comparison after carotid stenting.

Multiple oblique projections are necessary, including anteroposterior, lateral, and oblique views, to optimally visualize narrowing at the carotid bifurcation and proximal ICA. The lateral projection is the best to visualize the proximal ICA and carotid siphon.

The angiographic views commonly used to delineate the intracerebral course of the internal carotid arteries include the Towne view (AP cranial to bring the petrous ridge over the roof of the orbit) and the straight lateral views (with the pinnas of the ears superimposed). To calculate the percent diameter stenosis, the projection that demonstrates the highest degree of stenosis should be used. Many methods of calculating carotid artery stenosis have been used in previous trials; however, the NASCET methodology is the most widely accepted. It compares the stenotic area with the most normal-appearing artery distal to the stenosis.

### Renal Arteries

#### Anatomy

The renal arteries arise from the lateral aspect of the aorta at the L1–L2 level. Accessory renal arteries may occur in 25% to 35% of cases and usually supply the lower pole of the kidney. These may originate anywhere from the suprarenal aorta down to the iliac arteries.

#### Atherosclerotic Renal Artery Stenosis

Atherosclerotic renal artery stenosis (ARAS) is clearly more common than was previously believed, with increasing prevalence in certain patient populations. In one series of 395 arteriograms performed in patients with AAA, aortoi Iac atherosclerosis, or infrainguinal atherosclerosis, 33% to 50% had a renal artery stenosis of >50%. In 346 patients with aneurysmal or occlusive vascular disease prompting arteriography, 28% had significant ARAS. The presence of coronary artery atherosclerosis is also a marker for ARAS. In a prospective study of 1,302 patients undergoing coronary arteriography, concurrent abdominal aortography demonstrated significant RAS in 15% of patients. The number of coronary arteries involved with atherosclerosis also appears to predict the likelihood of renal artery stenosis in this series. For example, if one coronary artery demonstrated atherosclerosis, the incidence of significant ARAS was 10.7%. If three coronary arteries and the left main trunk were involved with atherosclerosis, the incidence of ARAS was 39.0%. Conversely, 58% of patients with ARAS had clinically overt coronary artery disease.

Several clinical clues may suggest the presence of ARAS. Patients who develop diastolic hypertension after 55 years of age, who have exacerbation of previously well-controlled hypertension, who demonstrate refractory hypertension (uncontrolled hypertension despite treatment with three antihypertensive medications of synergistic classes at maximal doses), who develop azotemia after treatment with an angiotensin-converting enzyme inhibitor, or who present with malignant hypertension (severe hypertension and papilledema, acute myocardial infarction, acute stroke or transient ischemic attack, aortic dissection, acute renal failure) should all be suspected of having renal artery stenosis. A discrepancy in renal size, the physical finding of a systolic and diastolic abdominal bruit with radiation to one or both flank regions, unexplained azotemia, or the presence of diffuse atherosclerosis with hypertension and azotemia without any obvious cause must prompt the physician to search for renal artery disease. Up to 24% of patients with end-stage renal disease (ESRD) being considered for dialysis in one series had severe ARAS. The 15-year survival of patients committed to ESRD because of ARAS was 0%, as compared with 32% in patients committed to dialysis for other causes such as polycystic kidney disease.

The natural history of ARAS has been studied extensively. Prospective data using duplex ultrasonography to assess renal artery patency demonstrated that 48% of renal arteries whose baseline stenosis was <60% progressed to >60% stenosis after 36 months, as compared with only 8% in vessels with no stenosis at baseline. A number of noninvasive diagnostic tests have been used to determine if renal artery stenosis is present. Historically, rapid-sequence intravenous pyelography was used, but this test has now been shown to be inaccurate. Equally inaccurate are plasma renin levels, elevated only in 50% to 80% of patients with RAS. Captopril-stimulated nuclear renography is an historically prominent diagnostic test for patients with suspected renal artery stenosis, with sensitivity and specificity in the range of 90%. However, in a comparison with clinical clues for the diagnosis of renal artery stenosis, the isotopic renal scan fared no better than the clinical prediction rule to predict renal artery stenosis, particularly in the presence of bilateral renal artery stenosis or impaired renal function.
Renal artery duplex ultrasonography can be an excellent test to diagnose renal artery stenosis if performed by a skilled operator. In one prospective series, of 29 patients (58 renal arteries) who underwent contrast arteriography and duplex ultrasonography, sensitivity of the latter was 84%, specificity was 97%, and positive predictive value was 94% for detection of >60% stenosis. Using peak systolic velocity (PSV) within the renal artery of >180 cm/second as the criterion, duplex scanning was able to discern between normal and diseased renal arteries with a sensitivity of 95% and specificity of 90%. The ratio of PSV in the area of renal artery stenosis to the PSV within the aorta (renal to aortic ratio, RAR) of >3.5 predicts the presence of >60% renal artery stenosis with a sensitivity of 92%. In another large prospective series of 102 consecutive patients who underwent both duplex ultrasonography and contrast arteriography within 1 month of each other, 62 of 63 arteries with <60% stenosis, 31 of 32 arteries with 60% to 79% stenosis, and 67 of 69 arteries with 80% to 99% stenosis were correctly identified by duplex ultrasonography. Occluded renal arteries were correctly identified in 22 of 23 cases. The overall sensitivity of duplex ultrasonography was 98%, specificity was 99%, positive predictive value was 99%, and negative predictive value was 97%.

Limitations of direct ultrasound visualization of the renal arteries include large body habitus and overlying bowel gas obscuring identification of the renal arteries. Some authors have suggested that renal hilar scanning (indirect technique) is easier than and as accurate as complete interrogation of the renal arteries. However, direct comparison of both techniques has revealed limitations of hilar scanning, including low sensitivity, inability to discriminate between stenosis and occlusion, and inadequate determination of accessory renal arteries. The sensitivity was 67% for hilar scanning, with a specificity of 89% to 99%. A measurement of resistive indices within the parenchyma is not felt to be predictive as to which patients will benefit from revascularization.

Duplex ultrasonography is an excellent method for determining patency following revascularization. Given the proliferation of endovascular therapy (percutaneous angioplasty with stent deployment), duplex ultrasonography is helpful in detecting restenosis. Modified criteria exist for restenosis, as compared with those for untreated arteries: peak systolic velocities of >300 cm/sec in the treated segment are generally accepted as evidence of in-stent RAS.

MRA has demonstrated great promise as a highly accurate noninvasive test for the diagnosis of renal artery stenosis. Limitations of this technology, predominantly, overestimating the degree of stenosis, are decreasing with the addition of intravenous gadolinium, a non-nephrotoxic contrast agent, and perhaps with the addition of captopril. There are emerging data suggesting that physiologic evaluation with blood oxygen level dependent magnetic resonance imaging may become a predictor of clinical improvement following renal artery revascularization.

CTA has demonstrated its efficacy in the diagnosis of renal artery stenosis. When compared with contrast arteriography, the sensitivity of CTA is 92%, with specificity of 95%. Recent studies have even suggested the potential use of CTA in determining the patency of renal artery stents.

Renal Arteriography

Access for renal angiography is most commonly achieved via the femoral approach. A brachial approach may be advantageous if there is significant infrarenal aortic atheroma or aneurysmal disease, or an extreme downward angulation of the renal arteries detected by preprocedural noninvasive testing. The first stage of renal angiography is an abdominal aortogram, allowing identification of ostia of the renal arteries and location of any accessory renal arteries, which is seen in as many as 25% of the population. Frequently, an aortogram will suffice in ruling out significant renal artery stenosis. As with abdominal aortography described above, a 4F to 5F multihole catheter placed at the L1–L2 interspace for power injection of a total of 15 to 30 mL of 50% diluted contrast at 15 mL/second using DSA at 4 frames per second is generally sufficient to provide adequate opacification. If DSA is not available, the concentration of contrast should be increased accordingly. In the setting of renal insufficiency, carbon dioxide can be used as a surrogated contrast agent. In this setting a bolus dose of 40 to 50 mL of carbon dioxide delivered by hand injection during breathholding using DSA (at least 4 frames per second) should be sufficient for adequate localization of the renal artery origins to allow selective angiography.

Using the abdominal aortogram, or noninvasive imaging, as a guide, the appropriate catheter can be selected for selective renal arteriography. Commonly used catheters include 5F internal mammary, hockey stick, or renal double-curve catheters. For downward angulated renal arteries, a reverse-curve catheter such as an Omni selective catheter may be more appropriate from the femoral approach or a 5F multipurpose catheter, from a brachial approach. Contrast should be injected at a rate of 5 mL/second for a total of 5 to 8 mL using DSA at 4 frames per second. Angiography should include both the arterial phase and the nephrographic phase.

The origin of the renal arteries is variable, necessitating varied angulations to adequately display the renal ostia en face. A useful technique is to modify the LAO/RAO angulation while fluoroscopically watching the catheter until its tip appears maximally opened. In addition, disease involving renal bifurcations may require cranial or caudal angulation to open out the lesion in its full severity.

If there is evidence of aortic atheroma, either by noninvasive imaging or by aortography, a technique of no-touch angiography is recommended. In this technique a 0.014 inch wire is left in the catheter, sitting in the abdominal aorta, to prevent the catheter from dislodging atheroma as its tip is manipulated toward the renal artery.

Occasionally, renal angiography will yield equivocal or indeterminate results, particularly in complex conditions.
such as fibromuscular dysplasia, Takayasu arteritis, radiation, aneurysms, or vasculitis. In this setting, measurement of a trans-stenotic gradient provides useful information regarding the hemodynamic significance of a stenosis. Pressure measurement is most accurately done using a 0.014 inch pressure wire, but alternatively can be performed by measuring the differential pressure between a 4F catheter placed beyond the lesion and a 5F or 6F sheath or guide placed in the aorta. Gradients higher than 10 mmHg mean or 20 mmHg systolic are considered significant (Figure 19.13).

IVUS provides a further method of renal artery evaluation for indeterminate lesions. IVUS is particularly useful in guiding or evaluating renal intervention. A standard 40 MHZ IVUS catheter affords sufficient image resolution for most renal sizes while maintaining a low profile.

PELVIC AND LOWER EXTREMITIES

Anatomy

Bifurcation of the abdominal aorta into the CIAs occurs at the level of L4-L5*4 (Figure 19.14A). The CIAs divide at the lumbar-sacral junction, with the internal iliac arteries (IIAs) taking off medially and posteriorly, and the external iliac arteries (EIAs) continuing anteriorly and laterally to the groin where they exit the pelvis just posterior to the inguinal ligament to become the CFA. The inferior epigastric artery takes off medially at the junction of the EIA and CFA. The deep iliac circumflex artery takes off laterally and superiorly.

The CFA originates at the inguinal ligament and then bifurcates (usually at the lower portion of the femoral head) into the superficial femoral artery (SFA) anteromedially and the deep femoral artery (DFA or “profunda”) posterolaterally (Figure 19.14B). The DFA has two major branches: the lateral circumflex and medial circumflex femoral arteries. The SFA proceeds down the anteromedial thigh and dives deep to enter the adductor (Hunter) canal, where it becomes the popliteal artery running posterior to the femur. Major popliteal branches include the sural and geniculate (superior, middle, and inferior) arteries around the knee (Figure 19.14C).

Below the knee, at the border of the popliteus muscle, the popliteal artery divides, with the anterior tibial (AT) artery proceeding laterally and anterior to the tibia toward the foot. As it passes over the ankle onto the dorsum of the foot, it continues as the dorsalis pedis (DP) artery. After the takeoff of the AT, the popliteal continues as the tibioperoneal trunk (TPT), which then bifurcates into the posterior tibial (PT) and peroneal (PER) arteries. The PT courses posteromedially in the calf, whereas the peroneal runs near the fibula between the AT and PT arteries. The peroneal artery then rejoins the PT above the ankle via its posterior division, and the AT via its anterior division (Figure 19.14D). On the dorsum of the foot, the DP artery has lateral and medial tarsal branches. After the PT artery passes behind the medial malleolus, it divides into medial and lateral plantar arteries. The lateral plantar and distal DP arteries join to form the plantar arch (Figure 19.14E).

![Figure 19.13](image-url)

A. Abdominal aortogram demonstrating normal renal arteries. B. Atherosclerosis of the aorta resulting in bilateral renal artery stenosis. C. Selective injection of the left renal artery depicting an apparent moderate degree of luminal narrowing. D. However, an intra-arterial pressure tracing obtained across the lesion demonstrates a peak systolic and mean gradient of 23 mmHg and 12 mmHg, respectively, indicating a hemodynamically significant lesion.
Normal pelvic and lower-extremity arteriogram. **A.** The distal abdominal aorta bifurcating into the iliac arteries. **B.** The common femoral artery (CFA) dividing into the deep femoral artery (DFA) and superficial femoral artery (SFA). **C.** The SFA traversing the thigh into the popliteal artery as it dives through the adductor (Hunter) canal. **D.** The popliteal artery dividing laterally into the anterior tibial (AT) artery and continuing directly into the tibioperoneal trunk (TPT), which bifurcates into the posterior tibial (PT) and peroneal arteries (PER). **E.** The dorsalis pedis (DP) artery originating from the AT artery beyond the ankle and PT artery, which gives off plantar branches. CIA, common iliac arteries; IIA, internal iliac arteries; EIA, external iliac arteries.

**Figure 19.14**
Lower-Extremity Peripheral Artery Disease

The prevalence of PAD remains difficult to appreciate among the general population. Since a significant segment of the population with PAD has no symptoms of the disorder, true prevalence rates are difficult to ascertain. Patients with asymptomatic PAD are at minimal risk of developing critical limb ischemia that threatens limb survival, with the obvious exception of the patient who suffers acute limb ischemia from an embolic event or trauma. Instead, patients first develop intermittent claudication to some degree before progressing to rest pain, a nonhealing ischemic ulcer, or gangrene. 

The United States National Institutes of Health suggests that PAD causes over 60,000 hospitalizations annually, each stay lasting an average of >11 days. Clinical manifestations of PAD, namely diminished pedal pulses and femoral bruits, occur with increasing frequency with increasing age of the population. Although intermittent claudication occurs more often in men than in women at any age, physical examination findings of peripheral arterial disease occur with identical frequency in both men and women. Several investigators have attempted to define the prevalence of PAD using noninvasive testing modalities and symptom questionnaires. In one series of 613 men and women with a mean age of 66 years, using segmental limb blood pressures, Doppler flow velocities, reactive hyperemia, and pulse reappearance times, researchers found an 11.7% incidence of large-vessel PAD. Although 11.7% of the population had evidence of PAD, only 2.2% of men and 1.7% of women had intermittent claudication. In this same population, however, 20.3% of men and 22.1% of women had abnormalities in the femoral or posterior tibial artery pulse examination. 

The currently accepted methods of determining the presence of PAD include an historical review of patient symptoms and atherosclerotic risk factors, physical examination, and the use of noninvasive vascular tests. Unfortunately, the history is often quite unreliable for confirming the diagnosis of PAD, as <50% of patients actually have classic symptoms of intermittent claudication. 

A simple, accurate, painless, and noninvasive test is the ankle-brachial index (ABI) test. This test compares the blood pressure obtained with a handheld Doppler in the DP or posterior tibial artery (whichever is higher) to the blood pressure in the higher of the two brachial pressures. Generally, an ABI of >0.9 is considered normal, >0.4 to <0.9 reflects mild to moderate PAD, and <0.4 suggests severe PAD. It is widely accepted that the presence of PAD increases the likelihood of myocardial infarction, stroke, renovascular disease, and cardiovascular mortality. The 5-year survival of a patient with intermittent claudication is only 70%, with 75% of deaths attributable to cardiovascular events. Many studies have confirmed the association between cardiovascular morbidity and mortality, and an abnormal ABI. Some have suggested that there is a significant proportion of the population with asymptomatic PAD and that their risk of cardiovascular morbidity and mortality is similar to that of their symptomatic counterparts. However, it is assumed that because of their lack of symptoms, this risk may not be recognized until an event has occurred.

The risk factors for the development of PAD include tobacco use, diabetes mellitus, hypertension, and hypercholesterolemia. Tobacco use remains the most important modifiable risk factor for PAD. Hughson et al. found that 56% of patients with intermittent claudication were active users of cigarettes and 24% were former smokers. In addition, active cigarette smoking causes more severe claudication pain and diminished peripheral circulation in comparison with patients who do not smoke, leading to a reduction in the exercise capacity of patients with claudication. Finally, the risk of progression of PAD and atherosclerosis in other vascular beds is significantly higher in those patients who continue to smoke as compared with those who stop smoking. In 343 patients with intermittent claudication, only 11% stopped smoking 1 year after the diagnosis. Ischemic rest pain developed in 16% of continued smokers after 7 years, whereas none of the former smokers suffered from rest pain. The incidence of myocardial infarction 10 years after the diagnosis of claudication was 11% in former smokers and 53% in active smokers. Ten-year overall survival rate was 82% in former smokers and 46% in active smokers.

Diabetes mellitus and PAD is an ominous combination. Although the prevalence of PAD is higher in the diabetic than in the nondiabetic population, it is the relatively rapid progression to ischemic rest pain and ulceration that portends a poor prognosis for the patients with diabetes. There is a twofold to threefold increase in risk of intermittent claudication in diabetic patients when compared with the nondiabetic population. This holds true for both men and women. The severity of PAD is also higher in the diabetic population. In a study of 47 patients with diabetes mellitus, all of whom had intermittent claudication at baseline, in comparison with 224 patients with intermittent claudication but no diabetes, the incidence of ischemic rest pain and/or gangrene after 6 years of follow-up was 40% and 18%, respectively. The duration of diabetes and the type of diabetes therapy (i.e., diet, oral hypoglycemic agent, and insulin) did not play a role in the incidence or severity of PAD.

Independent predictors of progression of PAD in diabetic patients include a decreased postexercise ABI, increased arm systolic blood pressure, and current smoking, demonstrating the additive effects of atherosclerotic risk factors on the natural history of PAD. Interestingly, among the risk factors for amputation in patients with diabetes mellitus, neuropathic symptoms and lack of outpatient diabetes education are of importance and must be viewed concomitantly with the location and severity of PAD. Unfortunately, there remains no definitive evidence suggesting that strict glycemic control can prevent macrovascular complications from diabetes mellitus. There are several other potential risk factors for peripheral arterial occlusive disease including Lp(a), hyperhomocysteinemia, fibrinogen, and C-reactive protein.
The specific role of each of these factors in the prevention and therapy of PAD remains unclear.

The most common symptom described by patients with PAD is intermittent claudication. Although the description of the symptom may vary among patients from pain to ache to numbness and weakness, there are several distinct characteristics of intermittent claudication. The discomfort is usually brought on by walking and alleviated by rest. The discomfort generally pertains to the muscle groups immediately distal to the arterial segments involved (e.g., SFA stenosis causes calf discomfort). The onset of intermittent claudication is quite predictable and occurs at similar distances provided the speed, incline, and terrain have remained unchanged. Patients generally stop, stand, and wait for 1 to 5 minutes for relief prior to resumption of walking.

Progression to critical limb ischemia manifests as ischemic pain at rest, generally in the arch of the foot or toes. This occurs when the patient is lying supine and is relieved by hanging the foot over the bedside. Paradoxically, patients with ischemic rest pain may note improvement in their pain with walking. Patients may resort to sleeping in a reclining chair to provide a dependent position to the foot. Ischemic ulcerations occur as a result of trauma to toes or areas where bony prominences are exposed. Even minimal trauma, such as that caused by an ill-fitting shoe, may result in ulceration. The presence of ischemic rest pain or ulceration warrants a prompt and aggressive strategy for revascularization.

Physical examination must include palpation of all pulses, including the superficial temporal and carotid arteries, the arteries of the upper extremities, and the arteries of the lower extremities. Auscultation for bruits in the region of the cervical carotid arteries, abdomen, flank, and inguinal regions should be routinely performed, and the phase of the cardiac cycle during which the bruit occurs should be noted. Attempts to palpate the abdominal aorta for aneurysmal dilation should be made. Close inspection of the feet and toes should include a search for ischemic ulceration or tinea infection. Kissing ulcerations between the toes, in the web spaces, are often subtle and easily missed during examination.

Once the ABI test has been performed to provide objective evidence of the overall severity of PAD, more specific information can be obtained noninvasively in the vascular laboratory. The addition of segmental limb pressures can aid in localizing stenoses or occlusions. A series of limb pressure cuffs are placed on the thigh (some centers prefer high- and low-thigh cuffs), calf, ankle, transmetatarsal region of the foot, and digit, respectively. The ABI is calculated, and then the pressure in the cuffs is gradually released, and the pressure at each segment is measured. If a decrease in pressure of >30 mmHg is identified between two consecutive levels, it suggests arterial occlusive disease of the artery proximal to the cuff. In addition, when comparing the two limbs, a 20 to 30 mmHg discrepancy from one limb to the other at the same cuff level also suggests a significant arterial stenosis or occlusion proximal to the cuff.

Pulse volume recordings (PVRs) are plethysmographic tracings that detect the changes in the volume of blood flowing through a limb. The equipment used for PVR is similar to that described previously; the cuffs are inflated to 65 mmHg, and a plethysmographic tracing is recorded at various levels. The normal PVR is similar to the normal arterial pulse wave tracing and consists of a rapid systolic upstroke and a rapid downstroke with a prominent dicrotic notch. With increasing severity of disease, the waveform becomes more attenuated, with a wide downslope, and in extreme cases the waveform is virtually absent.

Ankle-brachial indices, segmental pressures, and PVRs are useful as objective tests in patients with suspected lower-extremity arterial occlusive disease or limb discomfort without an obvious cause, as a method of evaluating the success of an intervention, and as a method of follow-up. The tests are inexpensive, painless, reproducible, and relatively easy to perform. The equipment required to perform these examinations is significantly less expensive than the modern color-flow duplex ultrasound units. Native vessel arterial duplex ultrasonography is widely performed. This examination is generally accepted as a method of defining arterial stenoses or occlusions (Figure 19.15A). The sensitivity of duplex ultrasonography to detect occlusions and stenoses has been reported to be 95% and 92%, respectively, with specificities of 99% and 97%, respectively. Limitations have included tandem stenosis, tibial vessel imaging, and difficulty imaging the inflow arteries. Using a 5.0 to 7.5 MHz transducer, imaging of the suprapingual and infrapingual arteries is performed. The vessels are studied in the sagittal plane, and Doppler velocities are obtained using a 60° Doppler angle. Vessels are classified into one of five categories: normal, 1% to 19% stenosis, 20% to 49% stenosis, 50% to 99% stenosis, and occlusion. The categories are determined by alterations in the Doppler waveform, as well as increasing peak systolic velocities. For a stenosis to be classified as 50% to 99%, for example, the PSV must increase by 100% in comparison with the normal segment of artery proximal to the stenosis and a plethysmographic tracing is recorded at various levels.
underwent surgical revision once a stenosis was detected, the 4-year patency was 88%, whereas in those grafts that did not undergo revision despite the detection of a stenosis, the 4-year patency was 57%. The use of an intensive surveillance program has been less beneficial in the case of prosthetic grafts.

The procedure for graft surveillance is performed in a similar manner as used in native vessel arterial duplex ultrasonography. The inflow artery to the bypass graft is initially imaged using a 5.0 to 7.5 MHz transducer and a Doppler angle of 60°. Subsequently, the proximal anastomosis; proximal, mid, and distal graft; distal anastomosis; and outflow artery are interrogated. Peak systolic and end-diastolic velocities are obtained at each segment and compared with those of the segment of graft proximal to the area being studied. If the ratio of the PSV within a stenotic segment to that in the normal segment proximal to the stenosis is >2, it suggests 50% to 75% diameter reduction. The additional finding of end-diastolic velocities of >100 cm/second suggest >75% stenosis.

Vein bypass grafts should be studied within 7 days of formation, and then in 1 month, followed by studies at 3-month intervals for the first year. If the graft remains normal after year 1, follow-up surveillance should be done every 6 months thereafter. Ankle pressures and waveforms should be obtained at the time of each surveillance study. The indication of development of a stenosis during a surveillance examination should prompt consideration toward arteriography, either with contrast or using magnetic resonance.

Magnetic resonance angiography has been promoted as an excellent method of evaluating the anatomy of the lower-extremity arteries. Though initially touted as a unique and effective method of identifying angiographically occult runoff arteries that would be suitable as targets for surgical revascularization, the use of MR angiography has also been investigated as the sole imaging modality prior to surgical revascularization. Recent comparative trials of MR angiography and standard contrast arteriography have revealed high sensitivity and specificity (97.1 and 99.2%, respectively) for MR angiography in patients suspected of having PAD.

CTA has also been studied in PAD as a primary method of diagnosis. Although there is a requirement for the administration of iodinated contrast and significant external beam
radiation exposure, CTA images have provided excellent anatomic visualization of the lower-extremity arteries, even in the most acute situations.\textsuperscript{217} Given the impressive advances in the field of endovascular therapy for PAD with percutaneous transluminal angioplasty, stent deployment, atherectomy, and stent-grafting for aneurysmal and occlusive disease, however, diagnostic arteriography continues to play an important role in the management of patients with PAD.

Pelvic and Lower-Limb Angiography

Although angiography remains the gold standard for evaluation of PAD, with improved noninvasive imaging, it should be reserved only for patients in whom endovascular or surgical interventions are contemplated. The history, clinical examination, and noninvasive imaging allow a targeted approach to peripheral angiography. Indications for arteriographic study of the upper and lower extremities include ischemia (either exertional or resting) owing to atherosclerosis, embolus, thrombosis, and vasculitis. Other potential causes warranting arteriography include peripheral aneurysms, vascular tumors, trauma, extrinsic compression (e.g., popliteal artery entrapment syndrome, cystic adventitial disease, and vasculitis), collagen vascular disease, and radiation.

Pelvic arteriography can be performed via the femoral or brachial approach. From either access point, a multiholed catheter (pigtail or Omni Flush) can be passed to the level of L4–L5 in the abdominal aorta. Power injection in the AP projection at a rate of 15 mL/second for a total of 30 mL using DSA at 4 frames per second will define the aortoiliac bifurcation and CIAs. If an iliac artery occlusion is suspected, the catheter should be positioned just below the renal arteries to visualize the lumbar arteries that provide important collaterals into the pelvis (Figure 19.16).

Selective angiography of the iliac arteries can similarly be achieved via femoral or brachial approach. From the brachial access, a 5F multipurpose catheter can selectively engage each common iliac. From the ipsilateral femoral access, iliac angiography can be performed by retrograde injections either through the access sheath or through a straight catheter placed retrograde in the common iliac. The contralateral femoral approach requires engaging the common iliac by unfolding an Omni Flush catheter using a guidewire and engaging the aorta bifurcation. A 0.035 inch angled glide wire can be manipulated through the catheter into the external iliac and used to anchor the catheter as it is advanced into the common iliac. Alternatively, a 4F or 5F glide catheter could be placed over the glide wire and selective angiography performed through it. Alternatives for engaging the contralateral common iliac include a Cobra, SOS-OMNI, hook, or internal mammary artery catheter.

No consensus has been reached as to which CFA should be punctured—the one on the side of the more symptomatic or the less symptomatic leg. The advantages of accessing the less symptomatic leg are that groin complications would not interfere with surgical bypass procedures; there is less risk of iliac artery trauma (e.g., dissection or occlusion); and the option remains to then perform an antegrade puncture of the affected leg.

The most favorable angulation for iliac angiography is the contralateral oblique angle, generally 30° to 40°. Hand injections or power injections at 10 mL/second for a total of 10 mL are usually sufficient. Translesional gradients in the iliac vessels are useful guides to the hemodynamic severity of a lesion and also predictors of the success of intervention. A 15 mmHg gradient is considered significant across an iliac stenosis.

Lower-extremity arteriography is also easily performed using a single femoral access point. The ipsilateral lower limb can be imaged through the common femoral access sheath, while the contralateral lower limb can be imaged using the technique described above for crossing the aortoiliac bifurcation and selective iliac angiography. The optimal view for the common femoral bifurcation is 30° to 45° of ipsilateral oblique angulation, performed with a hand injection of 6 to 8 mL of contrast using DSA (3 frames per second). Runoff of the lower limb can then be performed either in sequential stations using DSA or as a single angiographic run. DSA in sequential stations yields improved resolution and facilitates varied angulation for each station. In general, the SFA can be imaged in an anteroposterior view with the addition of an oblique angle if a stenosis is suspected. The popliteal artery, tibioepicondylar trunk, and trifurcation are best imaged in an ipsilateral oblique angle (30°). Infrapopliteal runoff can
be performed in either an anteroposterior or an ipsilateral oblique projection. If DSA is used, an image rate of 4 frames per second is suitable for above the knee and 2 frames per second for below the knee. To optimize the visualization of the tibial or pedal arteries, selective catheter positioning into the SFA with the use of vasodilating agents, such as nitroglycerin (100 to 300 μg), papaverine (30 to 60 mg), or tolazoline (12.5 to 25 mg), may enhance digital images.

Intra-arterial pressure monitoring may be more accurate than multiple angiographic images in assessing the hemodynamic significance of a vascular lesion. There exists no consensus as to the threshold that defines a significant gradient. However, a resting peak systolic gradient of 5 mmHg or an increase of >10 mmHg after augmentation with a vasodilator (e.g., nitroglycerin) is considered hemodynamically significant. IVUS permits direct planimetry of luminal cross-sectional narrowing, obviating the requirement for multiple oblique views to unwind and/or eliminate overlap, which may obscure important luminal obstructions.

REFERENCES


Section V
Evaluation of Cardiac Function

20

Stress Testing During Cardiac Catheterization: Exercise, Pacing, and Dobutamine Challenge

WILLIAM GROSSMAN and MAURO MOSCUCCI

Patients with significant heart disease may have entirely normal hemodynamics when assessed in the resting state during cardiac catheterization. Because most cardiac symptoms are precipitated by exertion or some other stress, however, it may also be important to assess hemodynamic performance during some form of stress such as muscular exercise, pharmacologic intervention (e.g., dobutamine infusion), or pacing-induced tachycardia. Such an evaluation enables the physician to assess the cardiovascular reserve and the relationship (if any) between specific symptoms and hemodynamic impairment. Physiologic information so obtained is often valuable in prescribing specific medical therapy, selecting patients for corrective cardiac surgery, and estimating prognosis.

Muscular exercise, both dynamic and isometric, has been studied extensively in the cardiac catheterization laboratory, and the normal hemodynamic responses are reasonably well understood. There are major differences between the hemodynamic responses to dynamic exercise (done either in the supine or in the erect position) and to static, isometric exercise, and these two types of exercise are discussed separately.

DYNAMIC EXERCISE

During dynamic exertion, skeletal muscles are actively contracting and developing force that is translated into motion and work. This is accompanied by an increase in both oxygen (O₂) consumption and carbon dioxide production by skeletal muscle, and a corresponding increase in alveolar gas exchange needed to support the higher metabolic rate.

Some material in this chapter was developed for previous editions by Drs. Beverly Lorell, Mark Feldman, and Raymond McKay.
In normal sedentary individuals, the level of O₂ consumption during maximal exercise (\( V_{O_2} \text{ max} \)) can increase about 12-fold in comparison with that during the resting state.¹ Age and fitness also modify \( V_{O_2} \text{ max} \). With aging, there is a decrease in \( V_{O_2} \text{ max} \) of about 5% per decade. \( V_{O_2} \text{ max} \) increases because of both cardiovascular and skeletal muscle adaptation. In marathon runners and Olympic-class athletes, \( V_{O_2} \text{ max} \) may represent an 18-fold increase in O₂ consumption above that of the resting state. The increased oxygen requirements of muscular exercise are met by both an increase in the cardiac output and an increased extraction of oxygen from arterial blood by skeletal muscle, which causes widening of the arteriovenous oxygen difference (AV O₂ difference).

The need for the heart to increase cardiac output appropriately for the increase in O₂ consumption resulting from exercise is met by an increase in heart rate and an increase in stroke volume. The relative contributions of these increases to the rise in cardiac output depend on the type of exercise (supine versus upright), the intensity of exercise, the limitation of diastolic filling at high heart rates, and the response to sympathetically stimulated Metabolic adaptations of exercising muscle include a switch from use of free fatty acids at rest to an accelerated breakdown of muscle glycogen stores and enhanced uptake of bloodborne glucose, which is supplied by increased hepatic gluconeogenesis. Because carbohydrate metabolism produces more carbon dioxide than fat metabolism does, the respiratory quotient (ratio of carbon dioxide production to O₂ consumption) rises from a resting value of 0.7 to 0.8 toward 1.0. The delivery of bloodborne oxygen and glucose to working skeletal muscle is enhanced in the presence of normal vasculature by a reduction in skeletal muscle vascular resistance mediated by metabolic byproducts and by sympathetically mediated vasodilatation elsewhere, which causes a redistribution of blood away from the renal and splanchnic beds to the exercising muscle.

Exercise depends on the adequacy of pulmonary function to increase oxygen supply. During progressive exercise, there is a linear increase in minute ventilation relative to the increase in O₂ consumption. When the intensity and duration of exercise are such that oxygen delivered to the exercising muscle is insufficient, anaerobic metabolism of glucose develops, causing metabolic acidosis and an increase in respiratory quotient to values > 1.0; minute ventilation increases out of proportion to O₂ consumption. Beyond this anaerobic threshold, the accumulation of hydrogen ions usually causes skeletal muscle weakness, pain, and severe breathlessness, followed by exhaustion and cessation of exercise. It is best to conduct exercise studies in the catheterization laboratory in such a way that the patient reaches a steady state level of submaximal exercise below the anaerobic threshold and exercise can be sustained for several minutes. This approach permits estimation of cardiovascular reserve and allows the physician to determine whether the increase in cardiac output is appropriate for the increase in O₂ consumption occurring at that particular level of exercise.

Oxygen Uptake and Cardiac Output

There is a linear relationship between O₂ consumption and increasing workload (Figure 20.1). Oxygen uptake increases abruptly after initiation of dynamic exercise, reflecting the additional work needed to overcome inertia of the legs, and then increases steadily over a few minutes to reach a new steady state that is directly related to the intensity or level of exercise.² Simultaneously, the mixed venous blood oxygen saturation decreases to a lower steady level related to the intensity of exercise, producing an increase in the AV O₂ difference.

The cardiac output increases linearly with increasing workload during both supine and upright exercise in normal subjects.² As can be seen from the regression equation for this relationship (Figure 20.2), for each increment of 100 mL/minute per m² of O₂ consumption during exercise, there is an increase in cardiac output of 590 mL/minute per m².

Exercise Index

The linear relationship between oxygen uptake and cardiac output during exercise, illustrated in Figure 20.2, may be used to assess whether the cardiac output response measured in an individual patient is appropriate to the level of exercise and increased oxygen uptake. The regression formula is CI = 0.0059X + 2.99, where CI is the cardiac index in liters per minute per square meter of body surface area (BSA) and \( X \) is the O₂ consumption in mL/minute per m² BSA. This formula may be used to calculate the predicted cardiac index for a given level of O₂ consumption (X), and the predicted cardiac index may then be compared with

![Figure 20.1](image-url) Oxygen consumption in normal subjects during exercise. Each group represents a different level of exercise, with the most intense exercise being performed by group 4. Note the prompt increase and establishment of a new steady state in oxygen uptake that is directly related to the intensity of the exercise. (From Donald KW, et al. The effect of exercise on the cardiac output and circulatory dynamics of normal subjects. Clin Sci 1955;14:37, with permission.)
A another way of using this relationship between cardiac output and oxygen consumption involves calculation of the exercise factor, which is the increase in cardiac output with exercise divided by the corresponding increase in \( O_2 \) consumption:

\[
\text{Exercise factor} = \frac{\text{Increase in cardiac output (mL/min)}}{\text{Increase in } O_2 \text{ consumption (mL/min)}}
\]  

(20.2)

A normal exercise factor represents an increase of 600 mL/minute in cardiac output per 100 mL/minute increase in \( O_2 \) consumption. An exercise factor <6 indicates a subnormal response in cardiac output; like exercise index of <0.8, such a factor suggests some pathologic process limiting the heart’s ability to meet the exercise induced increase in \( O_2 \) consumption with an appropriate increase in cardiac output, forcing an excessive reliance on oxygen extraction from arterial blood and widening of the AVO\(_2\) difference.

### Systemic and Pulmonary Arterial Pressure and Heart Rate

Systolic arterial pressure and mean arterial pressure also increase linearly in relation to \( O_2 \) consumption during dynamic exercise in normal subjects, although the response is somewhat variable. Despite this increase in arterial pressure, systemic vascular resistance decreases substantially during dynamic exercise, indicating that the elevated arterial blood pressure is secondary to increased cardiac output. Patients who are unable to generate an adequate increase in cardiac output during dynamic exercise may also increase their arterial pressure, that in this circumstance systemic vascular resistance does not decline and may actually increase.

The behavior of the pulmonary circulation in response to dynamic exercise is different from that of the systemic circulation in normal individuals. Mean pulmonary artery pressure increases almost proportionally with cardiac output (pulmonary blood flow), so that there is only a slight decrease in pulmonary vascular resistance, in contrast to the normal substantial decrease in the resistance of the systemic vasculature.

Heart rate increases consistently during both supine and upright dynamic exercise and tends to increase linearly in relation to \( O_2 \) consumption. During dynamic supine exercise in the catheterization laboratory, tachycardia is the predominant factor in increasing cardiac output. Tachycardia exerts a positive inotropic effect (the so-called treppe phenomenon, see below), but increased sympathetic nervous system activity appears to be the most significant factor leading to enhanced myocardial contractility. In most normal subjects, supine bicycle exercise is accompanied by an increase in ejection fraction and other ejection indices off left ventricular (LV) systolic function with a decrease in LV end-systolic volume.

Several investigators examining the responses of cardiac output, stroke volume, and heart rate to a given intensity of supine exercise in normal subjects and showed that the increase in cardiac output is caused primarily by an increase in heart rate with a negligible contribution by increased stroke volume. During repeat exercise when heart rate is held constant, there is a comparable increase in cardiac output caused by a marked increase in stroke volume. When heart
rate is artificially increased by electrical pacing in the absence of dynamic exercise, however, cardiac output remains unchanged and a major fall in stroke volume occurs⁹, indicating that further cardiovascular adjustments are required for an adequate hemodynamic response to dynamic exercise. Therefore, to adequately interpret the response to supine exercise in the catheterization laboratory, it is important to recognize that the increase in cardiac output in normal young subjects is caused by a proportionate increase in heart rate. As discussed later, when chronotropic reserve is depressed, an appropriate increase in cardiac output relative to O₂ consumption depends on the capacity to augment LV diastolic filling and end-diastolic fiber tension, leading to an increase in stroke volume by means of the Frank-Starling mechanism.

**Upright Versus Supine Exercise**

The contributions of heart rate and stroke volume to cardiac output differ in supine and upright bicycle exercise. End-diastolic volumes at rest are near maximum when normal subjects are supine, smaller when they are sitting, and smallest when they are standing⁶. When subjects are in the upright position, LV end-diastolic volume, cardiac output, and stroke volume are lower when they are in the supine position⁶-⁸. During erect bicycle exercise, most normal subjects demonstrate an increase in ejection fraction and reduction in end-systolic volume, some enhancement of left ventricular end-diastolic volume, and an increase in stroke volume as well as heart rate. LV end-diastolic volume and stroke volume tend to increase up to about 50% of peak O₂ consumption and then to plateau or actually decrease at high levels of exercise⁴. At high levels of exercise and fast heart rates, recruitment of the Frank-Starling mechanism may be blunted by the effects of tachycardia and limitation of diastolic filling owing to shortening of diastole. At high levels of upright exercise, the stroke volume is preserved by a progressive decrease in end-systolic volume and increase in ejection fraction in the presence of a constant or decreased LV end-diastolic volume⁴-⁹.

Caution must be used in interpreting the relative contributions of inotropic reserve and use of the Frank-Starling mechanism in patients studied during dynamic exercise in the catheterization laboratory. The effects of advancing age profoundly alter the exercise response. In healthy subjects, there appears to be no age related changes in resting cardiac output, ejection fraction, and systolic volume or end-diastolic volume⁹. With age, there is a reduction in both peak O₂ consumption and cardiac output during exercise. Also, with advancing age there is a reduction in heart rate and contractility response during exercise, so that the increase in cardiac output at any level of exercise is accomplished by significant increases in end-diastolic volume and in stroke volume⁹-¹⁰.

Therefore, as discussed earlier, studies of the effect of dynamic supine bicycle exercise in young adults have generally shown no changes or a fall in LV end-diastolic pressure (LVEDP) and volume during exercise. In contrast, studies of older normal subjects or patients with atypical chest pain and normal coronary arteries have generally shown that both dynamic supine and upright bicycle exercise are associated with an increase in LVEDP¹⁰,¹¹ which is consistent with an age-dependent reliance on an increase in preload during exercise. For example, in a group of 10 sedentary men whose average age was 46 years, there was a rise in LVEDP from 8 ± 1 to 16 ± 2 mmHg during supine bicycle exercise and a rise from 4 ± 1 to 11 ± 1 mmHg during upright bicycle exercise.⁸ The diminished heart rate and contractility responses during exercise and the resultant increased dependence on the Frank-Starling mechanism with aging may reflect an age-related decrease in responsiveness to β-adrenergic stimulation.¹²

There are also gender-related differences in the normal response to exercise. Normal men and women can achieve comparable increases in weight-adjusted peak O₂ consumption, heart rate, and blood pressure. However, normal women generally achieve increases in stroke volume during upright exercise through an increase in end-diastolic volume without an increase in ejection fraction, whereas normal men exhibit a progressive increase in ejection fraction to peak exercise.¹³

The interpretation of normal versus abnormal LV systolic performance during dynamic exercise may also be complicated by the effects of chronic β-adrenergic blockade. Studies of the hemodynamic effects of chronic β-adrenergic blockade on graded exercise in hypertensive but otherwise healthy young adults have shown that no impairment of maximal exercise capacity (maximal O₂ consumption) or cardiac output response occurs during chronic β-adrenergic blockade. β-Blockade, however, causes a reduction in heart rate at all levels of exercise, and this relative reduction in heart rate is compensated for by both a widening of the AV O₂ difference and an increase in stroke volume, associated with an increased LV end-diastolic volume and a reduced arterial blood pressure (decreased impedance to ejection).

In normal β-blocked subjects, increases in cardiac output during exercise depend on increasing stroke volume by means of the Frank-Starling mechanism. Therefore, the dynamic exercise response of a patient receiving chronic β-adrenergic blocking therapy may be associated with an inappropriately low increase in cardiac output relative to O₂ consumption, accompanied by excessive widening of the AV O₂ difference with an increased reliance on an increase in LV end-diastolic volume. During dynamic supine exercise in the catheterization laboratory, the finding that an increase in cardiac output depends on an increase in LV end-diastolic volume (and pressure) could be owing to either β-adrenergic blockade per se or intrinsic impairment of LV systolic function. For these reasons, strong consideration should be given to discontinuation of β-adrenergic blocking drugs at least 24 hours before catheterization if analysis of the hemodynamic response to dynamic exercise is planned to assess the adequacy of cardiovascular reserve.
Left Ventricular Diastolic Function

Interpretation of the changes in LV diastolic pressure with exercise depends to a great extent on an appreciation of the adaptations in diastolic function that occur. In normal subjects, multiple adjustments occur to accommodate an increased transmural flow into the left ventricle in the face of an abbreviated diastolic filling period and to maintain low pressures throughout diastole. Exercise is associated with a progressive acceleration of isovolumetric relaxation so that enhanced diastolic filling occurs with minimal change in mitral valve opening pressure.14 The exercise-induced enhancement of diastolic relaxation and filling is probably modulated by both β-adrenergic stimulation and increased heart rate.

In normal subjects, there is either no change or a downward shift in the LV diastolic pressure–volume relation during exercise (Figure 20.3). However, in the presence of ischemia or cardiac hypertrophy, and in patients with heart failure and preserved ejection fraction (HFpEF, see Chapter 43), exercise may provoke an upward shift in the LV diastolic pressure–volume relationship so that any level of LV end-diastolic volume is associated with a much higher LVEDP. In such patients, the left ventricle may be regarded as exhibiting increased chamber stiffness (decreased distensibility) during exercise. In patients with coronary artery disease, a transient but striking upward shift in the LV diastolic pressure–volume relation is common during episodes of ischemia.15 Patients with coronary artery disease who develop angina during dynamic exercise in the catheterization laboratory commonly show a marked rise in LVEDP. A careful study of the dynamics of LV diastolic filling during exercise in patients with coronary artery disease has been reported by Carroll et al.16 These authors studied LV diastolic pressure–volume relations in 34 patients with coronary disease who developed ischemia during exercise and compared the findings with those from 5 patients with minimal cardiovascular disease (control) and 5 patients with an akinetic area at rest from a prior infarction but no active ischemia during exercise (the scar group). There was an upward shift in the LV diastolic pressure–volume relationship during exercise-induced ischemia, which was not seen in either the scar or the control group (Figure 20.3). Therefore, interpretation of an exercise-induced rise in LVEDP in patients with coronary artery disease is complex and may be related to both a decrease in LV chamber distensibility and an increase in LV end-diastolic volume secondary to a reduction in ejection fraction.11,16

The presence of cardiac hypertrophy is frequently characterized by depression of the rates of LV relaxation and diastolic filling at rest, and this depression profoundly impedes LV filling during exercise-induced tachycardia. In patients with conditions such as hypertrophic cardiomyopathy or hypertensive hypertrophic cardiomyopathy, in whom baseline LV end-systolic volumes are small, there is no reserve to further enhance systolic shortening, and abnormal diastolic properties limit the capacity to recruit the Frank–Starling mechanism during exercise. Furthermore, tachycardia may provoke ischemia (owing to impaired coronary vasodilator reserve), accompanied by an upward shift in the diastolic pressure–volume relationship. These findings with exercise-induced tachycardia in patients with coronary disease and/or advanced LV hypertrophy are remarkably similar to the changes in diastolic function seen during angina induced by pacing tachycardia, as described later in this chapter.

Figure 20.3  Left ventricular (LV) diastolic pressure–volume relations at rest and during exercise in patients without heart disease (control), as compared with patients with coronary disease who developed ischemia during exercise (ischemia), and patients with akinetic areas owing to previous infarction but no active ischemia during exercise (scar). Pressure and volume are averaged at three diastolic points: early diastolic pressure nadir, mid-diastole, and end-diastole. The control group had a downward shift of the early diastolic pressure–volume relation, but the ischemia group showed an upward and rightward shift. (From Carroll JD, Hess OM, Hirzel HO, et al. Dynamics of left ventricular filling at rest and during exercise. Circulation 1983;68:59, with permission.)
Marked abnormalities in LV diastolic function occur with exercise in patients with clinical evidence of heart failure but normal resting systolic function (the so-called diastolic heart failure, and recently reclassified as heart failure with preserved ejection fraction, or HFpEF). Kitzman and Sullivan studied seven patients with New York Heart Association (NYHA) class III or IV heart failure with one or more documented episodes of pulmonary edema and no significant coronary artery disease. All had LV ejection fractions of ≥50%, without echocardiographic evidence of regional wall motion abnormalities, or valvular or pericardial disease. Four of these patients were elderly with a medical history remarkable only for chronic hypertension. Most patients had increased LV wall thickness and mass. Patients were studied by symptom-limited upright exercise with simultaneous hemodynamic and radionuclide measurements, and the data were compared to those seen in age- and sex-matched healthy volunteers who served as controls. As can be seen in Figure 20.4, maximum exercise capacity was reduced, and the cardiac output increased primarily as a result of tachycardia, with no change in stroke volume. Figure 20.5 shows that LV ejection fraction was normal at rest and with exercise for both patients and control subjects, but there was a striking rise in pulmonary capillary wedge pressure in patients with diastolic heart failure, as compared with the control subjects. Accordingly, these patients clearly have “pure” diastolic heart failure. Efforts to treat their heart failure by improving systolic function (e.g., digoxin) will not be successful. As seen in Figure 20.6, diastolic distensibility markedly decreased with exercise in these patients. More recently, Borlaug et al evaluated the exercise hemodynamics of 55 patients who presented with exertional dyspnea, EF of >50, no significant coronary disease, normal BNP, and normal resting hemodynamics [mean pulmonary artery (PA) pressure <25 mmHg and PA wedge pressure (PCWP) <15 mmHg; n = 55]. On the basis of exercise hemodynamics, 32 patients were classified as having HFpEF (PCWP > 25 mmHg; n = 32) and 23 patients were classified as having noncardiac dyspnea (PCWP <25 mmHg; Figure 20.7). These data support the

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**Figure 20.4** Seven patients with heart failure and normal left ventricular systolic function (open symbols) were compared with 10 age- and gender-matched healthy volunteers (solid symbols) who served as controls. All subjects underwent upright bicycle exercise with hemodynamic evaluation. Cardiac index increased for the patients with heart failure (A) as a result of an increase in heart rate (D), with fixed stroke volume (C). PT MAX, patient maximum exercise; NL MAX, normal subject maximum exercise. (From Kitzman D, et al. Exercise tolerance in patients with heart failure and preserved left ventricular systolic function: failure of the Frank-Starling mechanism. *J Am Coll Cardiol* 1991;17:1065, with permission.)
value of exercise hemodynamics in reaching the correct diagnosis in selected patients with unexplained dyspnea.

Examples of the Use of Exercise to Evaluate Left Ventricular Failure in the Cardiac Catheterization Laboratory

A suggested supine bicycle exercise protocol for the cardiac catheterization laboratory is illustrated in Table 20.1. Examples of the hemodynamic changes that can occur during supine bicycle exercise are shown in Tables 20.2 and 20.3. Table 20.2 illustrates the response to 6 minutes of supine bicycle exercise of a 36-year-old woman with idiopathic dilated cardiomyopathy (ejection fraction 40%) whose major symptom was exertional dyspnea. Because her ejection fraction was only moderately depressed and her hemodynamic values were almost normal at rest, resting hemodynamic data alone did not clarify whether her cardiovascular reserve was impaired and whether her exertional dyspnea was likely to be cardiac in origin. During exercise, the cardiac index increased appropriately in relation to the increase in $O_2$ consumption, yielding an exercise index of 1.1 and an exercise factor of 8.5.

$$\frac{\Delta \text{cardiac index}}{\Delta \text{O}_2 \text{ consumption index}} = \frac{3,300}{387} = 8.5 \quad (20.3)$$

The increase in cardiac output, however, was accomplished at the cost of a substantial increase in mean pulmonary capillary wedge pressure, which rose from 11 to 27 mmHg. These data suggest that the patient had some limitation of inotropic reserve and that her ability to increase cardiac output depended heavily on use of the Frank-Starling mechanism. Therefore, her dyspnea can be considered to be of cardiac origin.
The cause of exercise intolerance in some patients with LV failure was 0.85, with a low exercise factor at 4.9.

Working skeletal muscle but by the rise in pulmonary capillary wedge pressure associated with exercise (Table 20.2).

As illustrated in these examples, the relative contributions of the inability of the heart to augment cardiac output versus an exercise-induced rise in pulmonary capillary wedge pressure that could impair gas exchange are controversial. Exercise intolerance in patients with congestive heart failure is highly variable and correlates poorly with ejection fraction. Studies of the hemodynamic and ventilatory response to exercise have shown that as the clinical severity of congestive heart failure worsens, there is a progressive decrease in maximal O\textsubscript{2} consumption, premature onset of the anaerobic threshold, and decline in both maximal cardiac output and the cardiac output achieved at levels of submaximal O\textsubscript{2} consumption. Studies of brief exercise performed by patients with chronic congestive heart failure have shown that arterial oxygen saturation usually increases (presumably as a result of increased ventilation) despite elevation of the pulmonary capillary wedge pressure; maximal oxygen extraction is normal, and ventilatory mechanisms do not limit maximum O\textsubscript{2} consumption, so that both symptomatic limitation and the inability to normally increase oxygen delivery are caused by the failure to increase cardiac output adequately. Conversely, in patients with depressed LV ejection fraction who can achieve normal levels of exercise, factors that contribute to normal exercise capacity include normal augmentation of heart rate, the ability to increase cardiac output through further increases in LV end-diastolic volume and stroke volume, and tolerance of a high pulmonary venous pressure, possibly because of enhanced lymphatic drainage.

Therefore, in patients with severe depression of LV ejection fraction, the failure to increase cardiac output normally appears to be related both to the inability to increase stroke volume and to the inability to increase heart rate, as compared with age-matched subjects. This impaired chronotropic response appears to be caused by an impaired postsynaptic response to β-adrenergic stimulation that may be related to several defects, including a reduced cardiac β-receptor density, “uncoupling” of the β-receptor and adenylyl cyclase activity, and deficient production of cyclic adenosine monophosphate.

**Evaluation of Valvular Heart Disease**

**Valvular Stenosis**

Exercise may also be used in the cardiac catheterization laboratory to evaluate valvular heart disease. Gradients across the atrioventricular and semilunar valves may become apparent during exercise and may reach levels that account for the clinical symptoms of the patient. Exercise hemodynamics are especially useful when the resting transvalvular gradient or estimated valve area has borderline significance.

An example of the hemodynamic changes during supine dynamic exercise in a patient with moderate mitral stenosis is shown in Figure 20.8 and Table 20.4. As the result of increased mitral valve flow and a decreased diastolic filling period, the pressure gradient increased significantly, producing left atrial...
PCWP increased to a greater extent in HFP EF compared with NCD with leg elevation and during exercise (A).

**Figure 20.7** Exercise hemodynamics in patients with exertional dyspnea and preserved ejection fraction. PCWP increased to a larger extent in patients with heart failure with preserved ejection fraction (HFP EF) as compared to patients with noncardiac dyspnea (NCD) with leg elevation and during exercise (A). PCWP returned to baseline almost immediately in recovery. LVEDP (B) and mean PAP (C) also rose with exercise more dramatically in the HFP EF group (P for exercise change between groups). (Reproduced with permission from: Borlaug BA, Nishimura RA, Sorajja P, Lam CSP, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. *Circ Heart Fail* 2010;3:588–595.)

pressures of sufficient magnitude to cause symptoms. Cardiac output increased normally, yielding an exercise index of 1.2 and an exercise factor of 5.8.

![Graph showing hemodynamic changes during exercise](image)

These data are compatible with mild mitral stenosis and illustrate the changes in the diastolic pressure gradient across the mitral valve required to produce an increase in cardiac output appropriate to the increased oxygen requirements of strenuous exercise.

In evaluating hemodynamic changes across stenotic valves during exercise, it is often found that the calculated valve area during exercise varies somewhat from that calculated on the basis of resting data (it is usually slightly larger). This variance is usually small and may be related to actual changes in the degree of valvular obstruction (i.e., a higher gradient and greater flow may force the stenotic leaflets to open wider), deficient data, or computational errors inherent in the assumptions applied to the equation for calculating valve orifice size.

### Valvular Insufficiency

The hemodynamic consequences of valvular insufficiency with ventricular volume overload may be subtle at rest. Dynamic
**Section V Evaluation of Cardiac Function**

### Table 20.2
**Response to Supine Bicycle Exercise in a 36-Year-Old Woman with Dilated Cardiomyopathy**

<table>
<thead>
<tr>
<th>Hemodynamic Parameter</th>
<th>Resting</th>
<th>Exercise (6 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen consumption index (mL/min/m²)</td>
<td>117</td>
<td>504</td>
</tr>
<tr>
<td>Atroventricular oxygen difference (mL/L)</td>
<td>34</td>
<td>75</td>
</tr>
<tr>
<td>Cardiac index (L/min/m²)</td>
<td>3.4</td>
<td>6.7</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>80</td>
<td>140</td>
</tr>
<tr>
<td>Systemic arterial pressure (mmHg), systolic/diastolic (mean)</td>
<td>130/70 (95)</td>
<td>142/83 (110)</td>
</tr>
<tr>
<td>Right atrial mean pressure (mmHg)</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Pulmonary capillary wedge mean pressure (mmHg)</td>
<td>11</td>
<td>27</td>
</tr>
<tr>
<td>Left ventricular pressure (mmHg)</td>
<td>130/17</td>
<td>142/28</td>
</tr>
<tr>
<td>Exercise index</td>
<td>—</td>
<td>1.1</td>
</tr>
<tr>
<td>Exercise factor</td>
<td>—</td>
<td>8.5</td>
</tr>
</tbody>
</table>

Exercise, by calling on the heart to substantially augment its forward cardiac output, may elicit changes in LVEDP and volume (preload) and in systemic vascular resistance (afterload) that are useful in assessing the cardiovascular limitations imposed by the valve lesion. Of particular importance here is the inability of many patients with valvular insufficiency to increase forward cardiac output in an appropriate manner, resulting in a low exercise index and an abnormal exercise index.

### Table 20.3
**Response to Supine Bicycle Exercise in a 60-Year-Old Man with Dilated Cardiomyopathy**

<table>
<thead>
<tr>
<th>Hemodynamic Parameter</th>
<th>Resting</th>
<th>Exercise (6 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen consumption index (mL/min/m²)</td>
<td>128</td>
<td>469</td>
</tr>
<tr>
<td>AV O₂ difference (mL/L)</td>
<td>40</td>
<td>96</td>
</tr>
<tr>
<td>Cardiac index (L/min/m²)</td>
<td>3.2</td>
<td>4.9</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>90</td>
<td>141</td>
</tr>
<tr>
<td>Systemic arterial pressure (mmHg), systolic/diastolic (mean)</td>
<td>91/62 (73)</td>
<td>107/67 (88)</td>
</tr>
<tr>
<td>Right atrial mean pressure (mmHg)</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>Pulmonary capillary wedge mean pressure (mmHg)</td>
<td>12</td>
<td>34</td>
</tr>
<tr>
<td>Left ventricular pressure (mmHg)</td>
<td>91/16</td>
<td>107/34</td>
</tr>
<tr>
<td>Exercise index</td>
<td>—</td>
<td>0.85</td>
</tr>
<tr>
<td>Exercise factor</td>
<td>—</td>
<td>4.9</td>
</tr>
</tbody>
</table>
Figure 20.8 Simultaneous pressure recordings from left atrium and left ventricle at rest and at 5 minutes of bicycle ergometer exercise in a patient with mitral stenosis. The hemodynamic data for this patient are presented in Table 20.4.

factor. Dynamic exercise testing is especially valuable in such patients because the qualitative assessment of valvular insufficiency from angiograms may be unreliable and does not correlate well with the extent of functional impairment.

Figure 20.9 shows the hemodynamic response to dynamic bicycle exercise of a 55-year-old man with rheumatic heart disease and mitral regurgitation. The patient was able to increase cardiac output normally, but mean pulmonary capillary wedge pressure increased from 18 to 30 mmHg, with V waves rising to 60 mmHg, during 6 minutes of supine bicycle exercise. This patient had successful mitral valve replacement with relief of symptoms.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Resting</th>
<th>Exercise (5 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left atrial pressure (mmHg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>20</td>
<td>34</td>
</tr>
<tr>
<td>V</td>
<td>18</td>
<td>46</td>
</tr>
<tr>
<td>Mean diastolic</td>
<td>10</td>
<td>26</td>
</tr>
<tr>
<td>Left ventricular mean diastolic pressure (mmHg)</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Oxygen consumption (mL/min)</td>
<td>207</td>
<td>688</td>
</tr>
<tr>
<td>Atroventricular oxygen difference (mL/L)</td>
<td>31</td>
<td>74</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>6.5</td>
<td>9.3</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>72</td>
<td>108</td>
</tr>
<tr>
<td>Mitral valve area (cm²)</td>
<td>1.6</td>
<td>1.8</td>
</tr>
<tr>
<td>Exercise index</td>
<td>—</td>
<td>1.2</td>
</tr>
<tr>
<td>Exercise factor</td>
<td>—</td>
<td>5.8</td>
</tr>
</tbody>
</table>

*Same patient as in Figure 20.8.*
Performing a Dynamic Exercise Test

Dynamic exercise during cardiac catheterization is easily performed with a bicycle ergometer while the patient is supine. A protocol detailing the exercise test should be prepared beforehand to ensure that all essential data are obtained (Table 20.1). Pressures should be obtained so that the appropriate valve gradients can be evaluated, and LV pressure should be monitored if LV performance is in question.

Supine bicycle exercise tests are performed most easily when catheterization is done via the arm (e.g., brachial, radial) and/or neck (e.g., jugular vein) approach. However, supine bicycle exercise tests can also be conducted safely when catheterization is performed via the femoral approach if care is taken to place the right and left heart manifolds and transducers in a stable and accessible position on the chest, away from leg motion artifact, and if the femoral venous and arterial sheaths are visualized and secured in place by the hand of one operator during exercise to ensure that catheters and sheaths are not displaced by leg movement.

We usually carry out a supine bicycle exercise test immediately after baseline hemodynamic values and cardiac output have been measured, before contrast angiography. The patient's feet are secured in the bicycle stirrups, and the right heart, left heart, and systemic arterial catheters and attached manifolds are positioned in such a way that they are not kinked or under tension and will not be disturbed during the exercise. Next, the system for measuring O₂ consumption is put in place (see Chapter 11). Alternatively, cardiac output can be assessed with the use of an indicator dilution technique (e.g., thermodilution), and O₂ consumption can be estimated as the quotient of cardiac output and AV O₂ difference.

Before beginning exercise, the patient is instructed that he/she will be coached to achieve a certain level of submaximal exercise over the first 1 minute that can be sustained for an additional 4 to 6 minutes. Such detailed patient instruction is useful because some patients may be accustomed to the different format of progressively graded exercise aimed at achieving a transient level of maximal, exhaustion-limited exercise used in upright treadmill tests. A sufficient number of syringes for measuring systemic arterial and mixed venous (pulmonary artery) blood oxygen saturation content should be at hand.

With the patient resting quietly and feet positioned on the bicycle, all manometers are zeroed, phasic and mean pressures are recorded at 25 or 50 mm/second speed and at the gain to be used during exercise, and cardiac output measurements are repeated to obtain an accurate pre-exercise baseline with legs elevated in the stirrups. Manometers are zeroed once again, all pressures are then redisplayed, and the recording speed is slowed (to 5 to 10 mm/second). Exercise is then begun with all pressures displayed continuously on the monitor and recorded at slow speed. We generally record LV phasic pressure, systemic arterial (e.g., radial or femoral artery) mean pressure, and pulmonary capillary mean pressure simultaneously. It is desirable to choose a gain setting on the recorder such that all pressures may be visualized simultaneously (as shown in Figure 20.9). At each 1-minute interval, a brief recording of all three phasic pressures at a recording speed of 25 to 50 mm/second is accomplished, after which the pulmonary capillary and systemic arterial pressures are returned to mean and the recording speed is slowed to 5 to 10 mm/second. Continuous observation and recording of pressures is important because it permits accurate monitoring of any rise in filling pressure or fall in arterial pressure during exercise and ensures that catheters remain in correct position for measurements at peak exercise.

After the patient has achieved a steady state level of exercise for 4 minutes, simultaneous LV-systemic arterial, LV-PCW, and PCW-to-pulmonary artery pullback pressures are recorded during minutes 4 to 6, after increasing the recorder speed to 50 mm/second without attempting to rezero the transducers. The right heart catheter is pulled back to the pulmonary artery, and exercise cardiac output is measured by the Fick or thermodilution technique, at which time systemic arterial and pulmonary artery blood samples are drawn for measurement of oxygen saturation.
Precautions should be taken during exercise to ensure patient safety. The duration and intensity of the exercise must be tailored to fit the needs of the individual patient. The electrocardiogram (ECG) should be monitored constantly to avoid serious arrhythmias, and exercise should be terminated if significant symptoms or greatly abnormal hemodynamic alterations occur. Little additional diagnostic information can be obtained by continuing the exercise to the point of producing pulmonary edema.

**ISOMETRIC EXERCISE**

Sustained isometric contraction of the forearm flexor muscles produces a cardiovascular reflex consisting of increases in heart rate, arterial blood pressure, and cardiac output. The precise nature of this reflex is not completely understood, but it appears to require afferent neural impulses from the exercising extremity and may be related to inhibition of vagal activity. Although the cardiac output response may be blunted, the anticipated responses in heart rate and blood pressure are not blocked by administration of propranolol, indicating that more is involved than a simple increase in \( \beta \)-adrenergic stimulation.

**Hemodynamic Response**

The hemodynamic response to isometric handgrip exercise has been studied in a series of normal subjects and patients with heart disease.\(^22\) In normal adult subjects, heart rate, systemic arterial pressure, and cardiac output increase, whereas systemic vascular resistance shows no change, indicating that the increase in systemic arterial pressure is caused by the increased cardiac output rather than by a vasoconstrictor response. No significant or consistent change in LVEDP or stroke volume occurs, whereas stroke work, a function of both arterial pressure and stroke volume, usually increases. The augmentation of LV performance during isometric exercise may be caused by both increased LV myocardial contractility\(^22\) and the Frank–Starling mechanism.

Patients with heart disease and decreased LV function or contractile reserve commonly show an abnormal hemodynamic and contractile response to isometric exercise.\(^22\) Although the maximum rate of rise of LV pressure, peak \( dP/dt \), may increase in diseased hearts, the change is of less magnitude than in normal subjects. LV stroke work may increase, remain unchanged, or decrease in response to isometric exercise in pathologic states. This may itself be evidence of compromised LV function but is more apparent when the change in stroke work is compared with the change in LVEDP. Significant increases in LVEDP are seen commonly in the abnormal response to isometric exercise\(^22\) and indicate decreased contractile reserve, dependence on the Frank–Starling mechanism to augment LV performance, and probably some component of diastolic dysfunction.

**Performing an Isometric Exercise Test**

Isometric exercise is most commonly performed as sustained handgrip. The subject is first tested to evaluate maximal voluntary contraction strength. A partially inflated sphygmomanometer cuff or a specially designed handgrip dynamometer may be used. This testing may be done before cardiac catheterization and well before the actual handgrip test. The patient must be coached and encouraged to grip as hard as possible when maximal voluntary contraction strength is determined. Baseline resting hemodynamic data should include heart rate, systemic arterial pressure (phasic and mean), LV pressure, and cardiac output. Cardiac output is most easily determined for this form of exercise by the indicator dilution method (e.g., thermodilution) or by the Fick method with the continuous \( \dot{O}_2 \) consumption measurement technique.

Once baseline data are collected, the subject is asked to grip the dynamometer at a contraction level 30% to 50% of the previously determined maximal voluntary contraction. Some coaching is usually required to ensure that the patient sustains the grip. It is important that the patient not do a Valsalva maneuver during handgrip exercise and that the respiratory pattern be closely observed. Valsalva maneuver may be avoided simply by engaging the patient in conversation during the test. We have used 50% maximal voluntary contraction for 3 minutes, with repeat measurements of pressures and cardiac output beginning at 2.5 minutes, so that measurements are completed by 3 minutes and the test may be terminated. The ECG should be monitored continuously to exclude the appearance of arrhythmias.

**PACING TACHYCARDIA**

Graded tachycardia induced by atrial pacing was first introduced in 1967 by Sowton et al.\(^23\) as a stress test that could be used in the cardiac catheterization laboratory to evaluate patients with ischemic heart disease. They noted that artificially increasing the heart rate by pacing the right atrium usually could induce angina in patients with symptomatic coronary artery disease. Moreover, they found that the degree of pacing stress needed to produce ischemia, defined in terms of pacing rate and duration, was more or less reproducible in any given patient. Since this original report, numerous investigators have described characteristic pacing-induced ECG changes,\(^24-30\) alterations in adenosine production\(^31,32\) and myocardial lactate metabolism,\(^35,36\) hemodynamic abnormalities,\(^33-39\) regional wall motion abnormalities,\(^39,41\) and defects in thallium scintigraphy.\(^42,43\) Although agreement on the overall usefulness of atrial pacing has not been universal, it is clear that the technique can safely and reliably induce ischemia in most patients with coronary artery disease and that information obtained during the pacing-induced ischemic state is often helpful in the diagnosis and treatment of the patient’s underlying disease.
Hemodynamic Effects of Pacing Tachycardia

The principal form of stress that accompanies pacing tachycardia is an increase in myocardial $O_2$ consumption secondary to the increased heart rate and an increase in myocardial contractility because of the treppe effect. Associated with this increase in myocardial $O_2$ consumption is a reflex coronary vasodilatation with an increase in myocardial blood flow. Apart from these changes in oxygen demand and supply, pacing tachycardia appears to be associated with no major hemodynamic stress, at least in patients with normal coronary arteries. Artificially increasing the heart rate by pacing the right atrium is accompanied by a concomitant decrease in ventricular stroke volume with little or no overall change in cardiac output. Moreover, there appears to be no significant change in ventricular afterload, venous return, or circulating catecholamines during pacing tachycardia.

Differences between Pacing Tachycardia and Exercise Stress

The physiology of pacing is distinctly different from that of dynamic or isometric exercise, in which there are not only increases in heart rate and myocardial contractility but also major changes in ventricular loading conditions and cardiac output in response to the increased metabolic demands from the periphery. Because of the differences in physiology between atrial pacing and exercise, each technique has relative advantages and disadvantages as a form of stress testing in the catheterization laboratory. Unlike pacing, exercise is associated with an increase in both heart rate and systolic blood pressure. As a result, exercise is usually capable of achieving a higher rate–pressure product (i.e., heart rate × peak systolic pressure) and represents a more severe form of stress with larger increases in myocardial $O_2$ consumption. On the other hand, pacing is not associated with exercise-induced changes in cardiac output or ventricular loading conditions, and, as a result, characterization of ventricular function is easier. In addition, atrial pacing is superior to exercise for evaluating myocardial metabolic function, because the rapid rise in arterial blood lactate and adenosine levels that accompanies exercise may obscure alterations of myocardial lactate metabolism and adenosine production. Finally, unlike in the case of exercise, with the termination of pacing and the rapid diminution of myocardial oxygen requirement, myocardial ischemia almost always resolves rapidly (i.e., within 1 to 2 minutes). As a result, the physician has more control over the amount of stress that the patient experiences, with very little prolonged ischemia occurring in the poststress period.

Pacing tachycardia has been in use for more than 30 years as a form of stress testing in patients with heart disease. The technique has been most useful in the assessment of patients with coronary artery disease.

Method for a Pacing Stress Test

Atrial pacing protocols can usually be carried out in the cardiac catheterization laboratory without undue prolongation of the routine catheterization procedure or significant added risks to the patient. In our experience, pacing is best conducted after the routine diagnostic aspects of catheterization are completed and usually extends the procedure by no more than 15 to 30 minutes, depending on the details of the protocol. It is important that detailed planning of the protocol be done before the catheterization is begun to help incorporate atrial pacing into the routine catheterization procedure as much as possible without unnecessary repetition of maneuvers and excessive prolongation of arterial time.

The type of catheter used for the pacing protocol can vary depending on the type of information that is to be evaluated during the pacing procedure. In general, the pacing catheter can be either unipolar or bipolar. If pacing is to be conducted with simultaneous myocardial metabolic assessment, a Gorlin pacing catheter that allows simultaneous pacing and coronary sinus lactate sampling is ideal (Bard, Murray Hill, NJ). Sampling of both coronary sinus lactate and adenosine has been accomplished with the use of a specially designed catheter placed in the coronary sinus. If pacing is to be conducted with simultaneous measurement of left heart filling pressures and cardiac output, then both a pacing catheter and a second right heart catheter (typically a thermodilution flow-directed catheter) may be inserted into the right side of the heart.

Perhaps the most critical part of the atrial pacing technique is proper placement of the pacing lead because accidental displacement of the pacing tip during pacing can disrupt the protocol. The pacing lead can be placed at the junction of the superior vena cava and right atrium, at the lateral right atrial wall, or in the coronary sinus. Placement of the pacing lead is most stable at either the first or the last of these positions because displacement of the lead commonly occurs from the lateral atrial wall during respiration. Stimulation of the phrenic nerve with subsequent diaphragmatic stimulation also occurs commonly with placement of the catheter against the lateral atrial wall. To avoid problems with displacement of the pacing tip, we use a bipolar flared pacing catheter (AtrisPace I, Mansfield Scientific, Mansfield, MA).

Once the pacing catheter is positioned in the right atrium, it is connected to the pulse generator unit. This unit should be equipped with a fixed-rate mode, pacing at least up to 170 beats per minute (bpm), and a variable output from 0.5 to 10 mA. Bipolar pacing catheters may be connected directly to the pacemaker unit or attached through extension wires with alligator clamps. Unipolar catheters should have their negative pole grounded to the skin via either a needle electrode or standard ECG plates. Once the pacing catheter has been positioned properly and connected to the pulse generator, the ability of the pacemaker to stimulate the atrium and to control ventricular rate should be assessed. Initially, the output of the generator is set at 2 to 3 mA, and the pacing rate is adjusted to 10 bpm faster than the sinus rate. Pacing
is then begun, and if there is atrial and ventricular capture, the pacing rate is increased by 10 bpm every 5 seconds until a rate of 150 to 160 bpm is reached. Inadequate pacing may occur secondary to an inadequate output of the pulse generator, improper lead positioning, or the development of atrioventricular block. The output of the pulse generator may be increased, but, in general, stimulating energies in excess of 7 to 8 mA frequently result in painful phrenic nerve stimulation. If excessively high energies are required for capture, the electrode lead should be repositioned. If atrioventricular block develops at high stimulator rates, 1 mg atropine may be administered intravenously: This usually ensures adequate atrioventricular conduction up to rates of 140 bpm or more.

After the lead has been properly positioned and an adequate trial of pacing to assess capture has been performed, the actual pacing protocol may be begun. A pacing stress test usually begins with pacing at approximately 20 bpm above the baseline rate, with increases of 20 bpm every 2 minutes, until angina pectoris or characteristic hemodynamic alterations occur, or until 85% of maximum age-predicted heart rate is achieved. Placement of a thermodilution balloon-tip flow-directed catheter, a left heart catheter, and a radial arterial cannula (or femoral arterial sheath side arm) before pacing allows simultaneous assessment of right- and left-side heart pressures, cardiac output measurement by thermodilution and/or Fick method, and determination of systemic and pulmonary vascular resistances. Assessment of LV volumes also may be accomplished with standard angiographic, echocardiographic, or radionuclide techniques.

Following the induction of chest pain during pacing tachycardia, pacing may be continued at the same heart rate safely for up to 3 to 5 minutes, during which time hemodynamic, metabolic, and ECG data may be obtained. After cessation of pacing, chest pain usually resolves quickly, but it may occasionally persist for up to 1 to 2 minutes after the return to sinus rhythm.

Pacing-Induced Angina

Initial reports on the use of atrial pacing tachycardia suggested that pacing-induced angina was a sensitive marker for the presence of ischemic heart disease and could serve as a suitable ischemic end point of pacing protocols. Specifically, the induction of angina was thought to mark a highly reproducible anginal threshold defined in terms of pacing rate and duration. Subsequent investigators have found, however, that chest pain is neither a sensitive nor a specific indicator of the presence of coronary artery disease. For example, Robson et al. demonstrated that chest pain could be elicited in 80% of patients with normal coronary arteries if they were paced at extremely high rates (in excess of 180 bpm). Moreover, Chandraratna et al. demonstrated the absence of angina in some patients with coronary artery disease who were stressed with pacing tachycardia at a high rate. Similarly, in terms of defining the anginal threshold according to the pacing rate and duration, as many as 20% of individuals have been shown to have considerable variation in these parameters. In view of these results, it is clear that chest pain alone should not be used as a reliable marker for the presence of pacing-induced ischemia. However, improved sensitivity and specificity of pacing-induced chest pain are noted when additional evidence of ischemia, such as pacing-induced ECG changes or myocardial metabolic abnormalities, is present.

Electrocardiographic Changes in Response to a Pacing Stress Test

Like pacing-induced angina, the presence of ischemic ST-segment depression during pacing tachycardia has not been regarded previously as a sensitive or specific marker for the presence of coronary artery disease. For example, in terms of sensitivity, Rios and Hurwitz compared pacing tachycardia and exercise in 50 patients and found diagnostic ECG changes in only 20% of patients who underwent pacing tachycardia, as compared with 83% of patients who underwent exercise testing. Similarly, in terms of specificity, Robson et al. reported ST-segment depression of 1.5 mm or more during pacing tachycardia in as many as 80% of patients with normal coronary arteries. In addition to the poor overall sensitivity and specificity, pacing tachycardia is associated with certain distortions of the ECG that sometimes make interpretation of ischemic ST-segment changes difficult or impossible. Pacing is associated with prolongation of the PR interval in most patients, and extreme prolongation of this interval can cause the pacemaker spike to fall within the ST segment of the preceding paced complex, thereby obscuring potential ST-segment changes.

Despite the previously reported poor utility of pacing-induced ECG changes, work from our laboratory has suggested an improved sensitivity and specificity of ischemic ST-segment depression during pacing tachycardia if certain technical guidelines of the pacing protocol are followed. Several earlier pacing trials that reported a low sensitivity of pacing ECG changes used only limited 3-lead recording, and it is clear, at least with standard exercise testing, that sensitivity can be improved substantially with full 12-lead monitoring.

To maximize the utility of pacing-induced ECG changes, pacing trials should be conducted with the use of the following guidelines. First, a 12-lead ECG is used for monitoring, and the ECG is regarded as positive for myocardial ischemia if ≥1 mm of horizontal or downsloping ST-segment depression is produced. Second, pacing tachycardia is terminated when 85% of maximal age-predicted heart rate is achieved or when typical ischemic chest pain is accompanied by diagnostic ECG changes. Finally, if marked prolongation of the PR interval distorts the preceding ST-segment changes, the ECG is considered positive for ischemia only if there is ST-segment depression in the first five beats after the discontinuation of the pacing stimulus.
Using these guidelines, actual pacing protocols conducted in our laboratory had an overall sensitivity and specificity of 94% and 83%, respectively, with regard to pacing-induced ECG changes. In addition, distortion of the ST segment by the pacing stimulus because of marked prolongation of the PR interval appeared to occur infrequently when the peak pacing rate was no higher than 85% of the maximum age-predicted heart rate. Moreover, in at least one subgroup of patients who were tested with both atrial pacing and standard treadmill exercise, the concordance between pacing-induced and exercise-induced ECG changes was 90%. Examples of pacing-induced and exercise-induced ECG changes for a patient with normal coronary arteries are shown in Figure 20.10A and for a patient with coronary artery disease in Figure 20.10B.

Figure 20.10  A. Electrocardiographic (ECG) response to atrial pacing and exercise stress in a man with normal coronary arteries. From top to bottom, leads V4, V5, and V6 are monitored. B. Comparison of ECG response to atrial pacing and exercise stress in a man with severe three-vessel coronary artery disease. Leads V4, V5, and V6 are monitored (top to bottom) as in A. ST depression occurs to the same degree with both types of stress. (From Heller GV, et al. The pacing stress test: reexamination of the relation between coronary artery disease and pacing-induced electrocardiographic changes. Am J Cardiol 1984;54:50, with permission.)
The sensitivity of pacing-induced ECG changes may be further improved with the use of endocardial electrograms obtained during the pacing stress test. Nabel et al.\(^\text{10}\) reported on the use of local unipolar electrograms recorded from the tip of a 0.064-cm diameter guidewire positioned against the endocardial surface of potentially ischemic regions. Endocardial electrograms, LVEDP, and signals from multiple surface ECG leads were recorded before, during, and after rapid atrial pacing in 21 patients with coronary artery disease. Before pacing, endocardial electrograms in all 21 patients were free of ST-segment elevation. After rapid atrial pacing, marked ST-segment elevation was apparent in 17 of the 21 patients. This ST-segment elevation could be eliminated in all patients with the use of nitroglycerin. Moreover, in several patients, endocardial ST-segment elevation after pacing was eliminated by successful percutaneous coronary angioplasty of the critically stenosed artery supplying the ischemic region of myocardium. The authors concluded that endocardial electrographic changes are a reliable marker of pacing-induced myocardial ischemia and may be more sensitive than angina, pacing-induced hemodynamic changes, or ST-segment depression on the surface ECG.

### Myocardial Metabolic Changes Induced by a Pacing Stress Test

Abnormal myocardial metabolism has been documented during pacing-induced ischemia by means of coronary sinus sampling and the subsequent measurement of coronary arterial and venous blood lactate. Because lactate production is a byproduct of anaerobic glycolysis, its production by the heart and appearance within the coronary sinus is a sign of myocardial ischemia. Previous investigators have noted rapid increases in coronary sinus lactate levels during pacing tachycardia in patients with coronary artery disease, often before the appearance of angina.\(^\text{25,26}\) With cessation of pacing, the elevated coronary sinus lactate concentrations fall rapidly, representing a washout of the accumulated myocardial lactate and diminished lactate production as normal oxygenation is restored. Monitoring of arterial lactate levels while coronary sinus lactate levels are rising usually shows little or no elevation, in marked contrast to arterial lactate levels during exercise. As a result, atrial pacing tachycardia is superior to exercise for evaluating abnormal myocardial metabolic function because rapidly rising arterial lactate levels during exercise may obscure abnormal patterns of myocardial lactate metabolism.

Monitoring of coronary sinus lactate levels during pacing protocols is most easily accomplished with a Gorlin pacing catheter. Placement of the Gorlin catheter in the coronary sinus can usually be confirmed by injection of a small amount of contrast medium. Care must be taken not to perforate either the coronary sinus or the great cardiac vein, and not to place the pacing tip of the catheter too distally because placement of the distal catheter into the great cardiac vein may result in ventricular rather than atrial pacing.

Arterial and coronary venous blood lactate concentrations in response to a pacing stress test are illustrated in Figure 20.11. In the control state, the concentration of coronary sinus blood lactate is lower than the lactate concentration in arterial blood, reflecting the fact that the heart normally consumes lactate as a fuel. During pacing tachycardia, coronary sinus blood lactate concentration rises progressively and exceeds arterial blood lactate concentration, reflecting a shift to anaerobic metabolism of the ischemic myocardium. The lactate level falls rapidly after discontinuation of pacing because the heart rate returns to the control state immediately.

There has been interest in using coronary sinus adenosine as a marker of myocardial ischemia. Adenosine, a metabolite released by ischemic myocardium, elicits an increase in coronary artery blood flow in response to a decrease in the ratio of myocardial oxygen supply to demand. As a result, adenosine should be a more sensitive marker of myocardial ischemia than lactate, which requires anaerobic glycolysis. An early report demonstrated that adenosine increased in the arterial and coronary venous blood in patients with coronary artery disease and this persisted into recovery.

### Figure 20.11

Mean values for arterial (ART) and coronary sinus (CS) blood lactate concentration before (control), during (pacing), and after (recovery) tachycardia in 17 patients with coronary artery disease. Left ventricular end-diastolic pressure (LVEDP) changed little during pacing tachycardia but was elevated during brief periods of interruption of pacing (values in parentheses). ST-segment depression developed progressively during pacing tachycardia and resolved during recovery. Lactate extraction shifted to lactate production during ischemia, and this persisted into recovery for a brief period. (From Parker JO, Chiong MA, West RO, et al. Sequential alterations in myocardial lactate metabolism, S-T segments, and left ventricular function during angina induced by atrial pacing. Circulation 1969;40:113, with permission.)
coronary sinus blood of patients with ischemic heart disease during pacing tachycardia, and later Feldman et al. made several methodologic improvements regarding adenosine measurements. A double-lumen "metabolic" catheter was used that allowed the addition and mixing of a solution to stop adenosine metabolism at the tip of the catheter. Adenosine has a half-life of less than 1.5 seconds in human blood. Furthermore, there are numerous sources of artifactual adenosine production in human blood. It is therefore essential that a solution that inhibits both the breakdown and the production of adenosine be mixed with human blood at the site of collection. Using this technique, adenosine was demonstrated to be a more sensitive marker of myocardial ischemia than lactate. Every patient with coronary artery disease (n = 9) atrially paced to ischemia demonstrated at least a 1.5-fold increase in coronary sinus adenosine. In contrast, only three of these nine patients had lactate production. In a subsequent study with improved methodology, patients with coronary artery disease (n = 17) were found to have higher coronary sinus adenosine concentrations than found in a control group of patients (n = 6) at rest. This finding provides evidence that release of endogenous adenosine may be an intrinsic homeostatic mechanism to maintain resting flow distal to a stenotic coronary artery.

**Hemodynamic Changes during a Pacing Stress Test**

Patients without ischemic heart disease who are stressed by atrial-paced tachycardia generally demonstrate no significant change in cardiac output, mean arterial pressure, AV O2 difference, or systemic vascular resistance. LVEDP and pulmonary capillary wedge pressure usually fall during pacing tachycardia and then return to pre-pacing baseline levels in the immediate postpacing period. LV end-diastolic and end-systolic volumes fall during pacing tachycardia, with a decrease in stroke volume and no significant change in ejection fraction.

Patients with coronary artery disease who are paced to ischemia likewise manifest no significant change in cardiac output, mean arterial pressure, AV O2 difference, or systemic vascular resistance. Some investigators have documented slight decreases in cardiac output with slight increases in mean arterial pressure, AV O2 difference, and systemic resistance. However, these differences are probably related to the intensity of pacing-induced ischemia, its duration before the measurement of hemodynamic variables, and the amount of myocardium that has become ischemic, with more extensive hemodynamic abnormalities occurring in the setting of more extensive myocardial ischemia. The most dramatic differences in pacing hemodynamics between patients with normal coronary arteries and those with coronary artery disease are seen in terms of LV pressure–volume relationships during pacing tachycardia and in the immediate postpacing period. Of note, LV filling pressures do not show the progressive decrease seen in nonischemic patients, and elevations in pulmonary capillary wedge, mean pulmonary artery, and occasionally in LV end-diastolic pressures occur at maximum pacing. Most importantly, there is an abrupt rise in LVEDP in the immediate postpacing period. Similarly, LV end-diastolic and end-systolic volumes decrease less during pacing-induced tachycardia in patients with ischemic heart disease as compared with normal subjects, and there is often a significant decrease in LV ejection fraction.

A study looking at pressure–volume relationships during pacing tachycardia conducted by us well illustrates the differences between nonischemic and ischemic hemodynamic responses to pacing. In this study, 22 patients, including 11 patients with normal coronary arteries and 11 with significant coronary artery disease, underwent sequential atrial pacing with simultaneous monitoring of LV pressure and ventricular volume measured by gated radionuclide ventriculography. Using synchronized LV pressure tracings and radionuclide time–activity volume curves, three sequential pressure–volume diagrams were constructed for each patient, corresponding to baseline, intermediate, and maximum pacing levels. All 11 patients with coronary artery disease demonstrated angina and significant ST-segment depression at maximum pacing, but none of the 11 patients with normal coronary arteries showed any evidence of pacing-induced ischemia.

Figure 20.12 shows typical LV pressure–volume curves for a patient with normal coronary arteries stressed with pacing tachycardia. Notably, there is a progressive leftward shift for the loop, with increasing heart rate, and a progressive downward shift in the LV diastolic limb of each pressure–volume curve. It is clear that changes in both systolic and diastolic function have occurred in these patients during pacing tachycardia. In terms of systolic function, the progressive leftward shift of the end-systolic portion of the loop presumably represents increased contractility secondary to the tachycardia. Other investigators have likewise demonstrated a positive inotropic stimulus in response to increased heart rate, with increases in isovolumetric contraction indices (e.g., dP/dt) and ejection-phase indices (e.g., circumferential fiber shortening) during pacing tachycardia. With respect to diastolic function, the progressive downward shift of the diastolic limbs seen in Figure 20.12 suggests that LV distensibility has increased slightly during pacing tachycardia. Whether this downward shift is related to an increase in myocardial relaxation, an alteration in viscoelastic properties, or a change in factors extrinsic to the myocardium (e.g., right ventricle, pericardium) is not known. It is notable that some investigators have documented small increases in markers of diastolic relaxation during pacing-induced tachycardia, such as peak negative dP/dt and the time constant tau in normal animals and the peak rate of posterior wall thinning and LV internal dimension changes in humans.

Figure 20.13 shows sequential LV pressure–volume diagrams for a patient with coronary artery disease whose heart rate was increased progressively by atrial pacing. All patients in our study who developed chest pain and ischemic ECG
Sequential left ventricular pressure–volume diagrams for a patient with normal coronary arteries in response to atrial pacing tachycardia at three increasing heart rates (see text for discussion). (From Aroesty JM, et al. Simultaneous assessment of left ventricular systolic and diastolic dysfunction during pacing-induced ischemia. Circulation 1985;71:889, with permission.)

Changes demonstrated a similar pressure–volume pattern with an initial shift of the pressure–volume loop to the left at an intermediate heart rate, followed by a rightward shift at peak pacing when ischemia developed. In terms of systolic function, it is clear that pacing resulted in an initial treppe effect with a leftward shift of the end-systolic portion of the diagram at intermediate pacing, followed by systolic failure at peak pacing with an increase in ventricular volumes and a rightward shift in the end-systolic portion of the curve. Similarly, in terms of diastolic function, it is evident that the patient did not show a progressive downward shift of the diastolic limb of the LV pressure–volume curve, but actually exhibited an upward shift at intermediate and peak pacing. In part, the increase in LVEDP at peak pacing is related to systolic failure with an increase in ventricular volume. Because the patient did not exhibit evidence of systolic failure at the intermediate pacing level, however, it is also clear that this patient has experienced a primary decrease in LV diastolic distensibility so that pressure is higher at any given chamber volume throughout diastole.

Sequential left ventricular pressure–volume diagrams in a patient with three-vessel coronary artery disease who was paced at three increasing heart rates. The patient developed angina and ischemic ST depression at peak pacing. (See text for discussion.) (From Aroesty JM, et al. Simultaneous assessment of left ventricular systolic and diastolic dysfunction during pacing-induced ischemia. Circulation 1985;71:889, with permission.)
Speculation has continued over the last three decades as to whether the increase in diastolic pressures during pacing-induced ischemia is related to a primary decrease in distensibility or is secondary to systolic failure with increases in ventricular volume. At present, it seems clear that both mechanisms play some role in creating the elevated diastolic pressures. The evidence, however, suggests that changes in diastolic distensibility actually precede altered systolic function. The cause of the altered diastolic distensibility during pacing-induced ischemia has been debated, and a number of different mechanisms have been proposed, including incomplete myocardial relaxation, altered diastolic tone, partial ischemic contracture of some myofibrils within the distribution of the stenotic or occluded coronary artery, altered right ventricular loading, and influence of the pericardium. At present, it seems likely that relaxation of myocardial cells within the reversibly ischemic region is slowed and does not proceed to completion by end-diastole. This may be related to impaired diastolic calcium sequestration by sarcoplasmic reticulum, but data are insufficient to permit a firm conclusion.

The postpacing rise in LVEDP is perhaps the most concrete evidence of pacing-induced ischemia during atrial pacing protocols. In our protocols, this postpacing rise has been calculated on beats 5 through 15 after discontinuation of pacing, with >5 mmHg increase in LVEDP in comparison with the prepacing baseline being considered abnormal. Figures 20.14 and 20.15 summarize hemodynamic changes in response to a pacing stress test in patients with normal coronary arteries and in those with ischemic heart disease.

Quantification of the hemodynamic alterations induced by pacing tachycardia may also be useful in assessing myocardial performance in patients with other forms of cardiac disease. Feldman et al. used atrial pacing tachycardia to evaluate the systolic and diastolic myocardial reserve of patients with dilated cardiomyopathy. 

Regional Wall Motion Abnormalities During a Pacing Stress Test

Regional wall motion abnormalities during pacing-induced ischemia have been noted with contrast ventriculography, gated radionuclide ventriculography, and transesophageal

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**Figure 20.14** Changes in cardiac index, systemic vascular resistance (SVR), and arteriovenous oxygen (AV \( O_2 \)) difference in 5 patients with normal coronary arteries and 20 patients with coronary artery disease (CAD) during pacing tachycardia. Patients with CAD showed a significant decrease in cardiac index and increases in SVR and AV \( O_2 \) difference during maximum pacing tachycardia. (From McKay RG, et al. The pacing stress test reexamined: correlation of pacing-induced hemodynamic changes with the amount of myocardium at risk. *J Am Coll Cardiol* 1984;3:1469, with permission.)
Clinical Uses of Atrial Pacing

Echocardiography. Using contrast ventriculography, Dwyer et al. studied eight patients with coronary artery disease who were paced to angina and found that three developed regional hypokinesis in one area, while the remaining five developed at least two separate areas of hypokinesis or akinesis. In all cases, an associated coronary artery lesion could be identified in the vessel that supplied the area of the new regional wall motion abnormality. Similarly, Tzivoni et al., using radionuclide ventriculography, found that 9 of 11 patients developed new regional wall motion abnormalities in response to pacing-induced ischemia.

The overall specificity and sensitivity of pacing-induced regional wall motion abnormalities have been defined with the development of simultaneous transesophageal two-dimensional echocardiography and atrial pacing. Lambertz et al. first developed an ultrasound system in which an atrial pacing facility was incorporated. Fifty patients were evaluated prospectively by cardiac catheterization and pacing echocardiography; 44 had correlative exercise testing. Nine patients were found to have normal epicardial coronary arteries and normal pacing results (100% specificity). Thirty-eight of the 41 patients with significant coronary artery disease developed regional wall motion abnormalities with pacing (93% sensitivity). In contrast, the specificity and sensitivity for exercise testing were 50% and 53%, respectively.

**Clinical Uses of Atrial Pacing**

Complete evaluation of a patient's cardiac function in the catheterization laboratory often requires an examination of the patient's performance under stressed conditions, when ECG, metabolic, and hemodynamic abnormalities may manifest themselves fully. The role of stress testing is particularly important in the evaluation of patients with ischemic heart disease, in whom, for example, it may be useful to determine the anginal threshold, the magnitude of hemodynamic impairment during ischemia, and the efficacy of antianginal therapy, and to establish a need for coronary revascularization. Although standard dynamic and isometric exercise may serve as a form of stress for many patients, not all patients are able to exercise because of physical disabilities, old age, pulmonary disease, peripheral vascular disease, or possible beta-blockade. In each of these situations, atrial pacing may be used as a suitable form of stress.

**DOBUTAMINE STRESS TESTING**

Dobutamine is a racemic mixture of two enantiomers that activates α1, β1, and β2 adrenergic receptors. The (−) enantiomer has strong α-agonist properties, the effect of which is counteracted by the partial agonism of the (+) enantiomer and by vasodilation secondary to activation of β2 receptors. At doses commonly used, dobutamine has a predominant positive inotropic effect resulting in increased myocardial contractility and stroke volume. Higher doses lead to an increase in heart rate and to a modest peripheral vasodilation. The vasodilation is mediated by stimulation of β2 receptors that antagonizes the α effects of the (−) enantiomer. It should be noted that in patients who are on β-blockers, administration of dobutamine can...
increase peripheral vascular resistance, possibly owing to the unopposed α effect.57

Dobutamine stress testing is commonly used in conjunction with other imaging modalities for the evaluation of ischemia and myocardial viability, and it has been used in the cardiac catheterization laboratory to assess contractile reserve in patients with reduced left ventricular systolic function. In addition, dobutamine stress testing has emerged as a useful tool for assessing patients with low-flow, low-gradient aortic stenosis. The definition of severe aortic stenosis includes an aortic valve area of <1 cm², a peak transvalvular aortic valve velocity of ≥4 m/second and a mean gradient of ≥40 mmHg.58 However, there is a subset of patients who exhibit a discrepancy in these hemodynamic parameters. In these patients, the aortic valve area is <1 cm², but the mean gradient can be <30 mmHg (low-flow, low-gradient aortic stenosis).59 This discrepancy has been described in patients with left ventricular systolic dysfunction,60 although it can also occur in patients with preserved ejection fraction.61 The proposed mechanism for this discrepancy is that in patients with reduced ejection fraction, contractility and stroke volume are inadequate to lead to full opening of the aortic valve, thus resulting in underestimation of the actual aortic valve area. Inaccuracies related to the flow dependency of valve area calculations using the Gorlin formula have also been proposed (see Chapter 13 for a detailed discussion). Nishimura et al. evaluated with dobutamine challenge 32 patients who had a calculated aortic valve area of <1 cm², ejection fraction of <40%, and a mean gradient of <40 mmHg.69 Dobutamine infusion was started at 5 μg/kg/minute, with increments of 3 to 10 μg/kg/minute every 5 minutes. Contractile reserve was defined as an increase in stroke volume of ≥20% following dobutamine infusion. Endpoints used during dobutamine infusion were (a) maximum dose of 40 μg/kg/minute, (b) mean gradient of >40 mmHg, (c) 50% increase in cardiac output, (d) a peak heart rate of >140 beats/minute, or (e) development of any symptom. The average mean gradient was 27 ± 7 mmHg, and it increased to 41 ± 13 mmHg with dobutamine. Three patients who had a final aortic valve area of >1.2 cm² and four patients who had a final mean gradient of <30 mmHg were not referred for surgery. Four additional patients were not referred for surgery because they were felt to be at too high a risk. On the basis of the results of the dobutamine test, 21 patients underwent aortic valve replacement. Severe calcific aortic stenosis was found at the time of surgery in all the patients referred for surgery who had a final aortic valve area of <1.2 cm² at peak dobutamine infusion and a mean gradient of >30 mmHg. Among the patients who underwent surgery, the survival rate at follow-up was 80% (12/15) in the group with contractile reserve and 33% (2/6) in a small group without contractile reserve (Figure 20.16). These data suggest that in the setting of low-flow aortic stenosis, dobutamine challenge can aid in the identification of patients with true aortic stenosis, and it can further provide risk stratification on the basis of contractile reserve. The likelihood of true anatomic valvular stenosis is low when dobutamine challenge results in an increase in valve area without an increase in gradient (Figure 20.17).61 In addition, the poor prognosis in patients without contractile reserve has been confirmed by other studies that have assessed the value of dobutamine echocardiography in this patient population.60,63,64 While patients with contractile reserve tend to do significantly better with surgery when compared with medical therapy, patients without contractile reserve have a very poor prognosis with either surgery or medical therapy (Figure 20.18). Thus, the assessment of contractile reserve can be used for further risk stratification and, in conjunction with other factors, for triaging patients toward the appropriate therapy. On the basis of these and other studies, current guidelines for the management of patients with valvular heart disease list dobutamine echocardiography or cardiac catheterization with dobutamine challenge as a class IIa indication for the evaluation of patients with low-flow, low-gradient aortic stenosis.66

Figure 20.16

Clinical outcome of patients (pt) with low-output aortic stenosis (AS) who underwent aortic valve replacement (AVR). Contractile reserve was defined as an increase in stroke volume of >20% during dobutamine infusion. CHF, congestive heart failure; AVA, aortic valve area; periop, perioperative; Rx, treatment. (Reproduced with permission from: Nishimura, RA, Grantham, JA, Connolly HM, et al. Low-output, low-gradient aortic stenosis in patients with depressed left ventricular systolic function: the clinical utility of the dobutamine challenge in the catheterization laboratory. Circulation 2002;106:809–813.)
**Figure 20.17** Plot of the relationship between mean gradient (y-axis) and transvalvular flow (x-axis, bottom) according to the Gorlin formula for three different values of AVA (0.7, 1.0, and 1.5 cm²). Cardiac output (x-axis, top) is also shown, assuming a heart rate of 75 bpm and a systolic ejection period of 300 ms. At low transvalvular flows, mean gradient is low at all three valve areas. Two different responses to dobutamine challenge are illustrated for a hypothetical patient (○; Bsl) with a baseline flow of 150 mL/second, mean gradient of 23 mmHg, and calculated AVA of 0.7 cm². In one scenario (○; Dob 1), flow increases to 225 mL/second, mean gradient increases to 52 mmHg, and AVA remains at 0.7 cm², consistent with fixed AS. In the second scenario (●; Dob 2), flow increases to 275 mL/second, mean gradient increases to 38 mmHg, and AVA increases to 1.0 cm². This patient has changed to a different curve, consistent with relative or pseudo-AS. HR, heart rate; SEP, systolic ejection period. (Reproduced with permission from: Grayburn PA. Assessment of low-gradient aortic stenosis with dobutamine. *Circulation* 2006;113:604–606.)

**Figure 20.18** Kaplan–Meier survival estimates by group and treatment in patients with low-flow aortic stenosis evaluated with dobutamine echocardiography. In group I stroke volume increased by 33% and the ejection fraction increased by 12 ejection fraction units. The mean pressure gradient increased by 47%. In group II, stroke volume increased by 10%, ejection fraction increased by 7 ejection fraction units, and the mean pressure gradient increased by 32%. Cox proportional hazard analysis revealed that aortic valve replacement and left ventricular contractile reserve were independently associated with long-term survival. (Reproduced with permission from: Monin JL, et al. Low-gradient aortic stenosis: operative risk stratification and predictors for long-term outcome: a multicenter study using dobutamine stress hemodynamics. *Circulation* 2003;108:319–324.)
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Cardiac angiography was introduced initially to provide qualitative information regarding anatomic abnormalities of the cardiovascular system. Subsequently, it became apparent that quantitative information derived from cineangiography could provide insight into functional abnormalities of the heart as well. Direct measurement of ventricular dimension, area, and wall thickness allows calculation of volume, ejection fraction, mass, and wall stress. Assessment of pressure–volume relationships provides additional information regarding systolic and diastolic function of the ventricular chambers. Finally, the techniques developed to assess regional left ventricular wall motion have proved useful in the evaluation of patients with coronary artery disease. Therefore, the ventricular angiograms obtained by the techniques described in Chapter 17 can be used to derive quantitative descriptors of geometry and function.

**VOLUMES**

### Technical Considerations

As discussed in detail in Chapter 17, ventriculograms are generally recorded in digital format at 15 to 30 frames per second (fps), and radiographic contrast material is usually injected into the left ventricle at rates of 7 to 15 mL/second for a total volume of 25 to 45 mL. Alternatively, the left ventricle may be visualized from contrast injections into the pulmonary artery, the left atrium (by the trans-septal technique), or, in cases of severe aortic insufficiency, the aortic root. Attention to catheter position and injection rate minimizes the occurrence of ventricular ectopy during contrast studies; this is important because analysis of extrasystoles and postextrasystolic beats cannot be used for proper assessment of basal ventricular function.

With the widespread availability of computer systems, the technique of determining ventricular volumes has evolved from a handheld planimeter with pencil and paper (or a calculator) to semiautomated software packages. The principles important in accurate determination of volume, however, apply equally to manual and computer-based techniques. For example, the need for magnification correction applies to both manual and automated techniques of volume determination.

In the first step in assessing left ventricular chamber volume, the left ventricular outline or silhouette is traced. The ventricular silhouette should be traced at the outermost margin of visible radiographic contrast so as to include trabeculations and papillary muscles within the perimeter (Figure 21.1). The aortic valve border is defined as a line connecting the inferior aspects of the sinuses of Valsalva. Some computer-based systems require that the entire ventricular silhouette be traced manually; others incorporate a semiautomated edge-detection algorithm wherein some points on the ventricular silhouette are entered manually and others are supplied by the computer software.

To facilitate the calculation of left ventricular volume, the ventricle is often approximated by an ellipsoid. Alternatively, techniques based on Simpson’s rule, which is independent of assumptions regarding ventricular shape, may be used. According to this rule, the volume of any object is
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Figure 21.1 Left ventriculogram in the 30° right anterior oblique projection. The ventricular outline has been traced, as indicated by the broken line.

equal to the sum of the volumes of individual slices of known thickness composing the object. Thinner slices will result in more accurate measurements.4 Contemporary software programs may allow the user to choose between these two techniques. Because the x-rays emanate from a point source, they are nonparallel; correction must therefore be made for magnification of the ventricular image onto the detector. Finally, ventricular volumes calculated by most mathematical techniques overestimate true ventricular chamber volume, so that regression equations must be used to correct for the overestimation.

Biplane Formula

Biplane left ventriculography may be performed in the antero-posterior (AP) and lateral projections,2 the 30° right anterior oblique (RAO) and 60° left anterior oblique (LAO) projections,5 or angulated projections (e.g., 45° RAO and 60° LAO–25° cranial).6 Although it has a complex geometric shape, the left ventricle can be approximated with considerable accuracy by an ellipsoid2 (Figure 21.2). The volume of an ellipsoid is given by the equation

\[ V = \frac{4}{3} \pi \frac{L \cdot M \cdot N}{2 \cdot 2 \cdot 2} = \frac{\pi}{6} LMN \]  

(21.1)

where \( V \) is volume, \( L \) is the long axis, and \( M \) and \( N \) are the short axes of the ellipsoid. The long axis, \( L \), is taken practically to be \( L_{\text{max}} \), the longest chord that can be drawn within the ventricular silhouette in either projection. To determine \( M \) and \( N \), each of the biplane projections of the left ventricle is approximated by an ellipse. \( M \) and \( N \) are taken to be the minor axes of these ellipses. They are calculated by the area–length method, as introduced by Dodge et al.2 from the silhouette areas and long-axis lengths in each projection, using the standard geometric formula for the area of an ellipse as a function of its major and minor axes. For biplane oblique

Figure 21.2 Ellipsoid used as a reference figure for the left ventricle. The long axis, \( L \), and the short axes, \( M \) and \( N \), are shown.
(RAO/LAO) left ventriculography, for example, the areas of the two ventricular silhouettes are given as

\[ A_{\text{RAO}} = \pi \frac{L_{\text{RAO}}}{2} M \quad \text{and} \quad A_{\text{LAO}} = \pi \frac{L_{\text{LAO}}}{2} N \]  

(21.2)

\( L_{\text{RAO}} \) and \( L_{\text{LAO}} \) are the longest chords that can be drawn in the RAO and LAO silhouettes, respectively. The area of each traced silhouette (Figure 21.1) is obtained by planimetry, and \( M \) and \( N \) are calculated by rearrangement as follows:

\[ M = \frac{4A_{\text{RAO}}}{\pi L_{\text{RAO}}} \quad \text{and} \quad N = \frac{4A_{\text{LAO}}}{\pi L_{\text{LAO}}} \]  

(21.3)

Combining Equations (21.1), (21.2), and (21.3),

\[ V = \frac{\pi}{6} L_{\text{min}}^2 \left( \frac{A_{\text{RAO}}}{\pi L_{\text{RAO}}} \right) \left( \frac{A_{\text{LAO}}}{\pi L_{\text{LAO}}} \right) \]

\[ = \frac{8}{3\pi} \frac{A_{\text{RAO}} A_{\text{LAO}}}{L_{\text{min}}} \]  

(21.4)

where \( L_{\text{min}} \) is the shorter of \( L_{\text{RAO}} \) and \( L_{\text{LAO}} \). Because \( L_{\text{RAO}} \) is almost always longer than \( L_{\text{LAO}} \), \( L_{\text{LAO}} \) is usually substituted for \( L_{\text{min}} \).

Equation (21.4) is derived for projections at right angles, or orthogonal projections, and is applicable to biplane oblique ventriculography in the 30° RAO and 60° LAO views, as just described, or for the older AP and lateral format. Although it is not valid theoretically for non-orthogonal projections (e.g., RAO and angulated LAO), it has been demonstrated empirically to be useful in those situations as well.

Right ventricular volumes have been calculated from biplane AP and lateral images using a modification of the Dodge area–length technique, or Simpson’s rule. Because right ventricular volumes are rarely calculated from cineangiographic studies today, the reader is referred elsewhere for methodologic details.

Single-Plane Formula

The area–length ellipsoid method for estimating left ventricular chamber volume has been modified for use in the usual situation in which only single-plane measurements obtained in the AP or RAO projection are available. Inherent in single-plane methods is the assumption that the left ventricular shape may be approximated by a prolate spheroid—that is, an ellipsoid in which the two minor axes are equal. It is assumed that the minor axis of the ventricle in the projection used is equal to the minor axis in the orthogonal plane, which was not imaged. Recalling Eq. (21.1) for the general case of an ellipsoid:

\[ V = \frac{\pi}{6} LMN \]  

(21.5)

If only single-plane (e.g., RAO) ventriculography is done, we assume that \( M = N \) and that \( L \) in the plane presented is the true long axis of the ellipsoid. \( M \) is calculated from the single-plane silhouette area (\( A \)) and \( L \) by the area–length method as \( M = 4A/\pi L \). Therefore, the single-plane volume calculation becomes

\[ V = \frac{\pi}{6} LM^2 = \frac{\pi}{6} L \left( \frac{4A}{\pi L} \right)^2 = \frac{8A^2}{3\pi L} \]  

(21.6)

Magnification Correction: Single Plane

Correction may be accomplished by imaging a calibrated grid at the estimated level of the ventricle and submitting the grid to the same magnification process as that to which the ventricle is subjected. Use of x-ray systems in which the center of the ventricle can be positioned at a fixed point (isocenter), around which the x-ray tubes and image intensifiers rotate, allows for magnification correction without the use of grids.

The use of grids and other means of calculating magnification correction factors has been reassessed by Sheehan and Mitten-Lewis. They found that the error introduced by considering a large central square area of the grid rather than the portion encompassing a particular ventricular silhouette was negligibly small. Replacement of the grid by a circular disk did not significantly alter the calculated correction factor. Alternatively, the use of catheters with radiopaque markers separated by 1 cm also yielded accurate correction factors.

An approximation of the magnification correction may be obtained by considering the diameter of the catheter used for left ventriculography. However, there is a large potential percentage error in measurement of this small dimension, and the percentage error in volumes derived from it is roughly triple that in the linear correction factor. On the other hand, the error introduced into calculation of ejection fraction by this technique is much smaller than that in the calculation of ventricular volume; if it were not for the need for regression formulas (see later discussion), ejection fraction could be determined without regard to magnification.

In the single-plane formula, the cube of the linear correction factor adjusts the volume for magnification:

\[ V = \frac{8}{3\pi} (\text{CF})^3 \frac{A^2}{L} \]  

(21.7)

Magnification Correction: Biplane

In biplane studies, a correction factor (CF) must be calculated separately for each projection, yielding, in the case of biplane oblique cineangiography, \( \text{CF}_{\text{RAO}} \) and \( \text{CF}_{\text{LAO}} \). The linear correction factor is multiplied by the measured lengths, and the square of this correction factor is multiplied by planimetered areas to convert to true
lengths and areas. Accordingly, the corrected volume of the ventricle is

\[
V = \frac{8}{3\pi} \left( \frac{CF_{RAO}}{CF_{LAO}} \right)^2 \frac{A_{RAO}A_{LAO}}{L_{LAO}}
\]

where \( EDV \) is end-diastolic ventricular volume, \( ESV \) is end-systolic ventricular volume, and \( SV \) is the angiographic stroke volume.

In patients with aortic and/or mitral regurgitation, comparison of the angiographically determined stroke volume with the forward stroke volume determined by the Fick technique or (in the absence of concomitant tricuspid regurgitation) the thermodilution technique yields the regurgitant stroke volume, that portion of the ejected volume that is regurgitated and therefore does not contribute to the net cardiac output. The regurgitant fraction (RF) is defined as follows:

\[
RF = \frac{SV_{\text{angiographic}} - SV_{\text{forward}}}{SV_{\text{angiographic}}}
\]

Because the derivation of RF involves the difference between the two stroke volume measurements, both of which contain some degree of error, the error in RF itself may be significant; interpretation of this number should be influenced by qualitative assessment of the degree of regurgitation seen on the angiogram. In cases of combined aortic and mitral regurgitation, estimation of the relative contribution of the two lesions must be made from the cineangiograms.

### Table 21.1 Regression Equations to Correct for Overestimation in Calculation of Left Ventricular Volumes

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Angiographic Method</th>
<th>Age Group</th>
<th>Regression Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wynne et al.</td>
<td>Biplane cine RAO and LAO</td>
<td>Adults</td>
<td>( V_A = 0.989V_c - 8.1 )</td>
</tr>
<tr>
<td>Kennedy et al.</td>
<td>Single-plane cine RAO</td>
<td>Adults</td>
<td>( V_A = 0.938V_c - 5.7 )</td>
</tr>
<tr>
<td>Dodge et al.</td>
<td>Biplane serial AP and lateral</td>
<td>Adults</td>
<td>( V_A = 0.81V_c + 1.9 )</td>
</tr>
<tr>
<td>Graham et al.</td>
<td>Biplane cine AP and lateral</td>
<td>Children</td>
<td>( V_A = 0.733V_c )</td>
</tr>
<tr>
<td>Sandler and Dodge</td>
<td>Single-plane serial AP</td>
<td>Adults</td>
<td>( V_A = 0.951V_c - 3.0 )</td>
</tr>
</tbody>
</table>

AP, anteroposterior; LAO, left anterior oblique; RAO, right anterior oblique; \( V_A \), actual volume; \( V_c \), calculated volume.
volume and ejection fraction may be calculated from digital
subtraction ventriculograms using the area–length method,18
as described for standard ventriculograms. Ejection fraction
may also be determined by computer analysis of the attenua-
tion of x-rays by the contrast agent within the ventricle.19,20
This technique is independent of geometric assumptions
regarding the shape of the ventricle. Alternatively, ventricu-
lar volume may be assessed noninvasively through the use
of computerized tomography21 or magnetic resonance imaging.22
A multielectrode catheter capable of measuring intracavitary
electrical impedance has been introduced23-25 and has proved
useful for the measurement of ventricular volume and ejection
fraction without the use of contrast agents. Validation stud-
ies23,24 indicate that both left and right ventricular volumes can
be measured by this technique. An illustration of the potential
usefulness of this catheter in assessing left ventricular pres-
sure–volume relationships is shown in Figure 21.4. Newer
catheters, 5F to 7F in diameter, combine volume and micro-
manometer pressure measurements (Figure 21.5).

**LEFT VENTRICULAR MASS**

Measurement of left ventricular wall thickness, in addition to
the parameters measured for volume determination, allows
calculation of left ventricular wall volume and estimation

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**Figure 21.3** Left ventricular casts made from fresh postmortem specimens of human hearts, using an encapsulant mixed with barium sulfate powder. The shape of the left ventricle only roughly approximates an ellipsoid of revolution; nevertheless, amazingly good correlation was obtained between true volume of these casts (measured by water displacement of the actual cast) and calculated volume. (From Wynne J, Green LH, Grossman W, et al. Estimation of left ventricular volumes in man from biplane cineangiograms filmed in oblique projections. *Am J Cardiol* 1978;41:726, with permission.)

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**Figure 21.4** Use of multielectrode impedance catheter to obtain left ventricular pressure–volume loops every fourth beat during inhalation of amyl nitrate. (From McKay RG, et al. Instantaneous measurement of left and right ventricular stroke volume and pressure-volume relationships with an impedance catheter. *Circulation* 1984;69:703, with permission.)
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Figure 21.5 Pressure-Volume (P-V) catheter. This catheter includes two pressure sensors and 12 electrodes for simultaneous high fidelity pressure and volume measurements. The pressure sensors are between the 4th and 5th electrodes, and 5 cm proximal to the 12th electrode. (Courtesy of Millar Instrument Inc, Houston, Texas, http://millar.com)

of left ventricular mass (LVM). For these calculations, it is assumed that wall thickness is uniform throughout the ventricle. Wall thickness \( h \) is measured at end-diastole at the left ventricular free wall roughly two-thirds of the distance from the aortic valve to the apex in the AP or RAO projection. Appropriate magnification correction is applied. For biplane methods, the total volume of the left ventricular chamber and wall, \( V_{c+w} \), is approximated by that of the corresponding ellipsoid:

\[
V_{c+w} = \frac{4}{3} \pi \left( \frac{L + 2h}{2} \right) \left( \frac{M + 2h}{2} \right) \left( \frac{N + 2h}{2} \right)
\]

As with \( h \), appropriate correction for magnification must be applied to \( A \) and \( L \) so that \( V_{c+w} \) represents the total volume of the left ventricular chamber and wall corrected for magnification. For single-plane methods, it is assumed that \( M = N \), yielding the single-plane formula:

\[
V_{c+w} = \frac{\pi}{6} \left( L + 2h \right) \left( \frac{4A}{\pi L} + 2h \right)^2
\]

The volume of the chamber is calculated by the biplane or single-plane technique. To exclude the volume of the papillary muscles and trabeculae from the chamber volume (and thus include their mass in LVM), the appropriate regression equation is applied, so that \( V_c \) is the regressed value for chamber volume. LVM, then, is calculated as follows:

\[
LVM = 1.050 V_w = 1.050(V_{c+w} - V_c) \tag{21.13}
\]

where \( V_w \) is wall volume, and 1.050 is the specific gravity of heart muscle. This method has been validated by postmortem examination of hearts\(^{26,27} \), however, it may not be accurate in the presence of marked right ventricular hypertrophy or pericardial effusion or thickening, where accurate measurement of wall thickness from the RAO silhouette may be impossible. The left ventricular wall thickness may sometimes be seen clearly in the LAO projection in the region of the posterior wall, or it may be measured accurately by echocardiography, computed tomography, or magnetic resonance imaging. Values obtained by any of these methods may be used for calculation of LVM.

NORMAL VALUES

A number of investigators have reported normal values in adults and children for left ventricular volume, ejection fraction, wall thickness, and mass.\(^{28,30} \) These are summarized in Table 21.2.

WALL STRESS

Whereas consideration of ventricular pressure and volume is useful for the assessment of ventricular performance, direct evaluation of myocardial function requires attention to forces acting at the level of the individual myocardial fiber. In particular, correction must be made for differences in ventricular wall thickness \( h \) and chamber radius \( R \), which modify the extent to which intraventricular pressure \( P \) is borne by the individual fiber; this is especially important in disease states characterized by ventricular hypertrophy or dilation or both. Such a correction may be achieved by consideration of wall stress \( \sigma \)^{29,31-33} Several formulas are commonly used to calculate stress, all related to the basic Laplace relation

\[
\sigma = \frac{PR}{2h} \tag{21.14}
\]

Assumptions regarding the shape of the ventricular chamber and the properties of the ventricular wall have
led to a number of such formulas for wall stress components in the circumferential, meridional, and radial directions (Figure 21.6). Consideration of circumferential and meridional stress has been particularly useful for clinical applications. A representative formula for calculation of circumferential stress, \( \sigma_c \), is

\[
\sigma_c = \frac{Pb}{h} \left( 1 - \frac{h}{2b} \right) \left( 1 - \frac{hb}{2a^2} \right)
\]

(21.15)

where \( a \) and \( b \) are the major and minor semiaxes, respectively, at the midwall. Meridional stress, \( \sigma_m \), may be calculated as follows:

\[
\sigma_m = \frac{PR}{2h(1 + h/2R)}
\]

(21.16)

where \( R \) is the internal chamber radius as bounded by the endocardial surface. For more detailed consideration of wall stress formulas, the reader is referred to reviews on the subject.

Calculation of wall stress in disease states has provided information not apparent from consideration of pressure and volume data alone. For example, it has been demonstrated that peak stress does not necessarily occur at the same time in the cardiac cycle as does peak pressure and that, in compensated pressure overload, the increase in ventricular pressure is offset by a proportional increase in wall thickness, so that wall stress remains normal (Figure 21.7; 32).
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Figure 21.7 A comparison of changes in left ventricular pressure, wall thickness, and meridional stress throughout the cardiac cycle for representative normal (A), pressure-overloaded (B), and volume-overloaded (C) ventricles. These parameters are plotted at 40 ms intervals. In all three types of ventricles, peak stress occurs earlier than peak pressure. In the pressure-overloaded ventricle, peak pressure is markedly elevated, but peak systolic stress and end-diastolic stress are normal. In the volume-overloaded ventricle, peak systolic stress is normal, but end-diastolic stress is elevated. (From Grossman W, Jones D, McLaurin LP. Wall stress and patterns of hypertrophy in the human left ventricle. J Clin Invest 1975;56:56, with permission.)

PRESSURE–VOLUME CURVES

Simultaneous measurement of ventricular pressure and volume allows construction of the pressure–volume diagram \(^{34-37}\) (Figure 21.8). The position and slope of the diastolic portion of the pressure–volume curve provide information regarding diastolic properties of the ventricle. \(^{35,38}\) Construction of the systolic portion of the curve is useful for analysis of the end-systolic pressure–volume relation, a measure of ventricular contractile function (see Chapter 22).

REGIONAL LEFT VENTRICULAR WALL MOTION

The recognition that left ventricular regional dysynergy is a more sensitive marker of coronary artery disease than is depression of global function has led to attempts to quantify abnormalities of regional wall motion. Left ventriculography is performed in the RAO or RAO and LAO projections. The ventricle is divided into regions by one of two methods: (a) construction of lines perpendicular to the major axis that divide the major axis into equal segments \(^{39,40}\) or (b) construction of lines drawn from the midpoint of the major axis to the ventricular outline at intervals of a fixed number of degrees. \(^{39}\) The extent of inward (or outward) movement of individual segments can then be measured, usually with the aid of computer techniques, providing quantitative measures of hypokinesis, akinesis, and dyskinesis.

An automated method for processing the left ventricular cineangiogram was reported by Sasayama et al. \(^{41-43}\) End-diastolic and end-systolic ventricular silhouettes are superimposed (Figure 21.9), and 128 radial grids are drawn...
from the center of gravity of the end-diastolic silhouette to the endocardial margins. Measurement of the length of each radial grid between end-diastolic and end-systolic silhouettes provides a measure of segmental systolic and diastolic function. Figure 21.9 illustrates this technique in a patient with coronary disease before and after induction of angina pectoris by rapid atrial pacing. Simultaneous measurement of left ventricular pressure permits construction of segmental left ventricular pressure–length loops for both the normally perfused myocardial regions (Figure 21.9C and D) and the regions perfused by stenotic coronary arteries (Figure 21.9A and B). Depressed wall motion develops during angina in the latter, and compensatory hyperkinesis develops in the former.

Another approach has been used by Sheehan et al. Wall motion is measured along 100 chords constructed as perpendiculars to a line drawn midway between the end-diastolic and end-systolic left ventricular contours (Figure 21.10). The motion of each chord is compared with a normal range established from analysis of ventriculograms from patients without heart disease. Deviations from the normal range indicate hypokinesis or hyperkinesis. In studies of wall motion after thrombolysis, availability of the LAO projection in addition to the RAO projection proved particularly useful in patients with left circumflex coronary artery thrombosis.

Software for regional wall motion analysis is now available in commercial catheterization laboratory computer systems.

REFERENCES

Wall motion as assessed by the center line method. The center line (A, dotted line) is constructed midway between the end-systolic and end-diastolic silhouettes. B. Chords are drawn at right angles to the center line. C. The percentage of systolic shortening along each chord is plotted and compared with normal mean and standard deviation values (dashed and dotted lines). D. Deviation from the normal range is replotted. (From Sheehan FH, Bolson EL, Dodge HT, et al. Advantages and applications of the center line method for characterizing regional ventricular function. Circulation 1986;74:293, with permission.)

25. Pak PH, Maughan L, Baughman KL, Kieval RS, Kass DA. Mechanism of acute mechanical benefit from VDD pacing in hypertrophied


A critical aspect of most cardiac catheterization procedures is the evaluation of myocardial function. At its simplest, this consists of a visual assessment of the left ventricular (LV) contractile pattern from the left ventriculogram, together with measurement of LV end-diastolic pressure. In laboratories where most patients have right-sided heart catheterization and cardiac output measurement as part of the standard cardiac catheterization procedure, additional information about LV function may be gleaned from cardiac output, stroke volume, and pulmonary capillary wedge pressure, whereas right ventricular (RV) function is reflected by the values of right ventricular end-diastolic pressure (RVEDP) and right atrial pressure. Measurement of pressures and cardiac output gives important information about overall cardiac function, but may shed little light on whether dysfunction is caused by abnormal systolic or diastolic myocardial performance. This chapter describes some of the specific methods that can be used in the cardiac catheterization laboratory to examine myocardial performance in systole and diastole.

**SYSTOLIC FUNCTION**

**Preload, Afterload, and Contractility**

Systolic function of the myocardium is a reflection of the interaction of myocardial preload, afterload, and contractility. **Preload** is the load that stretches myofibrils during diastole and determines the end-diastolic sarcomere length. For the left ventricle, this load is often quantified as the LV end-diastolic pressure (LVEDP). This pressure ($P$), together with LV wall thickness ($h$) and radius ($R$), determines LV end-diastolic wall stress ($\sigma = P/Rh$), which is an estimate of the force stretching the myocardial fibers at end-diastole. The end-diastolic stress or stretching force is resisted by the intrinsic stiffness or elasticity of the myocardium, and the interaction of end-diastolic stretching force and myocardial stiffness determines the extent of end-diastolic sarcomere stretch. If the myocardium is diffusely fibrotic or infiltrated with amyloid, a very high end-diastolic stretching force may be required to produce even a normal end-diastolic sarcomere length. In such a case, LVEDP may be very high (e.g., $>25$ mmHg), and attempts to lower it by diuretic or venodilator therapy may lead to reduction in end-diastolic sarcomere stretch to subnormal values and a concomitant fall in cardiac output.

Changes in preload influence both the extent and the velocity of myocardial shortening in experiments using isolated cardiac muscle preparations. Increased preload augments the extent and velocity of myocardial shortening at any given afterload. In the intact heart, the relationship is more complex because increases in preload generally produce increases in LV chamber size and LV systolic pressure. Therefore, **afterload** (the force resisting systolic shortening of the myofibrils) also increases, and this increase tends to blunt the increases in the extent and velocity of myocardial shortening caused by increased diastolic fiber stretch. This point is discussed in more detail later in this chapter, under the section on ejection phase indices of systolic function.

Afterload varies throughout systole as the ventricular systolic pressure rises and blood is ejected from the ventricular chamber. LV systolic stress approximates the force resisting myocardial fiber shortening within the wall of the ventricle. The theory of and methods for calculation of wall stress are described in Chapter 21. End-systolic wall stress is
considered by many to be the final afterload that determines the extent of myocardial fiber shortening when preload and contractility are constant. An increase in end-systolic wall stress results in a decrease in myocardial fiber shortening. For the intact ventricle, an increase in afterload (end-systolic wall stress) therefore results in a fall in stroke volume and ejection fraction.

Contractility refers to the property of heart muscle that accounts for alterations in performance induced by biochemical and hormonal changes; it has classically been regarded to be independent of preload and afterload. Contractility is generally used as a synonym for inotropy; both terms refer to the level of activation of cross-bridge cycling during systole. Contractility changes are assessed in the experimental laboratory by measuring myocardial function (extent or speed of shortening, maximum force generation) while preload and afterload are held constant. In contrast to skeletal muscle, the strength of contraction of heart muscle can be increased readily by a variety of biochemical and hormonal stimuli, some of which are listed in Table 22.1.

Increased myocardial contractility may be present in patients with hyperadrenergic states, thyrotoxicosis, or hypertrophic cardiomyopathy or in response to various drugs. It manifests as an increase in the speed and extent of myocardial contraction at constant afterload and preload.

Experiments with isolated myocardial tissue have demonstrated that contractility is not truly independent of preload. Increased end-diastolic sarcomere stretch leads to an immediate increase in the strength of contraction owing to the Frank-Starling mechanism, followed by a gradual further increase in contractile strength over 5 to 10 minutes.

Evidence supports a role for both increased intracellular calcium (Ca++) release and increased myofilament sensitivity to any given level of cytosolic Ca++ as underlying factors in the length-dependent activation seen with increased preload.

Assessment of systolic function requires consideration of the simultaneous influence of afterload, preload, and contractility. Systolic function should not be regarded as synonymous with contractility. Major depression of systolic function can occur with normal contractility, as in conditions with the so-called afterload excess (see later discussion).

### Table 22.1  Hormones and Drugs That Influence Myocardial Contractility

<table>
<thead>
<tr>
<th>Agent</th>
<th>Presumed Mechanism</th>
<th>Influence on Contractility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catecholamines with β-agonist activity</td>
<td>β-receptor stimulation → ↑ adenylate cyclase activity → ↑ cyclic AMP → ↑ Ca++ influx through sarcolemma → ↑ cytosolic Ca++</td>
<td>+</td>
</tr>
<tr>
<td>Digitalis glycosides</td>
<td>Inhibition of Na+/K+ ATPase → ↑ intracellular Na+ → ↑ Na+/Ca++ exchange → ↑ cytosolic Ca++</td>
<td>+</td>
</tr>
<tr>
<td>Calcium salts</td>
<td>↑ Extracellular Ca++ → ↑ Ca++ influx via slow channels and Na+/Ca++ exchange → ↑ cytosolic Ca++</td>
<td>+</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Multiple actions:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Local release of catecholamines</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inhibition of sarcoplasmic reticular Ca++ uptake</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↑ Sensitivity of contractile proteins of Ca++</td>
<td></td>
</tr>
<tr>
<td>Milrinone, amrinone, other bipyrindines</td>
<td>Phosphodiesterase inhibition → ↑ cyclic AMP → ↑ cytosolic Ca++</td>
<td>+</td>
</tr>
<tr>
<td>Thyroid hormone</td>
<td>Increases myosin ATPase activity by altering production of certain myosin isozymes</td>
<td>+</td>
</tr>
<tr>
<td>Calcium Sensitizers (Levosimendan, Pimobendan, EMD-57033, MCI-154)¹</td>
<td>Augmentation of Ca++-Troponin C binding Activation of myosin Effect on cross-bridge association and dissociation rates</td>
<td></td>
</tr>
<tr>
<td>Calcium-blocking agents (verapamil, nifedipine, D600, diltiazem)</td>
<td>Block Ca++ entry via slow channels</td>
<td>–</td>
</tr>
<tr>
<td>Barbiturates, ethanol</td>
<td>Depress contractility by unknown mechanism</td>
<td>–</td>
</tr>
</tbody>
</table>

AMP, adenosine monophosphate; ATPase, adenosine triphosphatase.
Isovolumic Indices

One of the oldest and most widely used measures of myocardial contractility is the maximum rate of rise of LV systolic pressure, $dP/dt$. Wiggers noted more than 70 years ago that in animal experiments, the failing ventricle showed a reduced steepness of the upslope of the ventricular pressure pulse.\(^5\) In 1962, Gleason and Braunwald first reported measurement of $dP/dt$ in humans.\(^6\) They studied 40 patients with micromanometer catheters. Maximum $dP/dt$ in those patients without hemodynamic abnormalities ranged from 841 to 1,696 mmHg/second in the left ventricle and 223 to 296 mmHg/second in the right ventricle. Interventions known to increase myocardial contractility, such as exercise and infusion of noradrenaline or isoproterenol, caused major increases in $dP/dt$. Increased heart rate produced by intravenous atropine also caused a rise in maximum $dP/dt$, and the authors attributed this to the treppe phenomenon described by Bowditch and characterized by a gradual increase in contractility following rapid sequential stimulation. This phenomenon, also known as the staircase effect, is felt to be secondary to accumulation of intracellular Na\(^+\), leading to a reduction in Na\(^+\)/Ca\(^{2+}\) exchange (3 inward Na\(^+\) exchanged for 1 outward Ca\(^{2+}\)) during the repolarization phase of the action potential and a corresponding increase in cytosolic Ca\(^{2+}\). In the study by Gleason and Braunwald, acute increases in arterial pressure and afterload produced by infusion of the $\alpha$-adrenergic vasoconstricting agent methoxamine produced little change in $dP/dt$. These points are illustrated in Figures 22.1 and 22.2.

In normal subjects and in patients with no significant cardiac abnormality, maximum $dP/dt$ increases significantly in response to isometric exercise,\(^7\) dynamic exercise,\(^8\) tachycardia by atrial pacing, or atropine,\(^9\) $\beta$-agonists,\(^6\) and digitalis glycosides.\(^10\) Relatively few studies have been done in humans to assess the changes in $dP/dt$ induced by alterations in afterload and preload, but some studies do indicate that maximum positive $dP/dt$ tends to increase slightly (6% to 8%) with moderate increases in LV preload\(^11\) and shows little change with methoxamine-induced increases\(^6\) or nitroprusside-induced decreases\(^12\) in mean arterial pressure of 25 to 30 mmHg. Extensive studies in animals have examined the influence of changes in afterload, preload, and contractility on maximum $dP/dt$.\(^11\) These studies generally show that maximum $dP/dt$ rises with increases in afterload and preload, but the changes were quite small (<10%) in the physiologic range.

As discussed in Chapter 10, accurate measurement of $dP/dt$ requires a pressure measurement system with excellent frequency-response characteristics. Micromanometer catheters are usually required to achieve this frequency-response range.\(^13\) Differentiation of the ventricular pressure signal can be achieved by (a) analog techniques online (Figures 22.1 and 22.2), using a resistance capacitor (RC) differentiating circuit\(^6\); (b) computer digitization of the analog LV pressure tracing and subsequent differentiation of a polynomial best fit to the averaged LV isovolumic pressure\(^16\), or (c) computer digitization of the analog LV pressure tracing with subsequent Fourier analysis and differentiation.\(^19\)

In addition to $dP/dt$, several other isovolumic indices have been introduced in an attempt to obtain a “pure” contractility index, completely independent of alterations in preload and afterload.\(^11\) These indices include the maximum value of $(dP/dt)/P$, where $P$ is LV pressure [the maximum value of $(dP/dt)/P$ is sometimes called $V_{PM}$]; (peak $dP/dt$)/IIT, where IIT is the integrated isovolumic tension;
Section V Evaluation of Cardiac Function

FIRST DERIVATIVE OF VENTRICULAR PRESSURE

Figure 22.2 Micromanometer recordings of left ventricular (LV) pressure and \( \frac{dP}{dt} \), as in Figure 22.1. Methoxamine raises arterial and LV systolic pressure but does not increase \( +\frac{dP}{dt} \). In contrast, the combined \( \alpha \)- and \( \beta \)-adrenergic effects of norepinephrine increase LV systolic pressure and \( +\frac{dP}{dt} \). (From Gleason WL, Braunwald E. Studies on the first derivative of the ventricular pressure pulse in man. J Clin Invest 1962;41:80, with permission.)

(dP/dt)/CPIP, where CPIP is the common developed isovolumic pressure; \( V_{max} \), the extrapolated value of \( (dP/dt)/P \) versus \( P \) when \( P = 0; (dP/dt)/P_D \) when the developed LV pressure, \( P_D \), equals 5, 10, or 40 mmHg; and the fractional rate of change of power, which involves the second derivative of LV pressure.

Although changes in \( dP/dt \) reflect acute changes in inotropy in a given individual, the usefulness of \( dP/dt \) is reduced in comparisons between individuals, especially when there has been chronic LV pressure or volume overload. Peak \( dP/dt \) generally increases in patients with chronic aortic stenosis, even though contractility is normal or decreased in most of these patients. To account for chronic changes in LV geometry and mass that occur with chronic LV overload, some investigators have examined the rate of rise of systolic wall stress.18 The peak value of \( du/dt \) may be used as a contractility index, as may the spectrum plot that relates \( du/dt \) to instantaneous \( u \) (Figure 22.3).

Pressure–Volume Analysis

Since the time of Frank and Starling, pressure–volume (PV) diagrams have been used to analyze ventricular function. The normally contracting left ventricle ejects blood under pressure, and the relationship between its pressure generation and ejection can be expressed in a plot of LV pressure against volume. As can be seen in Figure 22.4, end-diastole is represented by point A, isovolumic contraction by line AB, aortic valve opening by point B, ejection by line BC, end-ejection and aortic valve closure by point C, isovolumic relaxation by line CD, mitral valve opening by point D, and LV diastolic filling by line DA.

Stroke Work

The area ABCD enclosed within the PV diagram in Figure 22.4 is the external LV stroke work (SW), represented mathematically as \( JpdV \). Although the calculation of LVSW is most accurate when it is derived by integrating the area within complete PV diagrams, a practical approximation can be obtained as follows:

\[
\text{LVSW} = (\text{LVSP} - \text{LVDP})SV \times 0.0136 \tag{22.1}
\]

where \( \text{LVSP} \) and \( \text{LVDP} \) are, respectively, the mean LV systolic and diastolic pressures (in mmHg), \( SV \) is the LV total stroke volume (in mL), and 0.0136 is a constant for converting mmHg-mL into g-m. \( \text{LVSP} \) and \( \text{LVDP} \) may be obtained from planimetry of direct pressure tracings, as shown in Figure 22.5. When the total LV stroke volume is the same as the forward stroke volume, \( SV \) may be calculated as cardiac output divided by heart rate. In cases where LV total stroke volume differs from forward stroke volume (e.g., mitral or aortic regurgitation, ventricular septal defect), the P–V diagram may differ substantially in configuration from that shown in Figure 22.4, and LVSW cannot be calculated from Eq. (22.1); instead, planimetric integration of the entire P–V plot is required.

If LV pressure tracings are not available, in the absence of major regurgitation, SW can be approximated from the aortic and pulmonary capillary wedge pressures as follows:

\[
\text{LVSW} = \left(\text{AoSP} - \text{PCW}\right)SV \times 0.0136 \tag{22.2}
\]

where \( \text{AoSP} \) is the aortic systolic mean pressure (planimetered from the aortic pressure tracing, Figure 22.5) and \( \text{PCW} \) is the mean pulmonary capillary wedge pressure. A further
Figure 22.3

Left ventricular (LV) isovolumic indices of contractility. A. Rate of pressure development (dP/dt) as a function of LV-developed pressure (P0). Mean values in control subjects (open circles), patients with aortic stenosis (AS, filled circles), and patients with dilated cardiomyopathy (CMP, crosses) are shown. Brackets represent standard errors of the mean (SEM). B. Rate of wall stress development (dσw/dt) as a function of LV-developed stress (σw) for the same groups. There are no significant differences for patients with AS as compared with controls, although patients with CMP clearly show depressed values for dP/dt and dσw/dt at all levels of P0 and σw (From Fifer MA, Gunther S, Grossman W, et al. Myocardial contractile function in aortic stenosis as determined from the rate of stress development during isovolumic systole. *Am J Cardiol* 1979;44:1318, with permission.)

Figure 22.4

Diagram of ventricular pressure (P) plotted against simultaneous ventricular volume (V) for a single cardiac contraction. For the left ventricle, point A represents end-diastole; segment AB, isovolumic contraction; point B, aortic valve opening; segment BC, LV ejection; point C, aortic valve closure and end ejection; segment CD, isovolumic relaxation; point D, mitral valve opening; and segment DA, LV filling. LV stroke work (SW) is represented by the cross-hatched area, and the stippled area represents diastolic work done on the left ventricle by the right ventricle and left atrium. (See text for details.)

approximation may be made by substituting mean systemic arterial pressure for \( \overline{AOSP} \), which it closely approximates.

LVSW is a reasonably good measure of LV systolic function in the absence of volume or pressure overload conditions, both of which may substantially increase calculated LVSW. The normal LVSW in adults is approximately 90 ± 30 g-m (mean ± SD); in adult patients with dilated cardiomyopathy or heart failure from extensive prior myocardial infarction, LVSW is often <40 g-m. Values, <25 g-m indicate severe LV systolic failure, and when LVSW is <20 g-m, the prognosis is grave.

LVSW is a measure of total LV chamber function and can be considered to reflect myocardial contractility only when the ventricle is reasonably homogeneous in its composition, as in most patients with dilated cardiomyopathy. For patients with coronary artery disease and extensive myocardial infarction, LVSW may be depressed even though well-perfused areas of the myocardium with normal contractility remain.

Because power is the rate at which work is done, LV power in the normal heart is the integral of the product of LV pressure during ejection and aortic flow. LV power may be regarded as a measure of overall LV contractile function; with refinement (such as the measurement of preload-adjusted maximal power), it can be used as a measure of the inotropic state.\(^{22}\)

**Ejection Phase Indices**

LV systolic function can be assessed using only the volume data from the P–V diagram. One of the most widely used
Figure 22.5 Left ventricular (LV) and aortic (Ao) pressure tracings illustrate areas planimetered to measure LV mean systolic pressure (LVSP), LV mean diastolic pressure (LVDP), and aortic mean systolic pressure (AoSP). LVSP is the area contained under the LV pressure curve, bounded by perpendicular lines defining end-diastole and mitral valve opening; LVDP is the diastolic area, similarly defined. AoSP is the area contained under the aortic pressure curve, bounded by perpendicular lines defining aortic valve opening and closure.

indices of LV systolic performance is the ejection fraction (EF), which is defined as follows:

\[
EF = \frac{\text{LVEDV} - \text{LVESV}}{\text{LVEDV}} \quad (22.3)
\]

where LVEDV and LVESV are the LV end-diastolic and end-systolic volumes, respectively. In the cardiac catheterization laboratory, left ventricular EF (LVEF) is most often derived from the LV angiogram, as discussed in Chapter 21. If the EF is divided by the ejection time (ET), measured from the aortic pressure tracing, the quotient is called mean normalized systolic ejection rate (MNSER).

\[
\text{MNSER} = \frac{(\text{LVEDV} - \text{LVESV})}{(\text{LVEDV})(\text{ET})} \quad (22.4)
\]

Finally, another ejection phase index of LV systolic function is the velocity of circumferential fiber shortening, \( V_{cf} \). This is calculated as the rate of shortening of a theoretic LV myocardial fiber in a circumferential plane at the midpoint of the long axis of the ventricle. For convenience, mean \( V_{cf} \) is used most often, rather than instantaneous or peak \( V_{cf} \). Mean \( V_{cf} \) is obtained by subtracting the end-systolic endocardial circumferential fiber length \((\pi D_{ed})\) from the end-diastolic endocardial circumferential fiber length \((\pi D_{es})\), and then dividing by ET and normalizing for end-diastolic circumferential fiber length:

\[
V_{cf} = \frac{(\pi D_{ed} - \pi D_{es})}{(\pi D_{es})(\text{ET})} = \frac{(D_{ed} - D_{es})}{D_{es}(\text{ET})} \quad (22.5)
\]

\( D_{es} \) and \( D_{ed} \) are end-diastolic and end-systolic minor axis dimensions. Although \( V_{cf} \) can be calculated from angiographic data using the area-length method \((D = 4A/\pi L)\), it is most commonly calculated from the values of \( D \) measured by M-mode echocardiography. Normal values for isovolumic and ejection phase indices are given in Table 22.2.

Ejection phase indices are easily obtained from LV angiogram and can also be derived reliably from a variety of noninvasive techniques such as radionuclide ventriculography and echocardiography. The most widely used ejection phase index, the EF, is generally depressed when myocardial contractility is diminished. However, the ejection indices depend heavily on preload and afterload and cannot be regarded as reliable indices of contractility in conditions associated with altered loading conditions. For example, increases in preload cause the EF (and other ejection indices) to rise; consequently, LVEF may be increased in patients with mitral or aortic regurgitation, severe anemia, or other causes of increased diastolic LV inflow and may mask underlying deterioration of myocardial contractility. Conversely, increases in afterload cause the EF to fall; consequently, LVEF may be low in patients with severe aortic stenosis or other causes of increased resistance to systolic ejection and may falsely suggest underlying depression of myocardial contractility.

In practice, acute elevation of LV preload causes some increase in LV chamber size and aortic pressure, and these increases in afterload (systolic \( \sigma \) resisting shortening) tend to decrease the EF and other ejection indices, offsetting the rise in EF that a pure rise in preload would produce. Rankin and coworkers\(^{29}\) produced changes in venous return by total body tilt in normal subjects; despite substantial changes in LV end-diastolic dimension and volume, there were no significant changes in EF, MNSER, or \( V_{cf} \). Similarly, acute elevation of afterload caused by rising aortic pressure causes an increase in LVEDP, and the resultant rise in preload (end-diastolic fiber stretch) tends to increase the EF and other ejection indices, offsetting the fall in EF produced by a pure rise in afterload.\(^{26}\) These physiologic adjustments explain why the ejection indices are much more useful clinically than might be expected on the basis of studies in the isolated heart or muscle preparation.
Table 22.2

Evaluation of Left Ventricular Systolic Performance: Normal Values of Some Isovolumic and Ejection Phase Indices

<table>
<thead>
<tr>
<th>Contractility Indices</th>
<th>Normal Values (mean ± SD)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Isovolumic indices</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum dP/dt</td>
<td>1,610 ± 290 mmHg/s</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>1,670 ± 320 mmHg/s</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>1,661 ± 323 mmHg/s</td>
<td>20</td>
</tr>
<tr>
<td>Maximum (dP/dt)/P</td>
<td>44 ± 8.4 s⁻¹</td>
<td>20</td>
</tr>
<tr>
<td>Vₚₘ or peak [dP/dt/28P]</td>
<td>1.47 ± 0.19 ML/s</td>
<td>24</td>
</tr>
<tr>
<td>(dP/dt)/P₀ at P₀ = 40 mmHg</td>
<td>37.6 ± 12.2 s⁻¹</td>
<td>20</td>
</tr>
<tr>
<td><strong>Ejection phase indices</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVSW</td>
<td>81 ± 23 g·m</td>
<td>7</td>
</tr>
<tr>
<td>LVSWI</td>
<td>53 ± 22 g·m/m²</td>
<td>25, 26</td>
</tr>
<tr>
<td></td>
<td>41 ± 12 g·m/m²</td>
<td>27</td>
</tr>
<tr>
<td>EF (Angiographic)</td>
<td>0.72 ± 0.08</td>
<td>28</td>
</tr>
<tr>
<td><strong>MNSER</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiographic</td>
<td>3.32 ± 0.84 EDV/s</td>
<td>20</td>
</tr>
<tr>
<td>Echographic</td>
<td>2.29 ± 0.30 EDV/s</td>
<td>29</td>
</tr>
<tr>
<td>Mean Vₜ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiographic</td>
<td>1.83 ± 0.56 ED circ/s</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>1.50 ± 0.27 ED circ/s</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>1.09 ± 0.12 ED circ/s</td>
<td>29</td>
</tr>
</tbody>
</table>

dP/dt, rate of rise of left ventricular (LV) pressure; P₀, developed LV pressure; ML, muscle length; LVSW, left ventricular stroke work; LVSWI, left ventricular stroke work index; MNSER, mean normalized systolic ejection rate; ED, end-diastolic; V, volume; Vₜ, velocity of circumferential fiber shortening; circ, circumference; EF, ejection fraction.

An LVEF of <0.40 indicates depressed LV systolic pump function, and if there is no abnormal loading to account for it, an LVEF of ≤0.40 can be taken to signify depressed myocardial contractility. An LVEF <0.20 corresponds to severe depression of LV systolic performance and is usually associated with a poor prognosis. Interpretation of EF and other ejection indices improves by consideration of the ventricular preload and afterload, and the latter values are defined most precisely by end-diastolic and end-systolic wall stresses, respectively.

End-Systolic Pressure–Volume and σ–Length Relations

Over the past 40 years, several groups have shown that the LV end-systolic P–V, pressure–diameter, and σ–length relationships accurately reflect myocardial contractility, independent of changes in ventricular loading. This has been established in a series of studies in animals and humans. The fundamental principle of end-systolic P–V analysis is that at end-systole there is a single line relating LV chamber pressure to volume, unique for the level of contractility and independent of loading conditions. The LV end-systolic P–V line can be generated by producing a series of P–V loops (such as the one in Figure 22.4) over a range of loading conditions (Figures 22.6 and 22.7). The line connecting the upper left corners of the individual P–V diagrams is the end-systolic P–V line (Figure 22.7A), characterized by a slope and by an x-axis intercept called V₀ (the extrapolated end-systolic volume when end-systolic pressure is zero). Current evidence indicates that an increase in contractility shifts the end-systolic P–V line to the left with a steeper slope, and a depression in contractility is associated with a displacement...
of the line downward and to the right, with a reduced slope. Although there is some uncertainty as to the meaning of $V_0$, it is generally agreed that an increase in slope of the end-systolic $P-V$ line is a sensitive indicator of an increase in contractility. However, the technique of end-systolic analysis may not be as useful in comparisons among subjects as it is in comparisons of values in a single subject measured before and after an intervention. The end-systolic $P-V$ lines for groups of patients with normal, intermediate, and depressed LV contractility are shown in Figure 22.8.

To obtain the end-systolic $P-V$ line, one can use aortic dicrotic notch pressure as end-systolic LV pressure and...
Chapter 22 Evaluation of Systolic and Diastolic Function of the Ventricles and Myocardium

Figure 22.8 Left ventricular (LV) end-systolic pressure ($P_{es}$) plotted against end-systolic volume index ($V_{es}$) at two levels of loading for each of three patient groups: Group A, patients with normal LV contractile function; Group B, patients with moderate depression of LV contractile performance; Group C, patients with marked depression of LV contractility. Depressed contractility shifts the $P_{es}-V_{es}$ relation to the right, with a reduced slope ($m$) and increased intercept ($V_0$). (From Grossman W, Braunwald E, Mann JT, et al. Contractile state of the left ventricle in man as evaluated from end-systolic pressure relations. Circulation 1977;45:845, with permission.)

Relationship between Peak dP/dt and End-Diastolic Volume

Little and coworkers examined the relationship between LV $dP/dt_{max}$ and end-diastolic volume and have proposed the slope of this relationship as an index of contractile state. They showed that, on theoretical grounds, this relationship can be derived from the LV end-systolic P-V relationship; both provide estimates of maximal myocardial elastance. This relationship is simpler to derive because both LV end-diastolic volume and $dP/dt_{max}$ are more readily defined than either end-systolic pressure or volume. One need not be concerned about a lack of coincidence between end-systole and maximal elastance, as with the end-systolic P-V relationship. The $dP/dt_{max}-$end-diastolic volume relationship, however, is yet to be evaluated extensively in the clinical setting. Also, the end-systolic P-V relationship can be estimated clinically by entirely noninvasive methods. Nevertheless, the relationship between $dP/dt_{max}$ and end-diastolic volume represents an intriguing concept and may prove to be a valuable index of contractile state.

Stress–Shortening Relationships

Another approach to the assessment of LV systolic performance and myocardial contractility involves measuring the extent of cardiac muscle shortening and relating this shortening to the systolic wall stress ($\sigma$) resisting shortening. If a ventricle is presented with progressively increasing resistance to ejection, $\sigma$ rises while the extent of myocardial shortening declines. Therefore, a plot of systolic $\sigma$ on the horizontal axis against myocardial shortening expressed as EF, $V_{CF}$, or percent fractional shortening ($%F_D$) on the vertical axis yields a tight inverse relationship (Figure 22.9). Data from studies of individual patients may then be compared with these normal values. In Figure 22.9, if the point relating end-systolic $\sigma$ ($\sigma_{es}$) and $%D$ for a given patient lies within the confidence lines of the normal population, myocardial contractility is likely to be normal; however, if the $\sigma_{es}-%D$ point lies below the normal range, contractility is depressed even if $%D$ is normal. Figure 22.10 shows that the $\sigma_{es}-%D$ relationship is shifted upward by an increase in contractility resulting from dobutamine infusion. One point of caution concerning the $\sigma_{es}-%D$ relationship is that it is preload sensitive. That is, increases in preload will increase $%D$ for any level of $\sigma_{es}$. There is some evidence that when $V_{CF}$ is substituted for $%D$, the preload dependence of the stress–shortening relationship is attenuated or eliminated.

Plots of systolic wall stress against LVEF have been analyzed for patients with a variety of conditions, including LV...
pressure overload (Figure 22.11). In these plots, comprised of multiple individual data points (each point relating LV wall \( \sigma \) and EF for an individual patient) an inverse systolic \( \sigma \)-EF relationship is apparent for patients with chronic LV pressure overload. This suggests that the depressed LVEF in some of these individuals is caused by excessive systolic \( \sigma \); that is, the load resisting systolic shortening is abnormally high and is responsible for a reduced extent of shortening.
This combination of high $\sigma$ and low EF is sometimes referred to as afterload mismatch,\textsuperscript{50-52} and it implies that hypertrophy has been inadequate to return systolic wall stress to its relatively low normal level. Patients in whom LVEF is diminished out of proportion to any increase in systolic wall stress can be assumed to have depressed myocardial contractility (Figure 22.12).

A refinement of this approach involves measuring the relation between end-systolic LV wall stress and the heart rate-corrected velocity of fiber shortening. This approach was found to be sensitive and preload independent in an assessment of LV response to nitroprusside and dopamine infusions in patients with dilated cardiomyopathy.\textsuperscript{53} In that study, this approach was more sensitive to detecting increased contractility than was LV dP/dt.

The advantage of $\sigma$-shortening analysis over P–V diagram analysis is that wall $\sigma$ takes into consideration changes in LV geometry and muscle mass that occur in response to chronic alterations in loading. For example, a systolic pressure of 250 to 300 mmHg imposed acutely on a normal left ventricle would result in considerable reduction in LVEF, perhaps down to the 20% to 30% range. This change occurs because, in the absence of any increase in LV wall thickness or decrease in chamber radius, systolic $\sigma$ would more than double in response to such an acute pressure overload, and this would lead to a major reduction in LVEF. However, if the increase in systolic pressure to 250 to 300 mmHg occurs gradually and is matched by the development of sufficient hypertrophy in the appropriate pattern, systolic wall $\sigma$ remains normal and fiber shortening and LVEF do not decrease. Therefore, in the presence of significant hypertrophy and/or altered LV geometry, $\sigma$–shortening analysis may have considerable value.

### Left Ventricular Diastolic Distensibility: Pressure–Volume Relationship

As pointed out by Henderson in 1923, “In the heart, diastolic relaxation is a vital factor and not merely the passive stretching of a rubber bag. Being vital, it is variable.”\textsuperscript{54} Analysis of diastolic function today requires appreciation that diastolic compliance is variable and may change substantially in a given patient from one minute to the next. Diastolic function is summated physiologically in the relation between LV pressure and volume during diastole (Figure 22.4, segment DA). Traditionally, an upward shift in this diastolic P–V relation is regarded as indicating increased LV diastolic chamber stiffness, and a downward shift indicates decreased stiffness or increased LV diastolic chamber compliance. In the terminology of physics and engineering, stiffness, and its opposite, compliance, relate a change in pressure ($\Delta P$) to a change in volume ($\Delta V$); therefore, some investigators have restricted these terms to refer to the slope of the diastolic P–V relation. In this regard, as seen in segment DA of Figure 22.4, LV diastolic stiffness ($\Delta P/\Delta V$) is low early in diastole and rises steadily throughout diastolic filling.

Figure 22.13 shows theoretical LV diastolic P–V plots for patients with normal, stiff, and compliant ventricular chambers. Several problems arise when stiffness and compliance are defined strictly in terms of the slope of the diastolic P–V diagram, and these problems are illustrated in Figure 22.14. First, in some clinical conditions (e.g., angina pectoris), the LV...
Section V Evaluation of Cardiac Function

Figure 22.14 Schematic illustration of the difference between diastolic distensibility and compliance. A. The left ventricular diastolic pressure-volume (P-V) relation has undergone a parallel upward shift. Distensibility is decreased (higher diastolic pressure required to fill the ventricle to the same chamber volume), but compliance, defined as the slope of the P-V relation, is unchanged. B. Superimposed on the parallel upward shift are curves that are steeper (decreased compliance) or less steep (increased compliance) than either of the two parallel P-V curves. This illustrates the importance of distinguishing distensibility from compliance, because the curve labeled “increased compliance” nevertheless exhibits decreased diastolic distensibility, as compared with the normal P-V relation. (From Grossman W. Relaxation and diastolic distensibility of the regionally ischemic left ventricle. In: Grossman W, Lorell BH, eds. Diastolic Relaxation of the Heart. Boston: Martinus Nijhoff; 1988:193.)

diastolic P–V plot shifts upward in a parallel fashion, without a noticeable change in slope. These patients have increased LV filling pressure, often with normal chamber volumes, and from a hydrodynamic point of view the LV chamber must be regarded as presenting increased resistance to diastolic filling. To say that LV diastolic stiffness and compliance are normal in such patients because the upward shift has been a parallel one (without slope change) seems inappropriate. In some other cases (e.g., after nitroprusside infusion in patients with heart failure), there is a downward shift in the LV diastolic P–V plot, with an increase in the steepness of the plot; again, to say that such patients exhibit increased LV diastolic stiffness seems inappropriate, because they require a lower filling pressure to achieve the same diastolic chamber dimension and fiber stretch. Therefore, the LV diastolic P–V plot can show changes of two types: displacement (movement of the entire relationship upward, downward, or laterally) and configuration change (including change in curvature). In our studies, we have referred to upward or downward displacement changes as being associated with a change in ventricular distensibility. Therefore, if the LV diastolic P–V plot shifts upward, we say that the LV chamber has become less distensible; a higher diastolic pressure is required to fill or distend the chamber to its earlier volume (Figure 22.14). Similarly, a downward shift in the diastolic P–V plot is said to indicate an increase in LV diastolic distensibility. The changes in curvature and/or configuration that may accompany these displacement changes are difficult to quantify and to interpret.

Various formulas have been developed for analyzing the curvature of the LV diastolic P–V plot. These generally assume that the curvature is exponential, an assumption that is often but not always reasonable. Diastolic P–V and P–segment length (SL) plots constructed from a series of end-diastolic points have been used in animal experiments to assess LV diastolic compliance, and this technique has been applied to clinical studies. When a series of end-diastolic P–V or P–SL points are plotted, the relation is more strictly exponential, and application of mathematical models and analysis is more easily justified by the good agreement of measured data and mathematical predictions.

Clinical Conditions Influencing Diastolic Distensibility

Factors that influence the position of the LV diastolic P–V plot (i.e., factors that influence LV diastolic distensibility) are listed in Table 22.3. Constrictive pericarditis and pericardial tamponade are associated with a striking upward shift in the diastolic P–V relation. This upward shift is a parallel shift without substantial change in curvature. Pericardial restraint is also important in the mechanism whereby altered RV loading can alter the LV diastolic P–V relation. When distended, the right ventricle can decrease LV diastolic distensibility by exerting an extrinsic pressure on the LV chamber in diastole through the shared interventricular septum, which may actually bulge into the LV chamber. Acute RV infarction causes dilatation of the RV chamber that, in the presence of an intact, previously unstressed pericardium, may lead to extrinsic compression of the LV
Table 22.3 Factors That Influence Left Ventricular (LV) Diastolic Chamber Distensibility

I. Factors extrinsic to the LV chamber
   A. Pericardial restraint
   B. Right ventricular loading
   C. Coronary vascular turgor (erectile effect)
   D. Extrinsic compression (e.g., tumor, pleural pressure)

II. Factors intrinsic to LV chamber
   A. Passive elasticity of LV wall (stiffness or compliance when myocytes are completely relaxed)
      1. Thickness of LV wall
      2. Composition of LV wall (muscle, fibrosis, edema, amyloid, hemosiderin) including both endocardium and myocardium
      3. Temperature, osmolality
   B. Active elasticity of LV wall owing to residual cross-bridge activation (cycling and/or latch state) through part or all of diastole
      1. Slow relaxation affecting early diastole only
      2. Incomplete relaxation affecting early-, middle-, and end-diastolic distensibility
      3. Diastolic tone, contracture, or rigor
   C. Elastic recoil (diastolic suction)
   D. Viscoelasticity (stress relaxation, creep)

in diastole with a hemodynamic pattern resembling that of cardiac tamponade. The effect of increased RV loading on LV diastolic distensibility is an example of ventricular interaction, which is more prominent in the presence of an intact and relatively snug pericardium. In animal experiments, it is difficult to demonstrate diastolic ventricular interaction once the pericardium has been opened wide.

Coronary vascular turgor can influence LV diastolic chamber stiffness. The LV wall has a rich blood supply, and engorgement of the capillaries and venules with blood makes the wall relatively stiff. For obvious reasons, this has been referred to as the erectile effect. Although the erectile effect is probably not of much importance when coronary blood flow and pressure (the two components determining the degree of turgor) are in the physiologic range, a marked fall in coronary flow and pressure (as occurs distal to a coronary occlusion when collateral flow is poor or absent) is associated with a decrease in stiffness of the affected myocardium and an increase in LV diastolic distensibility.

Experimental evidence supports an important role for increased coronary venous pressure as a major determinant of coronary vascular turgor. Increases in right atrial pressure from 0 to 15 and 30 mmHg led to substantial upward shifts in the LV end-diastolic P-V relation that could not be attributed to right ventricular distention and a shift in the interventricular septum. Extrinsic compression of the heart by tumor may cause decreased LV diastolic distensibility and may mimic cardiac tamponade.

When an upward shift in the diastolic P-V relation is present and the extrinsic factors listed in Table 22.3 cannot clearly explain the altered distensibility, a change in one of the intrinsic determinants of LV distensibility is likely to be present. Altered passive elasticity caused by amyloidosis, edema, or diffuse fibrosis may cause a restrictive cardiomyopathic pattern, with high LV diastolic pressure relative to volume in the presence of reasonably well-preserved systolic function. Clinically, heart failure may be present in such a scenario. Endomyocardial biopsy of the right or left ventricle may be needed to establish the diagnosis (see Chapter 26). Finally, in heart failure with reduced ejection fraction (HFrEF), the reduction in contractility is associated with an impairment in relaxation secondary to a combination of factors including abnormal calcium handling, abnormal loading conditions, and alteration in passive elasticity.

Myocardial Ischemia

Abnormal diastolic relaxation can cause the diastolic P-V relation to shift upward strikingly. During angina pectoris, a 10 to 15 mmHg rise in average LV diastolic pressure may occur with little or no change in diastolic volume; if this persists for a sufficient duration (>10 to 20 minutes), pulmonary
edema may occur. Such episodes of flash pulmonary edema in patients with essentially normal LV systolic function and normal LV chamber size generally indicate a large mass of ischemic myocardium and suggest three-vessel or left main coronary artery obstruction. The decreased LV distensibility during ischemia may be prevented in many patients by a Ca++ channel blocking agent. The mechanism of impaired myocardial relaxation during the ischemia of angina pectoris is not understood completely, but may be associated with diastolic Ca++ overload of the ischemic myocytes, in part related to ischemic dysfunction of the sarcoplasmic reticulum. During the ischemia of acute coronary occlusion, an upward shift of the diastolic P–V relation may occur if sufficient collateral blood flow is present to permit continued systolic contraction of the ischemic segment. If ischemia is sufficiently severe to cause complete akinesis of the affected myocardium, however, altered distensibility does not occur: incomplete relaxation can occur only in myocytes when there has been systolic cross-bridge activation. Also, the marked decrease in coronary vascular turgor distal to a coronary occlusion with poor or absent collaterals, together with local accumulation of hydrogen ions (H+), contributes to an increase in regional distensibility, so that the net effect on the ventricular diastolic P–V relation may be one of no change.

Cardiac Hypertrophy

Impaired relaxation with decreased LV diastolic distensibility is also seen in patients with hypertrophic cardiomyopathy, during angina pectoris in patients with aortic stenosis and normal coronary arteries, and in patients with cardiac hypertrophy secondary to hypertension.

Indices of Left Ventricular Diastolic Relaxation Rate

Much attention has been given to measures of LV diastolic relaxation during the isovolumic relaxation period and during early, middle, and late diastolic filling. These indices may be considered as either pressure-derived or volume flow-derived and may assess either global or regional diastolic relaxation. A listing of some of these indices and their normal values is given in Table 22.4.

Isovolumic Pressure Decay

The time course of LV pressure decline after aortic valve closure is altered in conditions known to be associated with abnormalities of myocardial relaxation. One of the simplest

Table 22.4 Evaluation of Left Ventricular Diastolic Performance: Normal Values for Some Indices of Relaxation and Filling

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal Values</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak –dP/dt</td>
<td>2,660 ± 700 mmHg/s</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>2,922 ± 750 mmHg/s</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td>1,864 ± 390 mmHg/s</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>1,825 ± 261 mmHg/s</td>
<td>86</td>
</tr>
<tr>
<td>T (logarithmic method, Eq. [22.7])</td>
<td>38 ± 7 ms</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td>33 ± 8 ms</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>31 ± 3 ms</td>
<td>86</td>
</tr>
<tr>
<td>T (derivative method, Eqs. [22.8] and [22.9])</td>
<td>55 ± 12 ms</td>
<td>86</td>
</tr>
<tr>
<td></td>
<td>47 ± 10</td>
<td>87</td>
</tr>
<tr>
<td>P8 (derivative method, Eqs. [22.8] and [22.9])</td>
<td>–25 ± 9 mmHg</td>
<td>86</td>
</tr>
<tr>
<td>PFR</td>
<td>3.3 ± 0.6 EDV/s</td>
<td>77</td>
</tr>
<tr>
<td>Time-to-PFR</td>
<td>136 ± 23 ms</td>
<td>77</td>
</tr>
<tr>
<td>Peak –dh/dt (posterior wall)</td>
<td>8.4 ± 3.0 cm/s</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>8.2 ± 3.7 cm/s</td>
<td>82</td>
</tr>
</tbody>
</table>

LV, left ventricular; peak –dP/dt, maximum rate of LV isovolumic pressure decline; T, time constant of LV isovolumic relaxation, calculated assuming both zero pressure intercept (Eq. [22.7]) and variable pressure (P8) intercept (Eqs. [22.8] and [22.9]); PFR, LV peak filling rate, from radionuclide ventriculography, normalized to end-diastolic volumes (EDV)/sec; peak –dh/dt, maximum rate of posterior wall thinning, measured by echocardiography.
ways of quantifying the time course of LV pressure decline is to measure the maximum rate of pressure fall, peak negative dP/dt. Although peak negative dP/dt is altered by conditions that change myocardial relaxation, it is also altered by changes in loading conditions. For example, LV peak negative dP/dt increases (i.e., rises in absolute value) when aortic pressure rises. For example, an increase in LV peak negative dP/dt from −1,500 to −1,800 mmHg/second could be caused by an increase in the rate of myocardial relaxation, a rise in aortic pressure, or both. An increase in peak negative dP/dt when aortic pressure is unchanged or declining, however, signifies an improvement of LV relaxation. LV peak negative dP/dt decreases during the myocardial ischemia of either angina pectoris or infarction and increases in response to β-adrenergic stimulation and the phosphodiesterase inhibitor milrinone. It is not increased by digitalis glycosides.

**Time Constant of Relaxation**

Because of the load dependency of peak negative dP/dt and the fact that it uses information from only one point on the LV pressure–time plot, other indices have been introduced that analyze the time course of LV isovolumic pressure fall more completely. In 1976, Weiss and coworkers introduced the time constant T (or tau) of LV isovolumic pressure decline,\(^{68}\) First, LV isovolumic pressure decline is fit to the equation

\[
P = e^{-t/T} + \text{Ae}^{-t/B}
\]  
(22.6)

where \(P\) is LV isovolumic pressure, \(e\) is a mathematical constant (natural logarithm base), \(t\) is time after peak negative dP/dt, and \(A\) and \(B\) are constants. This can also be expressed as

\[
\ln P = At + B
\]  
(22.7)

Then the natural logarithm of LV pressure versus time is plotted to allow calculation of the slope \(A\), a negative number the units of which are seconds\(^{-1}\). The time constant \(T\) of isovolumic pressure fall is then defined as −1/A (expressed in ms) representing the time that it takes for \(P\) to decline to 1/e times its value.

Studies by the Johns Hopkins group have suggested that myocardial relaxation is normally complete by approximately 3.5T after the onset of isovolumic relaxation. The normal value of \(T\) as calculated using a plot of \(\ln P\) versus \(t\) is 25 to 40 ms in humans. Therefore, by 140 ms after the dicrotic notch, LV diastolic P–V relations should be determined primarily by passive elastic properties of the myocardium. Because the normal LV diastolic filling period is >400 ms, it is unlikely, according to this concept, that late- and end-diastolic P–V relations are still influenced by the relaxation process. However, there is now considerable evidence that even in the normal myocardium, cross-bridge cycling persists to some extent throughout diastole. This resting myocardial activity or tone makes it difficult to know what significance is to be applied to the concept that relaxation is complete at 3.5T. Nevertheless, it is important to emphasize that the relaxation process does progress with time through diastole, so that slowing of the process (prolongation of \(T\)) or shortening of the diastolic filling period (e.g., tachycardia) results in a higher resistance to early and even late diastolic filling.

Another approach to the measurement of \(T\) uses a more general equation to describe LV isovolumic pressure decline\(^{69}\):

\[
P = P_0 e^{-t/T} + P_B
\]  
(22.8)

According to this formula, if diastole were infinite in duration (\(t = \infty\)), \(P\) would decay to a residual pressure, \(P_B\). In the initial formula by Weiss and coworkers,\(^{68}\) \(P\) always declines toward zero in long diastoles. The more general formula allows for two variables: \(T\) (which equals −1/A) and \(P_0\). Work by Carroll and coworkers,\(^{70}\) as well as by other groups,\(^{67}\) has shown that both \(P_0\) and \(T\) can vary with physiologic maneuvers (e.g., exercise, ischemia). The biologic meaning of \(P_0\) is uncertain, although there has been speculation that it may reflect the level of diastolic myocardial tone. A problem with both \(P_0\) and \(T\) is that there is experimental evidence that the speed of the relaxation process itself is altered by myofiber stretch that occurs after mitral valve opening.

When \(T\) is to be derived from the formulas that assume a variable pressure intercept (\(P_0\)), the calculation is often accomplished by taking the first derivative\(^{69}\):

\[
dP/dt = - \frac{1}{T} (P - P_0)
\]  
(22.9)

Here, a plot of dP/dt versus \((P - P_0)\) has the slope −1/T.

Normal values of \(T\) in humans calculated by either the logarithmic method (asymptote = 0) or the derivative method (variable asymptote) are listed in Table 22.4.

Interesting experimental data comparing the two methods of calculating \(T\) with a gold standard were published by Paulus and coworkers.\(^{71}\) They measured LV pressure decay with a micromanometer catheter during isovolumic beats generated using an Inoue balloon to occlude the mitral valve orifice in patients with mitral stenosis who were undergoing balloon valvuloplasty. LV pressure declined to an asymptote of 2 ± 3 mmHg, and \(T\) was calculated from a monoexponential curve fit using the measured asymptote pressure. This \(T\) was considerably shorter than the \(T\) calculated by the derivative (variable asymptote) method and was much closer to the value obtained by the original Weiss logarithmic method,\(^{68}\) which assumes a zero asymptote.

Not only slow myocardial relaxation but also asynchrony of the relaxation process within the ventricular chamber results in prolongation of \(T\). In addition, \(T\) is probably not completely independent of loading conditions, although the influence of altered loading is relatively small. Measurement of \(T\) should be attempted only from LV pressure tracings obtained with high-fidelity, micromanometer-tipped catheters, or from fluid-filled systems with demonstrated optimal damping and high (>25 Hz) natural frequencies (see Chapter 10). Of
interest, investigators have reported noninvasive assessment of LV relaxation by continuous-wave Doppler echocardiography in patients with some degree of mitral regurgitation.\textsuperscript{72,73} The Doppler mitral regurgitant velocity profile is recorded, digitized, and converted to ventriculooatrial pressure gradient curves with the use of the simplified Bernoulli equation and differentiated into instantaneous dP/dt. The relaxation time constant is then calculated assuming a zero-pressure asymptote (Figure 22.15). In general, close correlations are seen between measurements of T made by this technique and those made from simultaneous LV micromanometer pressure measurements.\textsuperscript{72,73} However, accurate prediction of actual T was improved substantially when a measure of left atrial pressure was incorporated in the analysis.

**Volume-Derived Indices of Relaxation**

### Peak Filling Rate

After mitral valve opening, ventricular filling usually proceeds briskly with an initial rapid filling phase, a middle slow filling phase, and a terminal increase in filling rate associated with atrial systole. The rapid filling phase may be characterized by a maximum or peak filling rate (PFR) and time-to-PFR. PFR is usually determined by plotting LV volume against time, fitting the initial portion of this plot after mitral valve opening to a third- (or higher-) order polynomial, and solving for the first derivative of this polynomial. LV volume for this calculation may be obtained from the LV cineangiogram or by radionuclide techniques.

As one might expect, PFR is preload dependent: interventions that raise left atrial pressure increase PFR, and interventions that reduce pulmonary venous return and left atrial pressure cause PFR to decrease.\textsuperscript{74} However, an increase in PFR that occurs when LV filling pressure (pulmonary capillary wedge pressure, left atrial pressure, or LV diastolic pressure) is unchanged or falling can reasonably be taken as an indication that LV relaxation has improved. For example, PFR has been shown to decrease during angina pectoris\textsuperscript{77} when LV filling pressure is increasing. Because the rise in LV filling pressure by itself would cause an increase in PFR, the fall in PFR that is actually observed most likely indicates slowed relaxation of the myocardium, consistent with the other findings in this condition (fall in peak negative dP/dt, prolongation of T) that suggest impaired relaxation of the ischemic myocardium. PFR is reduced in patients with coronary stenoses, even in the absence of overt ischemia, and improves after coronary angioplasty.\textsuperscript{76} PFR is also reduced in patients with hypertrophic cardiomyopathy and improves after administration of a calcium-blocking agent.\textsuperscript{77} PFR is usually normalized for end-diastolic volume (EDV) and expressed as EDV/second. Cardiac dilatation by itself tends to depress PFR, exaggerating its preload dependence.

### Regional Diastolic Dysfunction

Diastolic dysfunction of specific regions of the left ventricle may be difficult to assess solely by examination of a global

**Figure 22.15** Doppler technique for measuring left ventricular (LV) rate of pressure fall, dP/dt, and the time constant of LV relaxation, T, using Doppler mitral regurgitant velocity spectrum (A, top), LV-left atrial pressure gradient and its first derivative (A, bottom), and linear plot of log LV-estimated pressure (P) versus time (B), with $T = 1/$slope. (From C Chen, et al. Doppler derived dP/dt and T in mitral regurgitation. \textit{J Am Coll Cardiol} 1994;23:970, with permission.)
parameter of LV diastolic function such as the time constant of relaxation or the PFR. As pointed out by Pouleur and Rousseau, the time course of LV isovolumic pressure decline underestimates the severity of regional impairment in the rate of relaxation. Marked slowing of regional relaxation in an area of myocardial ischemia is partially masked by normal or enhanced rates of relaxation in adjacent normal regions of the myocardium. Regional wall stress measurements have been proposed as an ideal way to assess regional rates of relaxation, but these can be made only by having knowledge of simultaneous LV pressure wall thickness and geometry.

A more practical way of assessing regional LV myocardial relaxation involves measurement of changes in regional LV chamber volume during isovolumic relaxation (Figure 22.16) as well as regional PFR. Regional LV area may not be constant for each segmental area during "isovolumic" relaxation in the dysfunctional ventricle. Instead, some regions may increase while others decrease in area, owing to either asynchrony or regional slowing of the relaxation process, with resultant differences in active wall tension in different parts of the left ventricle. An example of the application of this approach to measurement of regional myocardial relaxation is seen in a hemodynamic study by Friedrich and coworkers of 20 adult patients with LV hypertrophy resulting from aortic stenosis (mean aortic valve area 0.7 ± 0.2 cm²). LV global diastolic function was abnormal, with a T of 58 ± 4 ms and a time-to-PEAK FILLING RATE of 378 ± 63 ms. Enalaprilat, an angiotensin-converting enzyme inhibitor, was infused into the left coronary artery, and regional LV diastolic function was assessed in both the anterior wall (perfused by enalaprilat) and the inferior wall. LV area change during isovolumic relaxation increased in anterior segments and decreased in inferior segments (Figure 22.17), suggesting improved diastolic relaxation of the hypertrophied myocardium in response to angiotensin-converting enzyme inhibition, something seen previously only in animal experiments.

Rate of Wall Thinning

Another index of diastolic function, similar in some ways to PFR, is the peak rate of diastolic LV wall thinning. This can be measured echocardiographically by plotting posterior or septal wall thickness against time, fitting the data to a polynomial, and taking the first derivative. The posterior wall thickness, h, and its first derivative, dh/dt, reflect regional diastolic function of the posterior wall myocardium. An advantage of peak negative dh/dt over PFR is that the former assesses regional myocardial function, whereas PFR describes behavior of the whole ventricle and is insensitive when equal and opposite changes in diastolic function are occurring in different parts of the LV chamber. Peak negative dh/dt decreases during angina, even though LV filling pressure rises.

Rate of Myocardial Motion

Tissue Doppler has emerged as a useful, noninvasive method to assess diastolic function. It is based on the Doppler principle according to which a target moving away from or toward an ultrasound source will backscatter the ultrasound waves with a wavelength higher (moving toward) or lower (moving away) than the wavelength of the source. The relationship between the velocity of the target and the Doppler shift in frequency is expressed by the Doppler equation.
Figure 22.17 Left ventricular (LV) regional area change during isovolumic relaxation before and after selective left intracoronary angiotensin-converting enzyme (ACE) inhibition with enalaprilat in patients with marked LV hypertrophy and normal coronary arteries. Because total LV volume is constant during isovolumic relaxation, the increase in anterior segment area (presumably caused by improved myocardial relaxation owing to regional ACE inhibition) is exactly counterbalanced by a decrease in inferior segment area. (From Friedrich S, et al. Intracardiac angiotensin-converting-enzyme inhibition improves diastolic function in patients with LV hypertrophy due to aortic stenosis. *Circulation* 1994;90:2761, with permission.)

Figure 22.18 The upper panel illustrates the conventional Doppler interrogation of mitral inflow. The normal mitral valve inflow pattern is characterized by E > A and an E-wave deceleration time of 150 to 220 ms. Impaired LV relaxation or decreased LV compliance is associated with a reversal of E and A waves and prolongation of E-wave deceleration to >220 ms. Pseudo-normalization of the E/A ratio can occur when increased left atrial pressure results in an increased driving pressure and a consequent increased E-wave velocity across the mitral valve into a noncompliant LV. With severe diastolic dysfunction, the mitral valve inflow pattern can become restrictive, reflecting rapid equilibration of elevated left atrial and LV diastolic pressures in the noncompliant LV. The lower panel illustrates the three basic waveforms of tissue Doppler interrogation: Sa (systolic myocardial motion, or $Sm$), Ea (early diastolic motion, or $Em$), and Aa (atrial contraction, or $Em$). (Reproduced with permission from: Ho CY, Solomon SD. A clinician’s guide to Tissue Doppler Imaging. *Circulation* 2006;113:e396–e398.)
Tissue Doppler Imaging (TDI) allows measurement of myocardial tissue velocities by focusing on the high amplitude, low frequency signals reflected by the myocardium. The region of interest (ROI) of tissue Doppler is placed on myocardial tissue velocities by focusing on the high amplitude, low frequency signals reflected by the myocardium. The tissue Doppler waveform is characterized by a positive Sm wave corresponding to the movement of the mitral annulus toward the apex during ventricular systole, a negative Em wave corresponding to early diastolic relaxation and a negative Am wave corresponding to atrial contraction (Figure 22.18). Tissue Doppler measurements are generally load independent when compared to mitral flow velocities, although experimental studies have suggested that they might be affected by early diastolic lengthening load, in addition to translation movements and tethering. Several studies have assessed Em velocities and Em/Am ratios in different age groups, disease states, and loading conditions. Em velocities of ≥12 cm/second and Em/Am ratios of ≥1 are associated with normal diastolic function, while Em velocities of <8 cm/second and Em/Am ratios of <1 have been used as cutoffs for diastolic dysfunction and impaired relaxation. It has also been shown that the ratio of early transmitral peak LV inflow velocity E to early myocardial velocity Em (E/Em ratio) correlates well with invasive measurements of LV stiffness and diastolic function (Figure 22.19), and that a ratio of >8 can be used as a parameter to identify patients with heart failure with preserved ejection fraction (HFP EF) and diastolic dysfunction (Figure 22.20).

Various other indices of diastolic myocardial relaxation have been proposed. Most are imperfect, as are the ones discussed here. However, important information about diastolic relaxation and distensibility can usually be gleaned from examination of the parameters discussed in this chapter, taken in the context of the clinical setting and other hemodynamic findings in an individual patient.
Figure 22.20 ROC analysis for TDI (Tissue Doppler Imaging) indexes $E'/A'_{\text{lat}}$ and $E/E'_{\text{lat}}$. The sensitivity/specificity ratio for $E'/A'_{\text{lat}}$ ($<1$) is 67%/84% and for $E/E'_{\text{lat}}$ ($\geq 8$) is 83%/92%. $E'/A'_{\text{lat}}$ early to late diastolic velocity ratio of mitral annulus at lateral site; $E/E'_{\text{lat}}$, LV filling index at lateral site. (Reproduced with permission from: Kasner M, Westerman D, Steendijk P, et al. Utility of Doppler echocardiography and tissue Doppler imaging in the estimation of diastolic function in heart failure with normal ejection fraction: a comparative Doppler-conductance catheter study. Circulation 2007;116:637–647.)

REFERENCES


Evaluation of Tamponade, Constrictive, and Restrictive Physiology

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The pericardium separates the heart from the surrounding structures, and it has important mechanical, membranous, biofeedback, and barrier functions. As a relatively inelastic sac, it contributes to maintenance of normal atrial and ventricular compliance and optimal ventricular shape, provides protection against excessive ventricular-atrial valve regurgitation, and limits excessive acute dilation or mismatch between right- and left-side chamber volume. A small amount of pericardial fluid is usually present and has the important role of reducing friction during cardiac contraction, and mechano-receptors in the pericardium may provide biofeedback regulating heart rate and blood pressure. In addition, the negative pericardial pressure and its changes during respiratory cycles contribute to enhancing venous return to the right atrium to aid filling during inspiration.

While the diagnosis of pericardial tamponade is relatively straightforward, the differentiation between constrictive pericardial disease and restrictive physiology often presents challenges requiring the integration of hemodynamic measurements, imaging, and occasionally an endomyocardial or pericardial biopsy. In this chapter, we will review the pathophysiology of the complex pericardial-myocardial interaction leading to these different hemodynamic profiles. Chapters 38 and 44 provide additional information on pericardial interventions and on clinical profiles in pericardial disease.

NORMAL HEMODYNAMICS DURING THE RESPIRATORY CYCLE AND THE ROLE OF THE PERICARDIUM

The hemodynamic changes that occur in the setting of pericardial tamponade, pericardial constriction, and restrictive physiology can be explained on the basis of the complex interactions between cardiac chambers, pericardial restraint, and pressure gradients. The normal pericardial pressure is subatmospheric, and it tracks intrapleural pressure during the respiratory cycle. The negative pericardial pressure has the important role of maintaining a positive transmyocardial pressure gradient (intracavitary pressure – pericardial pressure), resulting in a net chamber-distending pressure that is slightly higher than the intracavitary pressure. This transmyocardial pressure gradient facilitates diastolic filling, particularly in the low-pressure right heart. During inspiration, there is a reduction in intrapleural pressure that affects all structures within the thorax, associated with a fall in chamber pressures and pulmonary wedge pressure. The reduction in intrapericardial pressure tends to be larger than the fall in systemic venous pressure, and with descent of the diaphragm, intra-abdominal pressure increases, resulting in an increase in the pressure gradient from extrathoracic veins to the right atrium. These forces collectively serve to enhance right atrial and right ventricular filling during inspiration.
Because the decrease in intrapleural pressure with inspiration is more effectively transmitted to the pulmonary venous bed than to the left ventricle, the pressure gradient from pulmonary vein to left atrium decreases slightly, resulting in a slight drop in the transmitial pressure gradient and a mild reduction of left ventricular diastolic volume and stroke volume. Hence, the mild decrease in systemic arterial pressure observed during normal inspiration is attributable to the slight reduction in left ventricular preload and transmission of the negative intrathoracic pressure to the aorta and peripheral arteries. As ventricular systole begins, the rapid reduction in ventricular volume causes a drop in pericardial pressure, which increases atrial transmucardial gradients to further enhance atrial filling.

The right and left ventricles share the intraventricular septum and are contained in the relatively indistensible pericardial sac, creating the substrate for the hemodynamic phenomenon known as diastolic ventricular interaction when the pericardium becomes diseased or when the heart becomes enlarged to the pericardial limits. Within the setting of this enhanced ventricular interaction, an increase in volume of one ventricle (in the setting of a compliant septum and an intact pericardium) will affect filling and volume of the other ventricle. While the pericardium has limited role in ventricular systolic coupling, it plays an important role in diastolic coupling and this effect is markedly enhanced by any abnormality of the pericardium or the pericardial space. As described below, the compliance of the septum can explain at least in part the differences in ventricular interdependence observed with pericardial tamponade, pericardial constriction, and restrictive physiology.

**TAMPOONADE PHYSIOLOGY**

Under normal conditions the pericardial sac contains 15 to 35 mL of fluid. Given the relatively inelastic characteristics of the pericardium, rapid accumulation of pericardial fluid leads to a marked increase of intrapericardial pressure. In contrast, over a prolonged period of time (as with eccentric cardiac remodeling or slowly growing malignant effusion), the pericardium can stretch and accommodate larger volumes, shifting the pressure-volume curve to the right (Figure 23.1). Tamponade physiology develops when the size of the effusion becomes sufficient to increase total pericardial volume from the shallow, compliant portion of the pericardial pressure-volume relationship to the steep, noncompliant portion (arrows, Figure 23.1). If venous return remains unchanged, an increase in intrapericardial pressure will decrease transmural diastolic filling pressures in all heart chambers, resulting in typical changes in the atrial pressure waveform. As described in Chapter 10, the normal atrial waveform is characterized by three positive deflections (a, c, and v waves) and three negative deflections (x, x', and y descents). The x descent corresponds to atrial relaxation. During ventricular systole, continuous atrial relaxation and the descent of the atrioventricular valve annulus result in further reduction of atrial pressure and in the corresponding x' descent. After the nadir of the x' descent, the atrium fills during ventricular systole while the atrioventricular valve is closed (v wave). This phase is followed by the y descent, which corresponds to opening of the atrioventricular valve and rapid emptying of the atrium. In pericardial tamponade, as intrapericardial pressure increases, an increase in venous return will initially serve to maintain cardiac filling and prevent diastolic collapse of cardiac chambers. Further increase in pericardial pressure will lead to a progressive impairment in atrial emptying and ventricular filling, with blunting or disappearance of the y descent while the x descent is typically preserved or enhanced (Figure 23.2). There is also loss of the early dip in minimal LV diastolic pressure and equalization between right atrial and LV pressure at the onset of diastole (Figure 23.3).

As pericardial pressure continues to increase, diastolic filling pressures will equalize across the four cardiac chambers, eventually culminating in diastolic compression of the right-side and then the left-side cardiac chambers. Diastolic filling dynamics throughout the cardiac cycle essentially become a
zero-sum game—for any increase in ventricular volume there is an obligate decrease in atrial volume, and conversely when right-side filling volume increases (as during inspiration) there is a matched drop in left-side volume. This enhancement of ventricular interdependence explains the pathophysiology and most physical findings in tamponade. As described above, under normal conditions inspiration causes a decrease in intrapericardial and intrathoracic pressure, which is coupled with an increase in systemic venous return to the right heart. There is also an increase in the capacitance of the pulmonary vasculature and reduction in the pressure gradient from pulmonary vein to left atrium, which results in a decrease in left ventricular filling, stroke volume, and systolic pressure. In pericardial tamponade, these effects are magnified dramatically, and increased systemic venous return to the right side of the heart is coupled with acute reduction in left-side filling owing to reduction in the pulmonary capillary to LV diastolic gradient (Figure 23.4). The converse then occurs during expiration, when left-side filling is augmented at the cost of right heart filling—such that the diastolic volumes, stroke volumes, and accordingly developed pressures within one ventricle are 180° out of phase with those in the other ventricle (Figure 23.5). The reduction in left ventricular filling and thus stroke volume reduces aortic systolic blood pressure by >10 mmHg during inspiration (pulsus paradoxus, Figure 23.6). As stated above, this is really not a paradox but an exaggeration of the normal systemic pressure changes during respiration.

Figure 23.2 Right atrial and right ventricular pressure pulses, before and after removal of pericardial fluid, in a patient with subacute effusive-constrictive pericarditis that followed radiotherapy. The right atrial pulse shows a predominant systolic descent ($X > Y$) initially and a predominant diastolic descent ($X < Y$) after removal of fluid. The diastolic dip–plateau pattern in the right ventricular pulse is prominent only after removal of fluid, in association with the $X < Y$ right atrial pulse. (Reproduced with permission from: Hancock EW. Subacute effusive-constrictive pericarditis. Circulation 1971;43:183–192.)

Figure 23.3 A. Left atrial (red) and left ventricular (black) tracings in a patient with mitral stenosis prior to percutaneous balloon valvotomy. Note the y descent (arrows) and low minimal LV diastolic pressure (*). B. After balloon inflation, LV systolic pressure is reduced, the y descent is absent (arrows), and the LV minimal diastolic pressure has increased substantially (*), findings related to cardiac perforation and cardiac tamponade.
Figure 23.4  Mechanism of the pulsus paradoxus in cardiac tamponade. During inspiration (thick arrows), the pulmonary wedge pressure (red) drops below the right atrial pressure (which approximates pericardial pressure, blue) and the LV diastolic pressure (black), resulting in a reduction in transmural filling pressure, acute “underfilling” of the LV, reduced LV stroke volume, and reduced LV systolic pressure (arrows).

Cardiac tamponade is a clinical diagnosis based upon typical symptoms including fatigue, dyspnea, and air hunger together with physical findings including elevated venous pressure, sinus tachycardia, and pulsus paradoxus. The diagnosis can be confirmed by echocardiography which typically shows pericardial effusion, right atrial and right ventricular diastolic collapse, abnormal increase in blood flow velocity across the tricuspid valve and corresponding decrease in flow velocity across the mitral valve during inspiration (Figure 23.7), and dilated inferior vena

Figure 23.5  In tamponade, enhanced LV and RV diastolic filling are 180° out of phase with each other (thin arrows) as the septum bows from right to left during inspiration (thick arrows) (increase in pulmonary artery pressure, red, coupled with decrease in LV systolic pressure, black) and then back from left to right during expiration (decrease in PA pressure and increase in LV systolic pressure).
Chapter 23 Evaluation of Tamponade, Constrictive, and Restrictive Physiology

Low-Pressure Tamponade

A clinical syndrome characterized by low pericardial pressure leading to cardiac compression because of low filling pressures, without the typical clinical findings associated with tamponade, has also been described. In an analysis of 279 patients undergoing pericardiocentesis at a single institution, 29 patients met the criteria for low-pressure tamponade (defined as intrapericardial pressure of <7 mmHg before pericardiocentesis and right atrial pressure of <4 mmHg after pericardiocentesis, Group 1), whereas 114 patients met the criteria for classic tamponade (intrapericardial pressure of >7 mmHg before pericardiocentesis and right atrial pressure of ≥4 mmHg after pericardiocentesis, Group 2). Typical findings of tamponade were present in only 24% of patients in group 1, as compared to 71% in group 2. When compared with classic tamponade cases, patients with low-pressure tamponade had lower pulsus paradoxus.

Constrictive-Effusive Physiology

In rare cases, following pericardiocentesis the pericardial pressure returns to subatmospheric (<0 mmHg) levels, while the right atrial pressure and the right ventricular diastolic pressures remain elevated, with a typical dip and plateau pattern in the right ventricular pressure tracing (Figure 23.2). This pattern is consistent with effusive-constrictive physiology, and it has been suggested that this represents evolution of acute pericarditis with pericardial effusion toward pericardial constriction.

Cava without collapse during inspiration. Confirmation of tamponade physiology is obtained through hemodynamic measurements during cardiac catheterization and through documentation of elevation of pericardial pressure above atmospheric pressure, its equalization with right atrial pressure, and its decrease to subatmospheric levels following pericardiocentesis. Detailed understanding of the hemodynamic changes in tamponade and a high index of suspicion are especially important in the evolving era of advanced percutaneous treatments for structural heart disease and cardiac arrhythmias, where cardiac perforations may be more commonly observed.
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Figure 23.7 A. Two-dimensional echocardiogram in the four-chamber view from a patient with cardiac tamponade. There is a large pericardial effusion apparent as an echo-free space around the heart. In diastole, there is collapse of the right atrium (arrow). B. Doppler measurement of mitral valve and tricuspid flow velocities in a patient with cardiac tamponade. There is marked reciprocal respiratory variation: during inspiration, mitral valve flow velocity decreases and tricuspid valve flow velocity increases. (Reproduced with permission from: Little WC, Freeman GL. Pericardial disease. Circulation 2006;113:1622-1632.)

(10.41 ± 5.33 versus 23.7 ± 12.47 mmHg), lower intrapericardial pressure (2.5 ± 1.68 versus 12.93 ± 5.42 mmHg), and lower right atrial pressure (3.59 ± 1.57 versus 14.63 ± 5.42 mmHg), but similar transmural atrial pressure (0.07 ± 0.6 versus 0.35 ± 1.70 mmHg) and similar cardiac index (2.96 ± 1.26 versus 2.69 ± 1.79 L/min). Both patient groups had a significant increase in cardiac index following pericardiocentesis. Overall, these data support the importance of transmural or transmyocardial pressure as the primary determinant of atrial filling and highlight the importance of a high degree of suspicion in patients who might have symptoms or findings consistent with hemodynamic compromise and in whom classic findings of tamponade might be absent.

Regional Cardiac Tamponade

In the setting of large, circumferential pericardial effusions, cardiac tamponade presents with typical clinical and echocardiographic findings. In contrast, following cardiac surgery, cardiac tamponade is frequently secondary to a loculated effusion characteristically localized in the posterior wall, and in such patients the typical findings of tamponade are absent. Echocardiography may reveal evidence of regional left
ventricular diastolic collapse in the setting of these loculated pericardial effusions (Figure 23.8). It has been suggested that loculated effusion develops because of posterior adherence of the anterior right ventricular and atrial walls and anterior pericardium to the chest wall, and adhesions in the surrounding area. Common hemodynamic findings in these patients include elevated right atrial and right ventricular diastolic pressure, elevated pulmonary capillary wedge pressure, and equalization of right atrial and pulmonary capillary wedge pressure within 5 mmHg.

**CONSTRUCTIVE PHYSIOLOGY**

Pericardial constriction is the result of inflammatory processes of the pericardium leading to progressive fibrosis, thickening, and in some cases calcification of pericardial layers (Figure 23.9). While prior cardiac surgery
and radiation therapy are common etiologies, the most frequent cause remains idiopathic.\textsuperscript{14} The hemodynamic changes associated with constrictive pericarditis are similar to those observed with pericardial tamponade and are often difficult to distinguish from restrictive cardiomyopathy. Because constrictive pericarditis is a completely "curable" form of heart failure, it is critically important to accurately identify this disorder. As with pericardial effusion, pericardial constriction enhances ventricular coupling and impairs diastolic chamber filling. In constrictive pericarditis, ventricular filling occurs predominantly during early diastole as the ventricles cannot expand further during mid to late diastole owing to the pericardial constraint. Accordingly, the ventricular diastolic pressure tracing is characterized by an early dip followed by a positive "rapid filling wave" and plateau phase (dip and plateau pattern or square-root sign; Figure 23.10).\textsuperscript{15} It has been suggested that this early dip is secondary to a "rubber bulb" effect or "spring back" of the pericardial layer during early diastole.\textsuperscript{16} This rapid filling corresponds to the pericardial knock often appreciated on physical examination. The right atrial waveform will show steep x and y descents related to atrial relaxation and rapid early filling, creating the so-called M or W sign (Figure 23.11), and the mean right atrial pressure will often increase during deep inspiration (Kussmaul sign, Figures 23.12 and 23.13).\textsuperscript{15}
As described above, inspiration normally decreases left-side filling slightly because the pressure gradient from pulmonary vein to left atrium and left ventricle is reduced. In constriction, the rigid, fibrotic pericardium further “insulates” the left ventricle from the inspiratory drop in intrathoracic pressure—exaggerating this normal drop in the pulmonary vein to left ventricle gradient. This phenomenon, termed intrathoracic—intracardiac dissociation, can be identified by a variation in pulmonary wedge to left ventricular diastolic pressure gradient of ≥5 mmHg from inspiration to expiration (Figure 23.14). Thus, the left ventricle becomes acutely underfilled during inspiration, accounting for the drop in LV and aortic systolic pressure (pulsus paradoxus, Figure 23.15). Because of the markedly enhanced ventricular interaction mediated by pericardial restraint, the right ventricle then takes advantage of this left-side underfilling. The septum bows from right to left, and right ventricular diastolic volume increases7 (Figure 23.16) with acute increases in RV stroke volume, and RV systolic pressure will increase during inspiration. This discordant change in LV and RV systolic pressures (or pressure–time area) is the key hemodynamic finding of enhanced ventricular interdependence (Figure 23.17).

Additional “classical” hemodynamic findings associated with constrictive physiology include equalization of diastolic pressures across the four cardiac chambers (LVEDP – RVDEP < 5 mmHg), the absence of significant pulmonary hypertension (pulmonary artery systolic pressure <55 mmHg), and a right ventricular end-diastolic pressure to right ventricular systolic pressure (RVEDP/SVSP) ratio of >1/3 (Figure 23.18). While these findings are generally of high sensitivity, they are poorly specific for constriction and are often seen in restrictive disease or “garden variety” heart failure. In a seminal study, Hurrell and colleagues used high-fidelity micromanometer catheters to compare classical and dynamic respiratory hemodynamics in 15 patients with surgically proven constrictive pericarditis and 21 patients with other causes of heart failure.18 The authors found that the classical findings of constriction including LVEDP – RVEDP <5 mmHg, PASP <55 mmHg, RVEDP/RVSP >1/3, and dip and plateau filling were inadequate to discriminate between these groups (Figure 23.19). However, the findings of intracardiac–intraventricular dissociation and enhanced ventricular interdependence showed much higher specificity without compromising sensitivity18 (Figure 23.20; Table 23.1).

The hemodynamic findings of pericardial constriction are preload dependent, and the equalization of diastolic
Figure 23.14  Dynamic Criteria for pericardial constriction: Simultaneous recording of left ventricular and pulmonary capillary wedge pressure showing Intrathoracic–intracavitary dissociation during inspiration.

pressures might be absent in the setting of intravascular volume depletion. Thus, volume loading should be part of the cardiac catheterization protocol in those cases where initial filling pressures are low and the initial hemodynamic data are nondiagnostic19 (Figure 23.21). However, this latter group of occult constriction should also display a low cardiac output, and as a general rule of thumb, hemodynamically important constrictive pericarditis is virtually excluded in patients

Figure 23.15  During inspiration there is marked drop in LV systolic pressure (pulsus paradoxus) with no reduction in right atrial pressure (Kussmaul sign) in a patient with constrictive pericarditis. Note the prominent y descent in the right atrial tracing superimposed on the prominent “dip and plateau” in the LV tracing, which is in contrast to the absent y descent and minimal diastolic pressure in tamponade.
with normal right atrial pressure and normal cardiac output, even if pericardial disease is present.

**RESTRICTIVE PHYSIOLOGY**

As with constrictive pericarditis, restrictive cardiomyopathy is characterized by severe diastolic dysfunction and preserved ejection fraction. The fundamental difference is that diastolic filling is restricted by the myocardium in restriction rather than by the pericardium. Both constrictive pericarditis and restrictive cardiomyopathy are commonly associated with rapid x and y descents, the Kussmaul sign, and with typical right and left ventricular “dip and plateau” patterns during diastole. Echocardiography in restrictive cardiomyopathy often shows profound diastolic dysfunction, with a rapid early filling velocity (E), short deceleration time, and high “E/A” ratio. However, prior

![Image of Figure 23.16](image1)

**Figure 23.16** Assessment of increased ventricular coupling using real-time cine CMR in constrictive pericarditis. Short-axis cine CMR at onset of inspiration (A) and onset of expiration (B). The images were acquired at early ventricular filling. Septal inversion occurs at inspiration (A), with increased right-side septal motion at expiration (B), leading to an abnormal respiratory septal shift. The horizontal dotted lines indicate the position of the left hemidiaphragm. (Reproduced with permission from: Bogaert J, Francone M. Cardiovascular magnetic resonance in pericardial diseases. *J Cardiovasc Magn Reson* 2009;11:14.)

![Image of Figure 23.17](image2)

**Figure 23.17** Ventricular discordance. During inspiration, the increase in right ventricular pressure is associated with a reduction in left ventricular pressure.
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Figure 23.18 Left (black) and right ventricular (red) pressure tracings showing classical hemodynamic findings observed in constriction including near equalization in LV and RV end-diastolic pressures (LVEDP, RVEDP), a prominent “dip and plateau” with elevated rapid filling wave, ratio of RVEDP to RV systolic pressure of >0.33, and absent pulmonary hypertension (PA systolic pressure, PASP, <55 mmHg).

Figure 23.19 The classical hemodynamic criteria show marked overlap between patients with surgically proven constriction (Group I) and patients with myocardial disease (Group II). (Reproduced with permission form: Hurrell DG, et al. Value of dynamic respiratory changes in left and right ventricular pressures for the diagnosis of constrictive pericarditis. Circulation 1996;93:2007–2013.)
Restrictive cardiomyopathy typically involves the entire myocardium, including the interventricular septum, which impedes the septal shift toward the left during inspiration. Thus, left ventricular pressure tracks right ventricular pressure during systole with respiration in a concordant fashion (Figure 23.20B).

Tissue Doppler can be used as an additional noninvasive modality to aid in the differentiation of constrictive cardiomyopathy.
Table 23.1 Sensitivities, Specificities, Positive Predictive Values, and Negative Predictive Values as a Function of Criteria for the Diagnosis of Constrictive Pericarditis

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDP – RVEDP ≤5 mmHg</td>
<td>60</td>
<td>38</td>
<td>4</td>
<td>57</td>
</tr>
<tr>
<td>RVEDP/RVSP &gt; 1/3</td>
<td>93</td>
<td>38</td>
<td>52</td>
<td>89</td>
</tr>
<tr>
<td>PASP &lt;55 mmHg</td>
<td>93</td>
<td>24</td>
<td>47</td>
<td>25</td>
</tr>
<tr>
<td>LV RFW ≥7 mmHg</td>
<td>93</td>
<td>57</td>
<td>61</td>
<td>92</td>
</tr>
<tr>
<td>Respiratory change in RAP &lt;3 mmHg</td>
<td>93</td>
<td>48</td>
<td>58</td>
<td>92</td>
</tr>
<tr>
<td>Dynamic respiratory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCWP–LV respiratory gradient ≥5 mmHg</td>
<td>93</td>
<td>81</td>
<td>78</td>
<td>94</td>
</tr>
<tr>
<td>LV–RV interdependence</td>
<td>100</td>
<td>95</td>
<td>94</td>
<td>100</td>
</tr>
</tbody>
</table>

LVEDP, left ventricular end-diastolic pressure; NPV, negative predictive value; PASP, pulmonary artery systolic pressure; PCWP, pulmonary capillary wedge pressure, PPV, positive predictive value; RAP, right atrial pressure; RFW, rapid filling wave; RVEDP, right ventricular end-diastolic pressure; RVSP, right ventricular systolic pressure.


**Figure 23.21** Pressure curves showing increased left and right ventricular diastolic pressures (top) with dip and plateau (square root sign), consistent with constriction physiology, and equalization of diastolic pressures after volume loading (bottom). (Reproduced with permission from: Sharif D, et al. Images in cardiovascular medicine. Recurrent pericardial constriction: vibrations of the knock, the calcific shield, and the evoked constrictive physiology Circulation 2008;118:1685–1688.)
pericarditis from restrictive cardiomyopathy. Garcia et al evaluated 8 patients with constrictive pericarditis, 7 patients with restriction, and 15 normal volunteers. Peak early velocity of longitudinal axis expansion (Ea), transmitial early (E) and late (A) Doppler flow velocities, left ventricular systolic and diastolic volumes, ejection fraction, and mitral annular M-mode displacement were compared between the groups. Mean Ea values were significantly higher in controls (14.5 ± 4.7 cm/s [mean ± SD]) and in patients with constriction (14.8 ± 4.8 cm/s) than in those with restriction (5.1 ± 1.4 cm/s, P < 0.001 constriction versus restriction). Multivariate analysis identified Ea as the best variable for differentiating constriction from restriction. Similar findings have been reported by Ha and colleagues, including the observation of higher tissue Doppler velocities at the septal mitral annulus as opposed to that at the lateral annulus. Additional imaging of the pericardium by computed tomography or cardiac MRI also proves useful in the differentiation between pericardial and myocardial disease, though it is noteworthy that ~20% of patients with surgically-proven constriction may have a normal-thickness pericardium.

In addition to restrictive cardiomyopathy and constrictive pericarditis, other cardiovascular diseases can also cause similar hemodynamics. In particular, patients with right-side heart failure and severe tricuspid regurgitation also may display numerous classical findings and even some elements of enhanced interdependence. This is because right-side chamber enlargement increases pericardial restraint, even in the absence of pericardial pathology. However, in contrast to constriction, patients with severe tricuspid insufficiency will frequently display an increase in RV diastolic pressure above that of the LV during inspiration.

CONCLUSIONS

A careful hemodynamic assessment is extraordinarily useful in the evaluation of patients with suspected constrictive or restrictive physiology. However, none of the available methods is perfect, and in many cases the correct differentiation requires the integration of information gathered from multiple modalities including echocardiography, CT, MRI, and occasionally endomyocardial and/or pericardial biopsy. Such diagnostic differentiation is critical, as constrictive pericarditis can be cured with surgical pericardiectomy.

REFERENCES

Fundamental concepts of coronary physiology and myocardial blood flow, once the subject of research studies, are now used in daily clinical practice. The adoption of invasive coronary physiologic lesion assessment before percutaneous coronary intervention has become routine in many catheterization laboratories. Indeed, in the last decade, numerous studies have demonstrated favorable outcomes for revascularization decisions based on in-lab coronary physiologic evaluation in patients with a variety of difficult angiographic subsets. The rationale for the use of physiology in the cath lab is the necessity to overcome the limitation of angiography in reflecting the true ischemic potential of a coronary luminal narrowing. This chapter thus reviews the physiology of coronary blood flow, its regulation in response to cardiac metabolism, and the techniques most widely used to evaluate myocardial blood flow and metabolism. Catheter-based methods such as the intracoronary pressure and Doppler flow velocity guidewires, including clinical studies on the use of coronary physiology in the practice of PCI, are emphasized.

**CONTROL OF MYOCARDIAL BLOOD FLOW: THE MYOCARDIAL OXYGEN SUPPLY AND DEMAND RELATIONSHIP**

The control of myocardial blood flow is based on balancing the myocardial oxygen supply and demand relationship, which states that the heart requires a sufficient quantity (supply) of oxygen for any given oxygen need (demand), to prevent ischemia or infarction. The heart is an aerobic organ that relies almost exclusively on the real-time oxidation of substrates for energy generation, with little ability to accumulate
an oxygen debt as is seen with skeletal muscle. In a steady state, cardiac metabolic activity is thus accurately measured by myocardial oxygen demand (MVO₂). The total metabolism of an arrested, quiescent heart is approximately 1.5 mL/minute per 100 gm, as required to support the physiologic processes not directly associated with contraction. In contrast, a beating canine heart has MVO₂ ranging from 8 to 15 mL/minute per 100 gm.¹ ²

The heart metabolizes a variety of substrates such as glucose, free fatty acids, lactate, amino acids, and ketones. These substrates are critical for the generation of high-energy phosphates (ATP and creatine phosphate³ ⁴) that supply the energy requirements of the myocardium. At rest, the rate of force development and the frequency of force generation per unit time accounts for approximately 60% of myocardial energy use; myocardial relaxation accounts for approximately 15% of energy use; electrical activity accounts for 3% to 5%; and basal cellular metabolism accounts for the remaining 20% of energy use³ (Table 24.1). As workload increases, myocardial contractile function consumes an even larger fraction of high-energy phosphate availability. Any compromise in substrate availability causes the myocardium to minimize energy expenditure on mechanical work and divert the remaining high-energy substrates for the continued maintenance of cellular integrity, thus setting the stage for myocardial “hibernation.”⁶ ⁷

Under normal aerobic conditions, several substrates contribute simultaneously to meeting myocardial energy needs: free fatty acid (65%), glucose (15%), lactate and pyruvate (12%), and amino acids (5%), whereas glycolysis plays only a minor role. In fact, lactate is actually extracted by the myocardium, converted into pyruvate, and oxidized by way of the Krebs cycle. In the fasting state, when serum fatty acids are high, myocardial glucose uptake tends to be suppressed in favor of fatty acid utilization. But after an oral glucose load, or when a fall in myocardial blood flow or oxygen supply leads to a reduction or loss in mechanical function, glucose uptake is enhanced and fatty acid oxidation declines. Whereas glucose metabolism is preferentially aerobic, decreasing oxygen availability decreases high-energy phosphate and leads to the accumulation of ATP breakdown products (ADP, AMP, and other nucleosides). The myocardium then turns toward enhancing glycogenolysis and glycolysis to augment ATP production. In doing so, the pyruvate-lactate equilibrium is shifted toward lactate formation, causing net transmyocardial lactate production rather than extraction. Under extreme conditions, increasing cytosolic lactate and hydrogen ion concentrations lead to inhibition of residual glycolysis, deprive the cell of even anaerobic ATP production, and trigger a sequence of biochemical events that may lead to complete cessation of energy production with irreversible cellular injury.

The three major physiologic determinants of MVO₂ are heart rate, myocardial contractility, and myocardial wall tension or stress² (additional factors are shown in Table 24.2)

1. Heart rate is the most important determinant of MVO₂. When heart rate doubles, myocardial oxygen uptake approximately doubles. Heart rate is a dominant factor in the O₂ supply-demand ratio for two reasons: Increases in heart rate also increase oxygen consumption, and increases in heart rate reduce subendocardial coronary flow owing to shortening of the diastolic filling period. Subendocardial ischemia may thus occur

### Table 24.1 Myocardial Oxygen Consumption Components Total: 6–8 mL/min per 100 gm

<table>
<thead>
<tr>
<th>Distribution</th>
<th>Basal</th>
<th>Electrical</th>
<th>Effects on MVO₂ of 50% increases in</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20%</td>
<td>1%</td>
<td>Wall stress 25% Heart rate 50%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Contractility 45% Volume work 4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pressure work 50%</td>
</tr>
</tbody>
</table>

The table demonstrates the dominant contribution to myocardial oxygen consumption, MVO₂, made by pressure work and prominent effects of increasing pressure work and heart rate on MVO₂. (Reproduced with permission from Gould KL. Coronary Artery Stenosis. New York: Elsevier; 1991:8.)

### Table 24.2 Determinants of MVO₂

<table>
<thead>
<tr>
<th>Heart rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contractile state</td>
</tr>
<tr>
<td>Tension development</td>
</tr>
<tr>
<td>Activation</td>
</tr>
<tr>
<td>Depolarization</td>
</tr>
<tr>
<td>Direct metabolic effect of catecholamines</td>
</tr>
<tr>
<td>Family history of coronary artery disease</td>
</tr>
<tr>
<td>Fatty acid uptake</td>
</tr>
<tr>
<td>Maintenance of active state</td>
</tr>
<tr>
<td>Maintenance of cell viability in basal state</td>
</tr>
<tr>
<td>Muscle shortening against a load (the Fenn effect)</td>
</tr>
</tbody>
</table>
during tachycardia because of simultaneously increasing demand (tachycardia) and compromised flow for the subepicardium.3

2. Myocardial contractility is related to myocardial oxygen consumption by the degree of pressure work per heart-beat. The net effect of positive inotropic stimuli (e.g., \( \text{Ca}^{2+} \) and catecholamines) on \( \text{MVO}_2 \) is the result of wall tension (which declines with a reduction in heart size), and myocardial contractility (which is increased by inotropic stimuli). The decrease in \( \text{MVO}_2 \) that might be expected to result from falling ventricular wall tension is opposed by the increase in contractility, which tends to augment \( \text{MVO}_2 \). In the absence of heart failure, drugs that stimulate myocardial contractility elevate \( \text{MVO}_2 \) because heart size and therefore wall tension are not reduced substantially and do not offset the effect of enhanced contractility.

3. Myocardial wall tension is proportionate to the aortic pressure, myocardial fibril length, and ventricular volume. Myocardial oxygen consumption doubles as mean aortic pressure increases from 75 to 175 mmHg, at constant heart rate and stroke volume. Comparing the relative effects of ventricular pressure, stroke volume, and heart rate on \( \text{MVO}_2 \), researchers found that ventricular pressure development is a key determinant of \( \text{MVO}_2 \). \( \text{MVO}_2 \) per beat correlated well with the area under the LV pressure curve (time \( \times \) pressure), termed the tension–time index, a more accurate determinant of \( \text{MVO}_2 \) than is the developed pressure alone.4,5 Tachycardia elevates \( \text{MVO}_2 \) by increasing the frequency of tension development per unit time, as well as by increasing contractility.

\( \text{MVO}_2 \) is also influenced by the degree of myocardial shortening during stroke volume ejection, although less so than by tension development. The systolic pressure–rate product (also known as the double product) can be used as an estimate of \( \text{MVO}_2 \) in a clinical setting, such as exercise or pacing tachycardia, recognizing its limited accuracy. \( \text{MVO}_2 \) closely correlates with the LV systolic pressure–volume loop area, the external mechanical work, the end-systolic elastic potential energy in the ventricular wall, and the area enclosed by the systolic pressure–volume trajectory and the \( E_{\text{max}} \) line.

**Determinants of Myocardial Oxygen Supply**

Myocardial oxygen supply is provided by blood transiting the coronary and capillary circuit at an adequate perfusion pressure (mean arterial pressure) and with a satisfactory hemoglobin function and concentration to carry and deliver oxygen to the myocardial cells. A breakdown in any linkage of the supply side factors can result in an inadequate myocardial oxygen supply and myocardial ischemia.

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**MEASUREMENT OF MYOCARDIAL METABOLISM**

Measurement of myocardial metabolism may be performed noninvasively (e.g., positron emission tomography scanning) or invasively by transmyocardial sampling techniques that involve acquisition of simultaneous arterial and coronary venous (e.g., coronary sinus) blood. Specialized blood products commonly used in the determination of changes in myocardial metabolism include serum pyruvate, lactate, oxygen, and other metabolic or hemotologic blood components. Transmyocardial extraction of pharmaceutical agents after systemic or intracoronary delivery can also be determined by transmyocardial blood sampling for the measurement of arterial–venous concentration difference, along with measurement of blood flow per unit time.

In studies involving ischemic myocardial metabolism, the most commonly measured products are lactate and oxygen. Specialized chilled collection tubes containing an agent (perchloric acid) to stop red cell metabolism and prevent clotting are used for chemical assays to measure small differences in normal lactate levels across the myocardium. Clinical laboratory tests calibrated for the high lactate levels in lactic acidosis are unsuitable for the measurement of the small transmyocardial differences. Myocardial catecholamines (norepinephrine, epinephrine) and other vasoactive mediator products, such as prostaglandins, can be measured if sample tubes are placed immediately in ice to prevent platelet activation after blood withdrawal through a long narrow catheter lumen. Large-bore (≥6F) heparin-coated catheters may be required to assess platelet products. Measurement of myocardial metabolism requires preparation of the sampling tubes and other collection materials using advanced techniques.

**Regulation of Coronary Blood Flow and Resistance**

Coronary arterial resistance \( (R, \text{pressure} \div \text{flow}) \) is the summed up resistances of the epicardial coronary conduit \( (R1) \), and the precapillary arteriolar \( (R2) \) and intramyocardial capillary \( (R3) \) resistance circuits \( (R) \) (Figure 24.1). Normal epicardial coronary arteries in humans typically taper from the base of the heart with diameters of typically 5 to 6 mm to the apex where the vessel diameter is typically down to 0.3 mm. The epicardial vessels do not offer appreciable resistance to blood flow \( (R1) \) in their normal state. Even at the highest level of blood flow, there is no detectable resistance as would be manifest as a pressure drop along the length of human epicardial arteries,6 making even large epicardial vessel resistance \( (R1) \) trivial until atherosclerotic obstructions develop. Most of the epicardial vessel wall consists of a muscular media that responds to changes in aortic pressure and modulates coronary tone in response to flow-mediated endothelium-dependent vasodilators, circulating vasoactive...
The microcirculatory resistance (R3) circuit consists of a dense network of about 4,000 capillaries per square millimeter, which ensures that each myocyte is adjacent to a capillary. Capillaries are not uniformly patent because precapillary sphincters regulate flow according to oxygen demand. Several conditions, such as LV hypertrophy, myocardial ischemia, or diabetes, can increase the microcirculatory resistance (R3) and blunt the normal maximal increases in coronary flow. Increased R3 resistance may also be associated with elevated resting blood flow above that expected for the existing myocardial oxygen demand, resulting in reduced coronary flow reserve (i.e., the hyperemic/basal flow ratio).

As in any vascular bed, blood flow to the myocardium depends on the coronary artery driving pressure and the resistance produced by the serial vascular components. Coronary vascular resistance, in turn, is regulated by several interrelated control mechanisms that include myocardial metabolism (metabolic control), endothelial (and other humoral) control, autoregulation, myogenic control, extravascular compressive forces, and neural control. These control mechanisms may be impaired in diseased states, thereby contributing to the development of myocardial ischemia (Tables 24.3 and 24.4).

Coronary vasodilatory reserve (CVR) is the ability of the coronary vascular bed to increase flow from a basal level to a maximal (or near maximal) hyperemic level in response to a mechanical or pharmacologic stimulus. Such substances, and neurohumoral stimuli. Large-conduit arteries are unaffected by myocardial metabolites because of their extramural location, but can produce episodic increases in resistance during severe focal or diffuse contraction (vasospasm) in the absence of atherosclerosis. One exception is myocardial bridging, in which intramyocardial vessel segments may offer increased resistance during systole owing to mechanical compression of the bridged segment during ventricular contraction.

Changes in epicardial and arteriolar coronary resistances in response to physiologic or pharmacologic stimuli can be considered either primary or secondary vasomotor events. Primary vasodilation signifies an alteration in myocardial vessel tone and perfusion with no preceding change in myocardial oxygen demand. Secondary vasodilation refers to changes in vessel tone and blood flow that occur in response to alterations in myocardial oxygen consumption.\(^1\)

Precapillary arterioles are resistive vessels (R2) connecting epicardial arteries to myocardial capillaries and are the principal controllers of coronary blood flow.\(^8\) Precapillary arterioles (100 to 500 µm in size) contribute approximately 25% to 35% of total coronary resistance. The prearteriolar resistance function autoregulates the driving pressure at the origin of the precapillary arterioles within a finite pressure range. This regulatory function is also influenced by myogenic and flow-dependent vasodilatation related to shear stress.

### Table 24.3 Regulation of Coronary Circulation

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Effector</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoregulation</td>
<td>Intrinsic vasoconstrictor tone</td>
</tr>
<tr>
<td>Perfusion pressure</td>
<td>Aortic or poststenotic pressure</td>
</tr>
<tr>
<td>Metabolic pressure</td>
<td>Exercise, ischemia</td>
</tr>
<tr>
<td>Myocardial compression and myogenic mechanisms</td>
<td>Systolic–diastolic interaction</td>
</tr>
<tr>
<td>Neural control</td>
<td>Sympathetic, parasympathetic, pain</td>
</tr>
<tr>
<td>Endothelium</td>
<td>EDRF, EDCF</td>
</tr>
<tr>
<td>Pharmacologic</td>
<td>Dipyridamole, adenosine, acetylcholine, α-, β-agonists and antagonists, and so on</td>
</tr>
</tbody>
</table>

EDRF, endothelial derived relaxing factor; EDCF, endothelial derived constricting factor. (Modified from Gould L. Coronary Artery Stenosis and Reversing Atherosclerosis, 2nd ed. New York: Arnold and Oxford University Press; 1998.)
stimuli include the reactive hyperemia that follows transient coronary occlusion, exercise, and the administration of various pharmacologic agents. Coronary flow reserve is expressed as the ratio of maximal hyperemic flow to resting coronary flow—a ratio that averages from 4 to 7 in experimental animals and from 2 to 5 in man. In experimental animal studies, increasing conduit stenosis (R1) produces a predictable decline in coronary flow reserve, beginning at about a 60% artery diameter narrowing. At diameter stenoses of >80% to 90%, all available coronary reserve has been exhausted and resting flow begins to decline (Figure 24.2). (Factors responsible for reduced CVR in the absence of epicardial stenosis are listed in Table 24.5.) This relationship between increasing stenosis severity and reduced available flow reserve has been used in assessing the effective physiologic severity of any given coronary lesion and forms the basis of many noninvasive test modalities for ischemia. In clinical practice, however, for an individual patient, this relationship is unpredictable given the complex three-dimensional anatomy, imprecise correlation between angiographic estimate of diameter reduction owing to stenosis and true lumen cross-sectional area, and unknown status of microcirculation.

Furthermore, the influence of a stenosis on coronary blood flow is principally related to the morphologic features of the stenosis, with resistance to flow changing exponentially with lumen cross-sectional area (the most commonly used measure of severity) and linearly with lesion length (Figure 24.3). Additional factors contributing to stenosis resistance include the shape of the entrance and exit orifices, vessel stiffness, distensibility of the diseased segment (permitting active or passive vasomotion), and the variable lumen

---

### Table 24.4 Mediators of Coronary Vasodilation

<table>
<thead>
<tr>
<th>Stimulus</th>
<th>Epicardial Arteries</th>
<th>Arterioles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcholine</td>
<td>Nitric oxide</td>
<td>Endothelium</td>
</tr>
<tr>
<td>Flow shear</td>
<td>Endothelial</td>
<td>Nitric oxide</td>
</tr>
<tr>
<td>Exercise</td>
<td>Nitric oxide, neural</td>
<td>Metabolic, nitric oxide, neural</td>
</tr>
<tr>
<td>Pacing</td>
<td>Nitric oxide</td>
<td>Nitric oxide, metabolic</td>
</tr>
<tr>
<td>Ischemia or hypoxia</td>
<td>Metabolic, nitric oxide</td>
<td>Metabolic, nitric oxide</td>
</tr>
<tr>
<td>Perfusion pressure</td>
<td>Myogenic</td>
<td>Myogenic</td>
</tr>
<tr>
<td>Reactive hyperemia</td>
<td>Myogenic, flow shear</td>
<td>Myogenic, flow shear, metabolic, nitric oxide, prostacyclin</td>
</tr>
<tr>
<td>Dipyridamole, adenosine</td>
<td>No direct effect</td>
<td>Direct dilator, nitric oxide</td>
</tr>
<tr>
<td>Nitroglycerine</td>
<td>Direct dilator</td>
<td>No direct effect</td>
</tr>
</tbody>
</table>

*BOLD* indicates primary mechanism.

(From Gould L. Coronary Artery Stenosis and Reversing Atherosclerosis, 2nd ed. New York: Arnold and Oxford University Press; 1998.)
Table 24.5  Factors Responsible for Microvascular Disease and Reduction of Coronary Flow Reserve

<table>
<thead>
<tr>
<th>Abnormal vascular reactivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal myocardial metabolism</td>
</tr>
<tr>
<td>Abnormal sensitivity toward vasoactive substances</td>
</tr>
<tr>
<td>Coronary vasospasm</td>
</tr>
<tr>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Hypertrophy</td>
</tr>
<tr>
<td>Vasculitis syndromes</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Recurrent ischemia</td>
</tr>
</tbody>
</table>


Obstruction that may be superimposed by platelet aggregation and thrombosis compromising lumen area, a process active in acute coronary syndromes (ACSs).10

As blood traverses a diseased arterial segment, turbulence, friction, and separation of laminar flow causes energy loss resulting in a pressure gradient ($\Delta P$) across the stenosis. Using a simplified Bernoulli formula for fluid dynamics, pressure loss across a stenosis can be estimated from blood flow as follows:

$$\Delta P = f \frac{Q}{A_n} + sQ^2$$  \hspace{1cm} (24.1)

$$\Delta P = \frac{1.8Q}{d_{sten}^4} + \frac{6.1Q^2}{d_{sten}^4}$$  \hspace{1cm} (24.2)

where $\Delta P$ is the pressure drop across a stenosis in millimeters of mercury (mmHg), $Q$ is the flow across the stenosis in milliliters per second, and $d_{sten}$ is the minimal diameter of the stenosis lumen in millimeters. In Eq. (24.1), the first term ($f$) accounts for energy losses owing to viscous friction between the laminar layers of fluid and the second term ($s$) reflects energy loss when normal arterial flow is transformed first to high-velocity flow in the stenosis and then to the turbulent nonlaminar distal flow eddies at the exit from the stenosis (inertia and expansion).

$$f = \frac{8\sqrt{\frac{\mu}{p}}}{A_n^2} \quad \text{and} \quad s = \frac{p}{2} \left( \frac{d_{sten}}{A_n} \right)^{1.5}$$

Where $A_n$ = stenotic segment cross-sectional area, $p$ = blood density, $\mu$ = blood viscosity, $L$ = stenosis length, and $A_n$ = normal artery cross-sectional area.

It is important to note that the separation energy loss term ($s$) increases with the square of the flow while viscous energy loss ($f$) becomes negligible. Thus, increases in coronary blood flow increase the associated pressure gradient in an exponential manner. Despite augmentation of coronary blood flow, the increasing pressure loss across the stenotic segment reduces myocardial perfusion pressure and lowers the threshold for myocardial ischemia relative to demand.17

From Eq. (24.2), the trans-stenotic pressure drop is inversely proportional to the fourth power of the lumen radius. As a consequence, in a severe stenosis, relatively small change in luminal diameter (such as caused by active or passive vasomotion or transient obstruction by thrombus) can produce marked hemodynamic effects. For example, when the diameter stenosis increases from 80% to 90%, the resistance of a stenosis rises nearly threefold. For most stenoses, the length of the narrowing has only a modest effect on its physiologic significance. However, in very long narrowed segments, significant turbulence occurs along the walls of the stenotic segment and energy is dissipated as heat when eddies form and impact on the vessel wall. In addition, a preserved arc of vascular smooth muscle in some diseased arteries may be compliant and subject to dynamic changes that can alter luminal caliber and stenosis resistance. Dynamic changes in stenosis severity and resistance can also occur passively in response to changes in intraluminal distending pressure or selective dilation of distal resistance vessels. Thus for a given stenosis, there is a family of pressure–flow relationships reflecting altered stenosis diameter and variable distending pressure (Figure 24.4).

**Figure 24.3**  Diagrammatic illustration of the Bernoulli equation. $\Delta P$, pressure gradient; $A_n$, area of the stenosis; $A_n$, area of the normal segment; $L$, stenosis length; $Q$, flow; $f_v$, viscous friction factor ($f$); $f_s$, separation coefficient ($s$). See text for details.

Catheter-based methods used in the evaluation of coronary flow include angiography, coronary venous (sinus) efflux measurements, and intracoronary sensor-wire pressure and flow velocity measurements.
Chapter 24 Evaluation of Myocardial and Coronary Blood Flow and Metabolism

Figure 24.4
Resting and maximally vasodilated coronary pressure–flow relationships. Coronary flow reserve, the ratio of maximally vasodilated flow to resting flow, is a complex function of the actual position of the maximally vasodilated and resting flow curves. The slope of the maximal vasodilation curve can be shifted by hypertrophy and changes in hemodynamics as can the basal flow be altered by similar events, thus explaining different CFR (maximal vasodilation flow/basal flow ratio) under different conditions and in different patients. (With permission from Klocke FJ. Measurements of coronary flow reserve: defining pathophysiology versus making decisions about patient care. Circulation 1987;76:1183.)

Table 24.6 Thrombolysis in Myocardial Infarction Flow Grades

<table>
<thead>
<tr>
<th>Flow Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMI 3</td>
<td>Normal distal runoff, contrast material flows briskly into and clears rapidly from the distal segment</td>
</tr>
<tr>
<td>TIMI 2</td>
<td>Good distal runoff, contrast material opacifies the distal segment, but flow is perceptibly slower than in more proximal segments and/or contrast material clears from the distal segment slower than from a comparable segment in another vessel</td>
</tr>
<tr>
<td>TIMI 1</td>
<td>Poor distal runoff, a portion of contrast material flows through the stenosed arterial segment, but the distal segment is not fully opacified</td>
</tr>
<tr>
<td>TIMI 0</td>
<td>Absence of distal runoff, no contrast material flows through the stenosis</td>
</tr>
</tbody>
</table>

A quantitative method of TIMI flow counts the number of cine frames from the introduction of contrast in the coronary artery to a predetermined distal landmark. Cineangiography is performed with 6F catheters and filming at 30 frames per second. The TIMI frame count (TFC) for each major vessel is thus standardized according to specific distal landmarks. The first frame used for TIMI frame counting is that in which the contrast fully opacifies the artery origin and in which the contrast extends across the width of the artery, touching both borders with antegrade motion of the contrast. The last frame counted is that in which contrast enters the first distal landmark branch; full opacification of the distal branch segment is not required. The distal landmarks commonly used in analysis are the following: (i) for the left anterior descending (LAD) artery, the distal bifurcation of the left anterior descending artery; (ii) for the circumflex (CFX) system, the distal bifurcation of the left anterior descending artery; (ii) for the circumflex (CFX) system, the distal bifurcation of the branch segments with the longest total distance; (iii) for the right coronary artery (RCA), the first branch of the posterolateral artery (Figure 24.5).

The TFC can be further corrected (corrected TIMI frame count, or CTFC) by normalizing for the length of the LAD coronary artery in comparison with the two other major arteries; CTFC thus accounts for the distance the contrast has to travel in the LAD relative to the other arteries. The average LAD coronary artery is 14.7 cm long; the right, 9.8 cm; and the circumflex, 9.3 cm. CTFC divides the absolute frame count in the LAD by 1.7 to standardize the distance of contrast travel in all three arteries. Normal TFC and CTFC for LAD is 36 ± 3; for the CFX, TFC is 22 ± 4; and for the RCA, TFC is 20 ± 3; but CFX and RCA each has a CTFC of 21 ± 2. Table 24.7 provides reference values for CTFC. A high CTFC may be associated with microvascular dysfunction.

Angiographic Blood Flow Estimation—Thrombolysis in Myocardial Infarction Flow and Thrombolysis in Myocardial Infarction Frame Count

Since its introduction by the Thrombolysis in Myocardial Infarction (TIMI) investigators in 1985,18 a simple, qualitative grading of angiographic coronary flow rates (Table 24.6) to assess the efficiency of reperfusion therapy has been widely used to gauge the restoration of perfusion in clinical trials. Improved TIMI flow grades are associated with improved outcomes.19-21
**Figure 24.5**

Top. Anatomic landmarks used for TIMI frame counting in the left anterior descending coronary artery. The distalmost branch in the left anterior descending coronary artery (referred to as the pitchfork, mustache, or whale’s tail) usually occurs at the apex of the heart. In a wraparound left anterior descending coronary artery, the branch closest to the apex of the heart is used. **Second and third rows.** Anatomic landmarks used for TIMI frame counting in the left circumflex coronary artery. The artery used for TIMI frame counting is the artery with the longest total distance along which dye travels in the left circumflex coronary artery system and yet passes through the culprit lesion. When the culprit lesion is proximal to two arteries with equal total dye-path distances, the artery that arises more distally from the left circumflex coronary artery is used. For example, when the culprit lesion is located in the proximal left circumflex coronary artery, the marginal branch with the longest total dye-path distance is used, regardless of whether it is the first, second, or third marginal branch. If these second and third marginals have equal total dye-path distances, the third marginal branch is the target artery. The target artery is always the first marginal branch when the culprit lesion is in the first marginal and, likewise, always the second marginal branch when the culprit lesion is in the second marginal. In left and balanced dominant systems, the target artery is farther distal than the marginal branch that lies at the border of the inferior and lateral walls, usually the third or fourth marginal. The anatomic endpoint is the distalmost branch in the target artery. Usually, this endpoint branch can be found at approximately the midpoint of the distal third of the artery (five-sixths of the distance down the vessel from its origin), but occasionally is located just before the termination of the artery. **Bottom.** Anatomic landmarks used for TIMI frame counting in the RCA. The distal landmark is the first branch arising from the posterior lateral extension of the RCA after the origin of the posterior descending artery, regardless of the size of this branch. As shown, this branch will often be located just distal to the bifurcation and may be oriented either superiorly (RU) or inferiorly (RL). In some cases, this branch will lie farther along the extension of the distal RCA and either will course superiorly as the AV nodal artery (AV) or will be oriented inferiorly as the right inferior branch (RI). In the event that a very proximal posterior descending stenosis is the culprit lesion, the first branch off the posterior descending artery after the stenosis is the endpoint. Infrequently, the distal portion of the posterior descending artery is supplied by a proximally arising acute marginal branch, and the proximal portion of the posterior descending artery arises at the base of the heart. In these cases, it is the extension of the distal RCA past the posterior descending artery at the base of the heart, and not the proximal acute marginal branch, that is used for determining the TIMI frame count. In patients with left-dominant anatomy, the TIMI frame count endpoint is the distalmost branch of the RCA once it is no longer in the atrioventricular groove. (Adapted with permission from Gibson CM, Cannon CP, Daley WL, et al. TIMI frame count: a quantitative method of assessing coronary artery flow. Circulation 1996;93:879–888.)
with a second clamp, and the distance between the clamps.

Values are expressed as mean ± standard deviation and TIMI Fraunce and Corrected TIMI Frame Counts (CTFC) in coronary arteries without epicardial stenoses (normal) and in nonculprit and culprit arteries 90 minutes after myocardial infarction.

RCA, right coronary artery; LCx, left circumflex coronary artery; LAD, left anterior descending coronary artery; TIMI, Thrombolysis in Myocardial Infarction. Values are expressed as mean ± standard deviation and 95% confidence intervals. (Adapted with permission from Gibson CM, Cannon CP, Daley WL, et al. TIMI frame count: a quantitative method of assessing coronary artery flow. Circulation 1996;93:879–888.)

### Table 24.7 Reference Values for Thrombolysis in Myocardial Infarction Frame Counts

<table>
<thead>
<tr>
<th></th>
<th>Average</th>
<th>RCA</th>
<th>LCx</th>
<th>CTFC (LAD)</th>
<th>LAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>21.0 ± 3.1</td>
<td>20.4 ± 3.0</td>
<td>22.2 ± 4.1</td>
<td>21.1 ± 1.5</td>
<td>36.2 ± 2.6</td>
</tr>
<tr>
<td>Nonculprit at 90 min</td>
<td>25.5 ± 9.8</td>
<td>24.6 ± 7.1</td>
<td>22.5 ± 8.3</td>
<td>30.6 ± 11.5</td>
<td>52.0 ± 19.6</td>
</tr>
<tr>
<td>(10–57)</td>
<td>(13–36)</td>
<td>(10–52)</td>
<td>(16.5–57.1)</td>
<td>(28–97)</td>
<td></td>
</tr>
<tr>
<td>Culprit at 90 min</td>
<td>39.2 ± 20.0</td>
<td>37.2 ± 19.3</td>
<td>33.7 ± 9.0</td>
<td>43.8 ± 22.6</td>
<td>74.5 ± 38.4</td>
</tr>
<tr>
<td>(13–164.7)</td>
<td>(13–112)</td>
<td>(19–51)</td>
<td>(17.1–164.7)</td>
<td>(29–280)</td>
<td></td>
</tr>
</tbody>
</table>

TIMI Frame Counts and Corrected TIMI Frame Counts (CTFC) in coronary arteries without epicardial stenoses (normal) and in nonculprit and culprit arteries 90 minutes after myocardial infarction.

RCA, right coronary artery; LCx, left circumflex coronary artery; LAD, left anterior descending coronary artery; TIMI, Thrombolysis in Myocardial Infarction. Values are expressed as mean ± standard deviation and 95% confidence intervals. (Adapted with permission from Gibson CM, Cannon CP, Daley WL, et al. TIMI frame count: a quantitative method of assessing coronary artery flow. Circulation 1996;93:879–888.)

Despite an open artery, whereas CTFCs of <20 frames are associated with normal microvascular function and a low risk for adverse events in patients following myocardial infarction (Table 24.7).

The TMC method has several limitations. Gibson et al. and Kern et al. suggested that visual estimates of TIMI flow in the usual clinical setting bear little relationship to the quantitative TMC or measured Doppler flow velocity and that even noninfarct-related coronary arteries may show prolonged frame counts as compared with normal values. Most likely, these prolonged TMCs are associated with microvascular dysfunction, even in the presence of an open artery. CTFCs >20 but <40 frames per second (the cutoff value for TIMI grade 3 flow) marked a higher risk for adverse outcome. Prolonged CTFCs 4 weeks after myocardial infarction appear to be associated with impaired infarct-artery-related flow at 1 year.

Injection technique can also have an impact on the CTFC. Using 7F diagnostic catheters, a mean increase of 1.0 mL/second on standard hand injections (10th to 90th percentile of left coronary injections: 1.5 to 2.5 mL/second; right coronary injections: 1.1 to 2.1 mL/second) induced a decrease of two frames in the CTFC.

To measure absolute angiographic coronary flow velocity, a guidewire can be used to determine the intravascular distance between ostium and TIMI landmark. The guidewire tip is positioned distally and marked with one Kelly clamp. The wire is withdrawn to the coronary ostium and marked with a second clamp, and the distance between the clamps is measured. Velocity is then calculated using the following formula:

\[
\text{Velocity (cm/second) = \frac{\text{Distance (cm)}}{\text{Frame count/frames per second}}}\]

The angioplasty guidewire velocity takes into account specific artery length in a particular patient, but its usefulness in clinical practice remains to be evaluated. In general, TIMI frame counting is a simple, reproducible method for the assessment of angiographic coronary flow, which is widely applicable and provides additional information related to treatment success and clinical outcome.

### Thrombolysis in Myocardial Infarction Blush Score

Angiographic successful reperfusion in acute myocardial infarction has been defined as TIMI 3 flow. However, TIMI 3 flow does not always result in effective myocardial reperfusion. Myocardial blush grade (MBG) is an angiographic measure of myocardial perfusion at the capillary level. MBG is defined as follows: 0 indicates no myocardial blush or contrast density; 1 indicates minimal myocardial blush or contrast density; 2 indicates moderate myocardial blush or contrast density, but less than that obtained during angiography of a contralateral or ipsilateral non-infarct-related coronary artery; and 3 indicates normal myocardial blush or contrast density, comparable with that obtained during angiography of a contralateral or ipsilateral non-infarct-related coronary artery. When myocardial blush is persistent (staining), it suggests leakage of contrast medium into the extravascular space and is also graded 0. To determine blush grading, the length of the angiographic run needs to be extended in order to visualize the venous phase of the contrast passage. When the left coronary artery is involved, use of the left lateral view is preferred, and for the right coronary artery, the right oblique view. MBG after primary angioplasty for acute myocardial infarction appears to be an important prognostic feature and should be added to the commonly used TIMI flow...
Coronary Venous (Sinus) Efflux

The principal use of coronary venous measurements is determination of transmyocardial metabolism of blood products or drugs using the arterial–coronary sinus differences per unit flow. The measurement of coronary venous flow can be performed using the coronary sinus thermodilution technique. Coronary sinus blood flow (CSBF) is an approximation of blood flow to the left ventricle. Approximately two-thirds of LAD coronary artery flow drains into the great cardiac vein, the continuation of the anterior intraventricular vein as it reaches the atrioventricular groove. The great cardiac vein then becomes the coronary sinus at the point marked by the valve of Vieussens and the oblique vein of Marshall (a left atrial venous remnant of the embryonic left-sided superior vena cava). The remaining portion of LAD venous drainage enters the coronary sinus along with blood from the circumflex territory by way of the left marginal vein and circumflex venous branches. Great cardiac vein flow thus represents primarily LAD venous outflow, whereas coronary sinus flow represents a mixture of both LAD and left circumflex coronary artery outflow, accounting for 80% to 85% of total left coronary outflow drained by this route.

The principle of thermodilution flow measurement states that the heat loss by the blood equals the heat gained by a cold indicator solution. Room-temperature fluid (5% dextrose or normal saline) is continuously infused by a control pump upstream in the coronary sinus. Coronary venous flow is then computed by the temperature reduction of blood/indicator mixture flowing over the proximal catheter thermistor. A full discussion of CSBF is available elsewhere. Regional myocardial oxygen consumption (MVO₂) is computed as follows:

\[ \text{MVO}_2 = Q \times (A_O - C_SO) \]

where Q equals coronary venous flow, AO₂ is arterial oxygen content, and CSO₂ is coronary sinus oxygen content.

Standard techniques for cannulation of the coronary sinus from either the superior or the inferior vena cava approach can be used. Reproducible coronary sinus flow measurements require a stable catheter position, avoiding variable inclusion of blood entering from venous tributaries adjacent to the temperature thermistor.

Technique of Angioplasty Sensor-Guidewire Use

After diagnostic angiography or during angioplasty, the sensor angioplasty guidewire is passed through a standard Y connector attached to either the diagnostic or the guiding catheter (5F or 6F catheters are suitable). Standard anticoagulation is given as in the case of angioplasty (e.g., 60 units of unfractionated heparin per Kg) before introducing the guidewire. Intracoronary (IC) nitroglycerin (100 to 200 µg) given before guidewire introduction vasodilates and fixes the epicardial vessel diameter for 10 to 15 minutes. Nitroglycerine has no effect on fractional flow reserve (FFR) unless the stenosis is vasotonically constricted, and thus is useful to reduce guidewire-induced vasospasm but not mandatory for an accurate FFR measurement.

For flow velocity, the Doppler sensor, located at the very distal guidewire tip (Figure 24.6), is advanced at least 5 to 10 artery-diameter lengths (>2 cm) beyond the stenosis to measure laminar flow (otherwise the turbulent flow close to the stenosis may underestimate true velocity). Resting flow velocity is recorded, and then coronary hyperemia is induced by IC or IV adenosine (or other suitable agents) with continuous recording of the flow velocity signals. CVR is computed as the ratio of maximal hyperemic to basal average peak velocity (APV; Figure 24.7). Because of the highly position-dependent signal, poor signal acquisition may occur in 10% to 15% of patients even within normal arteries. As with transthoracic echo Doppler studies, the operator must adjust the guidewire position (sample volume) to optimize the velocity signal.

To measure translesional pressure gradients for the calculation of the pressure-derived FFR, the pressure wire sensor, located 3 cm proximal to the wire tip, is first zeroed to atmospheric pressure on the table, along with the guide catheter pressure, and then advanced through the guide catheter to the coronary ostium. The sensor pressure is matched to the guide catheter pressure (by electronically equalizing or normalizing the two pressures). The guidewire is then advanced into the artery with the sensor beyond the stenosis. The distance beyond the stenosis should be 2 to 3 cm distal to the lesion. Baseline pressure is recorded, followed immediately by induction of coronary hyperemia, continuously recording both guide catheter and sensor-wire pressures. FFR is computed as the ratio of distal coronary to aortic pressure at maximal hyperemia occurring at the lowest distal coronary pressure (Figure 24.8). If a small (<5F) guide catheter is being used, flushing the catheter liberally with saline will reduce pressure wave damping. Signal drift can be detected by observation of the pressure waveform.

The safety of intracoronary sensor-wire measurements is excellent, with benign problems related mostly to adenosine.
Coronary Hyperemia for Stenosis Assessment

Stenosis severity should always be assessed using measurements obtained during maximal hyperemia. At maximal hyperemia, autoregulation is abolished and microvascular resistance remains fixed and minimal. Under these conditions, coronary blood flow is directly related to the driving pressure. Therefore, maximal hyperemic coronary blood flow is closely dependent on the coronary arterial pressure at the time of the measurement, a fact that is used in the derivation of pressure-derived fractional coronary flow reserve of the myocardium.

The most basic form of coronary hyperemia is reactive hyperemia. When a coronary artery is transiently occluded, release of the occlusion (reperfusion) is followed by a marked increase in coronary flow, a response termed reactive hyperemia. Reactive hyperemia follows an occlusion as short as 200 ms. Maximal reactive hyperemia occurs after coronary occlusion of 20 seconds. Longer occlusion periods increase the duration but not the amplitude of hyperemia.

The most widely used pharmacologic agent to induce coronary hyperemia in the cath lab is adenosine. Hyperosmolar ionic and low-osmolar, nonionic contrast media do not produce maximal vasodilatation. Nitrates increase volumetric flow, but since these agents also dilate epicardial conductance vessels, the increase in coronary flow velocity is less than those with adenosine or papaverine. Intracoronary papaverine (8 to 12 mg) increases coronary blood flow velocity four to six times over resting values in patients with normal coronary arteries and produces a response equal to that of an IV infusion of dipyridamole in a dose of 0.56 to 0.84 mg/kg of body weight, but can cause QT prolongation and, rarely, ventricular tachycardia or fibrillation.

Adenosine is a potent short-acting hyperemic stimulus with the total duration of hyperemia only 25% that of papaverine or dipyridamole. Adenosine is benign at appropriate dosages (20 to 30 µg in the right coronary artery and 30 to 60 µg in the left coronary artery or infused intravenously at 140 µg/kg per minute). A sustained hyperemia, weight-based dosing, and lack of operator interaction make IV preferable to IC adenosine. IV and IC adenosine produce equal levels of hyperemia. Jeremias et al. compared IC (15 to 20 µg in the right and 18 to 24 µg in the left coronary artery) with IV adenosine (140 µg/kg per minute) and found a strong linear relationship between the two methods (r = 0.978 and P < 0.001). The mean measurement difference for FFR was −0.004 ± 0.03. In 8% of cases, IC adenosine FFR was >0.05 units different from IV FFR. Thus, in a small percentage of cases, maximal coronary hyperemia requires increased IC adenosine doses. Table 24.8 lists the characteristics of pharmacologic hyperemia-inducing agents that can be used in coronary flow studies.

Other agents that produce maximal coronary hyperemia include ATP, nitroprusside, and dobutamine. Coronary flow reserve was comparable for ATP and papaverine with IC ATP doses of >15 µg. IV dobutamine (10 to 40 µg/kg per minute) has also been used to assess lesion severity with FFR. As compared with IV adenosine, peak dobutamine infusion produced similar distal coronary pressure and pressure ratios (P/P., 60 ± 18 versus 59 ± 18 mmHg; FFR, 0.68 ± 0.18 and 0.68 ± 0.17, respectively; all P = NS). Moreover, high-dose IV dobutamine did not modify the angiographic area of the epicardial stenosis, and much like adenosine, fully exhausted myocardial resistance regardless of inducible left
ventricular dysfunction. Intracoronary nitroprusside (50, 100 µg bolus) produces nearly identical results to those of IV and IC adenosine.43

Theobromines, theophylline, and caffeine can attenuate adenosine- and dipyridamole-induced hyperemia. Controversy exists as to whether the concentration of caffeine after a cup of coffee prior to induction of hyperemia interferes with FFR measurement. An example of the interaction of caffeine, adenosine, dipyridamole, and aminophylline is shown on the coronary velocity trend plot in Figure 24.9. A review of the literature44 suggests that a serum caffeine level of 3 to 4 mg/L at the time of an adenosine-induced hyperemia does not affect perfusion stress imaging studies to detect coronary artery disease. These same considerations hold true for patients undergoing cardiac catheterization and intravenous adenosine-induced hyperemia.

**Coronary Doppler Flow Velocity**

The coronary Doppler guidewire measures the velocity of red blood cells moving past the ultrasound emitter/receiver on the end of a Doppler-tipped angioplasty guidewire (Figure 24.10). Coronary flow velocity is calculated from the difference between the transmitted and returning frequency (called the Doppler frequency shift), using the following equation:

\[
V = \frac{(F_1 - F_0)C}{2F_0 \cos \varphi}
\]

where \(V\) is the velocity of blood flow; \(F_0\) is the transmitting (transducer) frequency; \(F_1\) is the returning frequency; \(C\) is a constant (speed of sound in blood); and \(\varphi\) is the angle of incidence.

When the transducer beam is nearly parallel to blood flow (\(\cos \varphi = 1\)), velocity can be accurately measured. Changes in blood flow velocity are reflected by changes in the Doppler frequency shift. The Doppler technique measures red blood cell velocity directly. Because the Doppler guidewire has a cross-sectional area of 0.164 mm², it is generally considered to be nonobstructive within any, but most severe, coronary stenosis.

**Guidewire Thermodilution Blood Flow Technique**

The coronary thermodilution technique uses thermistors on a pressure-sensor angioplasty guidewire and measures the arrival time of room-temperature saline bolus indicator
Figure 24.8  Pressure tracings depicting the aortic phasic and mean pressure (red) as well as the distal coronary phasic and mean pressure (green). As can be seen on the left side of the figure, there is a resting gradient between the mean pressures prior to adenosine being administered. After adenosine, the pressure gradient widens. The largest pressure difference at steady hyperemia is then used to determine fractional flow reserve (FFR). In this case, it is calculated as $63/82$, or 0.77.

Injections through the guiding catheter into the coronary artery. The shaft of the angioplasty pressure-monitoring guidewire (St. Jude Medical Systems) has a temperature-dependent electrical resistance and acts as a proximal thermistor, which allows for the detection of the start of the indicator (saline) injection (Figure 24.11). A microsensor mounted 3 cm from the tip also enables simultaneous high-fidelity pressure measurements. Pressure and temperature are sampled at a frequency of 500 Hz. The wire is connected to a dedicated interface with modified software for online analysis of the thermodilution curves. Thermodilution CFR ($\text{CFR}_{\text{thermo}}$) is defined as the ratio of hyperemic flow to resting coronary flow ($F$).

$$\text{CFR} = \frac{F_{\text{at hyperemia}}}{F_{\text{at rest}}} \quad (24.3)$$

Flow, $F$, is the epicardial volume ($V$) divided by transit time ($T_{mn}$). Thus, CFR can be expressed as follows:

$$\text{CFR} = \frac{\left(\frac{V}{T_{mn}}\right)_{\text{at hyperemia}}}{\left(\frac{V}{T_{mn}}\right)_{\text{at rest}}} \quad (24.4)$$

Assuming the epicardial volume ($V$) remains unchanged, CFR can be calculated as follows:

$$\text{CFR} = \frac{T_{mn_{\text{at rest}}}}{T_{mn_{\text{at hyperemia}}}} \quad (25.5)$$

In animal experiments, a significant linear relation was found between flow velocity and $1/T_{mn}$. A significant correlation was found between $\text{CFR}_{\text{doppler}}$, which was calculated as the ratio of hyperemic to resting flow velocities, and $\text{CFR}_{\text{thermo}}$, which was calculated as the ratio of resting to hyperemic $T_{mn}$ ($r = 0.76$; SEE [standard error of the estimate] = 0.24; $P < 0.001$). Simultaneous measurements of CFR and FFR are thus obtained for research studies on coronary resistance. When combined with poststenotic pressure measurements, coronary flow reserve measurements can provide a complete description of the pressure–flow relationship and the response of the microcirculation.

Normal Coronary Flow and Flow Velocity Reserve

Normal coronary flow velocity varies based on the location of the sensor and the size of the vessel. The phasic patterns of coronary flow differ between the left and right coronary arteries. Diastolic flow velocity is higher than systolic flow velocity in the left coronary, but both are often equal in the right coronary artery. Average peak velocities range from 5 to 20 cm/second at rest in normal arteries.

Whereas the ranges of normal absolute coronary flow velocities at baseline and during hyperemia are large, normal CFR in young patients with normal arteries commonly exceeds 3.0. In adult patients with chest pain undergoing cardiac catheterization, with angiographically normal vessels, the CFR averages $2.7 \pm 0.64$, which is related, in part, to
Table 24.8 Characteristics of Pharmacologic Hyperemic Agents for Coronary Flow Studies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Plateau</th>
<th>T1/2</th>
<th>Side Effect</th>
<th>Pitfall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papaverine IC</td>
<td>15 mg LCA 10 mg RCA</td>
<td>30–60 s</td>
<td>2 min</td>
<td>Transient QT prolongation and T-wave abnormalities; very rarely, ventricular tachycardia/torsade des pointes</td>
<td>Do not use with heparin or heparinized saline, as it forms a precipitate</td>
</tr>
<tr>
<td>Adenosine IC</td>
<td>40–60 μg LCA 24–36 μg RCA</td>
<td>5–10 s</td>
<td>30–60 s</td>
<td>Occasional transient AV block after injection in RCA</td>
<td>Submaximum stimulus in some patients; interruption of aortic pressure. Must repeat with escalating doses to ensure that maximal hyperemia is reached. No pullback curve possible</td>
</tr>
<tr>
<td>Adenosine IV</td>
<td>140 mg/kg/min</td>
<td>≤1–2 min</td>
<td>1–2 min</td>
<td>Decrease of blood pressure by 10–15%. Burning or angina-like chest pain during infusion (harmless, not ischemia). Not to be used in patients with severe obstructive lung disease (potential for bronchospasm)</td>
<td></td>
</tr>
<tr>
<td>Dobutamine IV</td>
<td>10–40 μg/kg/min</td>
<td>1–2 min</td>
<td>3–5 min</td>
<td>Tachycardia, mild increase in blood pressure</td>
<td></td>
</tr>
<tr>
<td>Nitroprusside IC</td>
<td>0.3–0.9 μg/kg</td>
<td>20 s</td>
<td>1 min</td>
<td>20% decrease in blood pressure</td>
<td></td>
</tr>
</tbody>
</table>


Comorbid conditions such as hyperlipidemia, hypertension, or diabetes mellitus. CFR values of <2.0 have been associated with inducible myocardial ischemia on stress testing. Changes in heart rate, blood pressure, and contractility alter CFR by changing resting basal flow or maximal hyperemic flow or both. Tachycardia increases basal flow, reducing CFR. Increasing mean arterial pressure increases basal flow and reduces maximal vasodilatation, reducing hyperemic flow more than it increases basal flow. CFR may be reduced in patients with essential hypertension and normal coronary arteries and in patients with aortic stenosis and normal coronary arteries. Diabetes mellitus increases basal flow and independently reduces coronary flow reserve, especially in patients with diabetic retinopathy, owing to reduced volumetric coronary blood flow (velocity × vessel cross-sectional area) during hyperemia and higher baseline flow in diabetic patients, with and without retinopathy, as compared with controls.

**Measurement of Translesional Pressure-Derived Fractional Flow Reserve**

Using coronary pressure distal to a stenosis measured at constant and minimal myocardial resistances (i.e., maximal hyperemia), Pijls et al. derived an estimate of the percentage of normal coronary blood flow expected to go through a stenotic artery. This pressure-derived ratio is called the FFR and can be subdivided into three components describing the flow contributions by the coronary artery, the myocardium, and the collateral supply. FFR of the coronary artery (FFR coronary) is defined as the maximum coronary artery flow in the presence of a stenosis divided by the theoretical normal maximum flow of the same artery (i.e., the maximum flow in that artery if no stenosis were present). Similarly, FFR of the myocardium (FFR myocardium) is defined as maximum myocardial (artery and bed) flow distal to an epicardial stenosis divided by its value if no
epicardial stenosis were present. Stated another way, FFR represents that fraction of normal maximum flow that remains despite the presence of an epicardial lesion. The difference between FFR$_{myo}$ and FFR$_{cor}$ is FFR of the collateral flow.

The following equations are used to calculate the FFR of a coronary artery and its dependent myocardium:

\[
\begin{align*}
\text{FFR}_{cor} &= \frac{(P_d - P_w)}{(P_a - P_w)} \\
\text{FFR}_{myo} &= \frac{(P_d - P_p)}{(P_a - P_p)} \\
\text{FFR}_{collateral} &= \text{FFR}_{myo} - \text{FFR}_{cor}
\end{align*}
\]

where $P_a$, $P_d$, $P_p$, and $P_w$ are the aortic, distal arterial, venous (or right atrial), and coronary wedge (during balloon occlusion) pressures, respectively; because FFR$_{cor}$ uses $P_w$, it can be calculated only during coronary angioplasty.

FFR$_{myo}$ can be readily calculated during either diagnostic or interventional procedures. In most clinical circumstances $P_p$ is negligible relative to aortic pressure and hence omitted from the calculations. FFR reflects both antegrade and collateral (or bypass graft) myocardial perfusion rather than merely the trans-stenotic pressure loss (i.e., a stenosis pressure gradient). Because it is calculated only at peak hyperemia and thus excludes the microcirculatory resistance from the computation, FFR is differentiated from CVR as being largely independent of basal flow, driving pressure, heart rate, systemic blood pressure, and status of the microcirculation.

In contrast to the resting or hyperemic absolute pressure gradient, FFR is strongly related to provokable myocardial ischemia as demonstrated by comparisons with different clinical stress testing modalities in patients with stable angina. The nonischemic threshold value of FFR is >0.75. In patients with an abnormal microcirculation, a normal FFR indicates that the epicardial conduit resistance (e.g., a stenosis) is not a major contributing factor to perfusion impairment, and that focal conduit enlargement (e.g., stenting) would not restore normal perfusion. FFR is thus specific for stenosis resistance and by design excludes the assessment and influence of the microcirculation.

Pijls et al.\textsuperscript{35} reviewed potential pitfalls of coronary pressure measurements. Suitable guide catheters can be as small as 5F—and commonly 6F guides—preferably without side holes. For best pressure fidelity, contrast should be flushed out of the catheter and replaced with normal saline. If catheter side holes are present, increasing intracoronary bolus doses of adenosine may be needed since excess drug can exit the side holes.

The guide catheter and wire pressure are both set to zero (atmospheric pressure) outside the body before introducing the guidewire into the guide catheter. The zero reference height is set to approximately 5 cm below the sternum at the level of the right atrium. However, this estimation may be incorrect; the real aortic pressure may be different from the sensor-wire pressure when measured below the level of the atrium, depending on the course of the artery being studied. Lowering the transducer level will increase the aortic pressure, thus assisting in the match when these two signals are not identical.

The matching of aorta guide catheter pressure and sensor-wire pressure is important prior to crossing the lesions. At this time, the distal wire crosses the lesion and FFR is measured. After lesion assessment, confirmation of matched pressures is made by pullback pressure recordings. The withdrawal of the
Figure 24.10  Phasic Doppler coronary flow velocity. As can be seen, there is a higher flow velocity during diastole (D) as there is during systole (S). The blue line of the tracing represents the computer planimetered velocity envelope, which is then used to derive peak velocity and mean velocity values.

Figure 24.11  An example of determining coronary flow using the St. Jude Medical pressure wire system. As can be seen in the top panel of the figure, the red signals reflect the guide catheter pressure (Pa), the green signals reflect the coronary pressure (Pd), and the yellow line represents the calculated FFR for the corresponding pressures. The particulars of the measurement of coronary flow can be seen in the bottom panel of the figure. The curves at the bottom represent the thermodilution temperature changes during rest and subsequently at maximal hyperemia. The numbers just above the curves depict the calculated transit time corresponding to each of the color-coded thermodilution curves. The average of the baseline and hyperemic transit times are then used to calculate the coronary flow reserve (CFR), as shown on the right side of the figure.
sensor proximal to the stenosis in question with the distal wire across the lesion will identify proximal signal equivalency to eliminate questions of drift. Often pressure waveforms (especially the loss of the dicrotic notch across a critical stenosis) will be changed indicating true pressure loss and not signal drift.

Other pitfalls of FFR measurements that can hamper their accuracy include pressure leakage through the retained guidewire introducer or a loose Y connector, guide catheter pressure damping owing to contrast media within the small guiding catheters (Figure 24.12), or deep catheter seating. With regard to guide catheter side holes, the pressure signal recorded through a side-hole guide catheter does not necessarily correspond to the proximal segment of the coronary artery since aortic pressure enters the guide through these holes.

**SIMULTANEOUS PRESSURE–FLOW VELOCITY (P–V) RELATIONSHIPS**

In a manner similar to that proposed by Gould et al., Marques et al. showed that the pressure–velocity flow relationships (P–V) could effectively characterize mild, moderate, and severe human coronary stenoses. P–V data demonstrated that the variability of microvascular resistance contributed to discrepancies between FFR and coronary blood flow velocity reserve in intermediate coronary lesions with concordance between FFR and CFR occurring in 73% of patients (Figure 24.13). Minimum microvascular resistance (the ratio of mean distal pressure to average peak blood flow velocity during hyperemia) was significantly higher in patients with FFR >0.75 and CFR <2.0. A hyperemic stenosis resistance (HSR) index (defined as the ratio of hyperemic stenosis pressure gradient [mean aortic minus mean distal pressure] to hyperemic average peak velocity) had better agreement with single photon emission computed tomography (SPECT) scanning in lesions with discordant FFR and CFR. Thus, combined P–V measurements for research describe the contribution of both the epicardial and microvascular resistance to myocardial perfusion.

Escand et al. compared the instantaneous hyperemic diastolic velocity–pressure slope to other indices of coronary reserve. The instantaneous hyperemic diastolic velocity–pressure slope correlated with capillary density ($r = 0.70$, $P = 0.019$), whereas CFVR and coronary resistance reserve

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**Figure 24.12** An example of pressure signals (red tracing is from the guide catheter and green signal is from the pressure wire in a coronary artery). In panel 1, both tracings can be seen showing a widened pulse pressure and a “ventricular” appearance. In panel 2, the guide catheter is flushed and the signal now reveals a decreased pulse pressure, a dicrotic notch, and the true pressure gradient across the coronary bed (difference between the red and green mean signals).

**Figure 24.13** A scatterplot of FFR versus CFR values in 150 patients. Group A patients had an FFR of <0.75 but a CFR of >2.0. Group B patients had an FFR of >0.75, but a CFR of <2.0. Overall, 109 of the 150 patients had concordant values for FFR and CFR (73%). (See text for further details.) (From Meuwissen et al. *Circulation* 2001;103:184, Figure 1A.)
Coronary Pulse Wave Analysis

Davies J et al.\textsuperscript{57} reported on the use of coronary pulse wave analysis to better understand the relationship between myocardial contraction, myocardial resistance, aortic and coronary pressures, and their reflected pressure waves. The pulse analysis begins with the acquisition of simultaneous high-fidelity intra-coronary pressure and flow velocity signals obtained from sensor-tipped angioplasty guidewires positioned during coronary angiography. Normal coronary perfusion is the net result of pressure waves and flow generated initially in the proximal aorta and those counterbalancing pressure waves moving back toward the aorta originating in the distal end of the coronary flow path. The cycle of cardiac contraction and relaxation produces six pressure waves having different magnitude (intensity), direction, and velocity owing to competing accelerations and decelerations (Figure 24.15). Coronary blood flow into the myocardium is largely determined by the prominent coronary suction wave of LV relaxation at the beginning of diastole (wave 5), increasing coronary flow from the aorta into the epicardial coronary artery and into the myocardium. During systolic ejection with a normal aortic valve, LV and aortic pressures are coupled, with LV pressure being the major determinant of intramyocardial stress. As pressures at each end of the coronary artery (aortic and LV-myocardial) are similar during systole, the net change in coronary flow during systole is normally minimal. In diastole, the aortic valve closure uncouples aortic from LV pressure producing an aortic–LV myocardial pressure gradient accelerating coronary blood flow (via the diastolic suction wave) into the epicardial artery and myocardium (Figure 24.16).

Outcome studies characterizing patients by pulse wave analysis will assist our understanding of the complex relationships between peripheral vascular disease, coronary artery disease, and LV mechanics in individuals having valvular, nonvalvular, and microcirculatory cardiac pathologies.
Figure 24.15 Representation of acceleration and deceleration waves within the coronary artery (see text for further details). (From Davies JE, Whinnett ZI, Francie DP, et al. Evidence of a dominant backward-propagating “suction” wave responsible for diastolic coronary filling in humans, attenuated in left ventricular hypertrophy. Circulation 2006;113:1768–1778, Figure 3.)

are associated with negative ischemic results with a predictive accuracy of 95%. Single stress testing comparisons with variations in testing methods and patient cohorts have produced a zone of FFR with overlapping positive and negative results (0.75 to 0.80). The use of FFR in this zone requires clinical judgment. A meta-analysis of 31 studies comparing the results of FFR to quantitative coronary angiography (QCA) and/or noninvasive imaging of the same lesions reported (18 studies, 1,522 lesions) found that QCA had a random effects sensitivity of 78% and specificity of 51% against FFR (<0.75 cutoff). As compared with noninvasive imaging (21 studies, 1,249 lesions), receiver/ operator characteristic estimates were similar for comparisons of FFR with perfusion scintigraphy (976 lesions, sensitivity 75%, specificity 77%) and dobutamine stress echocardiography (273 lesions, sensitivity 82%, specificity 74%). Given the variances in sensitivity, specificity, positive and negative predictive accuracy among patients, and methods of stress testing, it is not surprising that, unlike the initial validation study comparing FFR to three different stress tests in the same patient before and after PCI, this meta-analysis showed only modest concordance of FFR with noninvasive imaging tests. Furthermore, because perfusion scintigraphy compares relative and not absolute myocardial flow in different coronary beds, scintigraphy, though considered the clinical “gold standard” of ischemia, has limitations in identifying the hemodynamic significance of individual lesions in patients with multivessel CAD. Similarly, in stress echocardiography, severe ischemia in one region may
At the onset of ventricular contraction the myocardium compresses the coronary microcirculation, generating an early backward-travelling pushing wave.

Continued compression of the micro-circulation and wave reflection (at bifurcation sites and vascular beds) generates the late backward-travelling pushing wave.

With continued ventricular relaxation, relief of myocardial compression of the coronary microcirculation generates the dominant backward-travelling suction wave.

The slowing of ventricular contraction creates a suction effect at the proximal end of the artery, generating the forward-travelling suction wave.

As the cardiac cycle progresses, contraction of the ventricle lumen generates the dominant forward-travelling pushing wave.

Later in the cardiac cycle, closure of the aortic valve generates the late forward-travelling pushing wave.
mask the consequences of a less severe albeit hemodynamically significant lesion in another region. In contrast to noninvasive tests, FFR is a vessel-specific index of ischemia.

Although no longer used for stenosis assessment, a Doppler-tipped sensor guidewire can measure CFR. An abnormal CFR (<2.0) corresponded to reversible myocardial perfusion imaging defects with high sensitivity (86% to 92%), specificity (89% to 100%), predictive accuracy (89% to 96%), and positive and negative predictive values (84% to 100% and 77% to 95%, respectively). The uncertainty of the microcirculatory contribution to an abnormal CFR makes CFR alone less useful for epicardial lesion assessment unless normal. Combined pressure and flow data have produced a novel set of invasive physiologic tools for epicardial lesion assessment, such as HSR, and for microvascular assessment, such as index of microcirculatory resistance (IMR) and hyperemic myocardial resistance (HMR). Defined as the hyperemic change in pressure across a stenosis divided by the hyperemic distal velocity, HSR may have better predictive value than that of FFR for detecting noninvasive ischemia. A summary of coronary physiologic measurements and derivations is provided in Table 24.9. The American College of Cardiology and the American Heart Association have produced a consensus statement and guidelines for the physiologic assessment of CAD in the cardiac cath lab (Table 24.10).

### Fractional Flow Reserve and Intravascular Ultrasound

Based on the factors that cause pressure loss across a stenosis, it is incorrect to assume that a single minimal lumen area

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**Table 24.9** Coronary Physiologic Measurements in the Cath Lab

<table>
<thead>
<tr>
<th>Fractional Flow Reserve, FFR</th>
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<tbody>
<tr>
<td><strong>Derivation:</strong></td>
</tr>
<tr>
<td>[ FFR = \frac{Q_{\text{sten}}}{Q_{\text{normal}}} \text{ at maximal hyperemia} ]</td>
</tr>
<tr>
<td>where ( Q = \text{flow, sten} = \text{stenotic artery, normal} = \text{theoretically same artery without stenosis.} )</td>
</tr>
<tr>
<td>( Q_{\text{sten}} = \frac{P_{\text{sten}}}{\text{Resistance}_{\text{sten}}} )</td>
</tr>
<tr>
<td>( Q_{\text{normal}} = \frac{P_{\text{aorta}}}{\text{Resistance}<em>{\text{sten}}} ), then ( \frac{Q</em>{\text{sten}}}{Q_{\text{normal}}} = \frac{P_{\text{sten}}}{P_{\text{aorta}}} )</td>
</tr>
<tr>
<td>Hence, ( FFR = \frac{P_{\text{distal to stenosis}}}{P_{\text{aorta}}} )</td>
</tr>
<tr>
<td>(complete derivation includes venous pressure ( P_v ) as ( FFR = \frac{P_{\text{distal to stenosis}} - P_v}{P_{\text{aorta}} - P_v} ); see Reference 2)</td>
</tr>
<tr>
<td><strong>Features:</strong> Nonischemic threshold range of &gt;0.75–0.80; Normal value of 1.0 for every artery and every patient; Epicardial lesion specific; Linear relation with relative maximum blood flow; Independent of hemodynamic alterations; Value that accounts for total myocardial blood flow including collaterals; Highly reproducible; High spatial resolution (pressure pullback recording).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Coronary Flow Velocity Reserve, CFVR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Derivation:</strong></td>
</tr>
<tr>
<td>[ CFVR = \frac{Q_{\text{hyperemia}}}{Q_{\text{base}}} \text{ where } Q = \text{Velocity if cross-sectional area remains unchanged during hyperemia.} ]</td>
</tr>
<tr>
<td><strong>Features:</strong> Nonischemic threshold range of &gt;2.0; Coronary flow reserve in nonobstructed vessels assesses microvascular integrity; Useful for studies of coronary endothelial function; Accurate estimation of volumetric flow when vessel cross-sectional area available.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Combined Pressure and Flow Velocity measurements: e.g., hyperemic stenoses resistance, (HSR)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Derivation:</strong></td>
</tr>
<tr>
<td>[ HSR = (P_{\text{aorta}} - P_{\text{distal to stenosis}}) / Q_{\text{hyperemia}} ]</td>
</tr>
<tr>
<td><strong>Features:</strong> Separate assessment of stenotic and microvascular resistances; Allows construction of pressure-flow curves (assessment of compliant lesions, hemodynamic gain after PCI); For Stenosis Resistance Index, nonischemic threshold values of &lt;0.8 mmHg/cm/sec; Normal value of 0; Lesion Specific, Highly reproducible; High sensitivity; Useful in cases of discordance between CFR and FFR.</td>
</tr>
</tbody>
</table>

### Table 24.10  Current Role of Physiologic Measurements in the Cath Lab

<table>
<thead>
<tr>
<th>A. PCI Guideline Recommended Uses&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Assessment of the effects of intermediate coronary stenoses (30–70% luminal narrowing) in patients with anginal symptoms. Coronary pressure or Doppler velocimetry may also be useful as an alternative to performing noninvasive functional testing (e.g., when the functional study is absent or ambiguous) to determine whether an intervention is warranted. (Class IIa, <em>Level of Evidence: B</em>)</td>
</tr>
<tr>
<td>2. Assessing the success of PCI in restoring flow reserve and to predict the risk of restenosis. (Class IIb, <em>Level of Evidence: C</em>)</td>
</tr>
<tr>
<td>3. Evaluating patients with anginal symptoms without an apparent angiographic culprit lesion. (Class IIb, <em>Level of Evidence: C</em>)</td>
</tr>
<tr>
<td>4. Routine assessment of the severity of angiographic disease in patients with a positive, unequivocal noninvasive functional study is not recommended. (Class III, <em>Level of Evidence: C</em>)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Applications of FFR under Study&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Determination of one or more culprit stenoses (either serially or in separate vessels) in patients with multivessel disease.</td>
</tr>
<tr>
<td>2. Evaluation of ostial or distal left main and ostial right lesions, especially when these regions cannot be well visualized by angiography.</td>
</tr>
<tr>
<td>4. Determination of significance of focal treatable region in vessels with diffuse coronary artery disease.</td>
</tr>
<tr>
<td>5. Determination of prognosis after stent deployment.</td>
</tr>
<tr>
<td>6. Assessment of stenosis in patients with previous (nonacute, &gt;6 d) myocardial infarction.</td>
</tr>
<tr>
<td>8. Assessment of the collateral circulation.</td>
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</tbody>
</table>

<table>
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<tr>
<th>C. Applications of Coronary Doppler Flow under Study&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Assessment of Microcirculation</td>
</tr>
<tr>
<td>2. Endothelial function testing</td>
</tr>
<tr>
<td>3. Myocardial viability in acute myocardial infarction</td>
</tr>
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<table>
<thead>
<tr>
<th>D. Applications of Combined Coronary Pressure and Doppler Flow Velocity under Study&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Assessment of intermediate stenosis</td>
</tr>
<tr>
<td>2. Assessment of the microcirculation</td>
</tr>
<tr>
<td>3. Identification of lesion compliance (change of pressure–velocity relationship)</td>
</tr>
<tr>
<td>4. Assessment of coronary pressure wave analysis</td>
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</tbody>
</table>


<sup>b</sup>(Not yet incorporated into PCI Guidelines).

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by IVUS will accurately reflect flow limitation in all locations in the coronary tree.<sup>53</sup> There are at least six characteristics of a stenosis that contribute to resistance and pressure loss. These factors include entrance angle, minimal lumen diameter, eccentricity of lesion, length of lesion, exit angle, and size of the normal reference segment in which the stenosis resides (Figure 24.17). The loss of pressure across a stenosis can be computed from the simplified Bernoulli principle which includes not only the stenosis area but also the length of the narrowing.

\[
\Delta P = \frac{1}{A_s} \times \text{length} \times V^2
\]

where \( P \) is the pressure drop across the stenosis, \( A_s \) is the minimal cross-sectional stenosis area (MCSa), and \( V \) is blood flow velocity through the tube.
The lack of strong correspondence between FFR and IVUS measurements is not surprising owing to the unmeasured and unknown factors described above and the use of only minimal lumen area (MLA) as a single correlative parameter. For example, Takagi et al. found that most MLA values were >4 mm² and were associated with FFR values of >0.75 (Figure 24.18), whereas Ahn et al. found that an MLA of 2.1 mm² predicted ischemia on myocardial SPECT. The discrepancy in published IVUS criteria to detect ischemia makes it hard to recommend a single value and warrants further thought on whether this type of a cutoff to make clinical decisions is warranted. A 4 mm² MLA may limit flow in a large proximal vessel segment but will not impair flow in a smaller segment of the same artery. The area of a normal 2.5 mm diameter vessel is 4.9 mm². Thus, a stenosis with MLA of 4 mm² (a 28% area stenosis) in this vessel should not be considered obstructive or in need of PCI. Functionally significant coronary lesions must be >50% diameter stenosis (approximately 75% area stenosis). A coronary narrowing with MLA of 4.0 mm² in a 3.0 mm vessel (area of 7.1 mm²) yields a 44% area stenosis, again questionably associated with ischemia (Figure 24.19). However, deferring PCI in a lesion with an IVUS-defined MLA of >4 mm² is associated with excellent clinical outcome.

Ahn et al. compared IVUS to myocardial perfusion imaging and Nam et al. evaluated the long-term clinical outcomes of two strategies of PCI, a FFR-guided PCI strategy as compared with an intravascular ultrasound (IVUS)-guided PCI.
Figure 24.18 Relationship between FFR and IVUS parameters. FFR significantly correlated with MLA \(r = 0.507, P < 0.001\), PB \(r = -0.387, P < 0.001\), area stenosis \(r = -0.388, P < 0.001\), and length with a lumen area <3.0 mm\(^2\) \(r = -0.472, P < 0.001\). (From Kang S, et al. Circ Cardiovasc Interv 2011;4:65–71.)

for intermediate coronary lesions in 167 consecutive patients (FFR-guided, 83 lesions versus IVUS-guided, 94 lesions). Cut-off value for FFR-guided PCI was 0.80 and for IVUS-guided PCI was a minimal lumen cross-sectional area of 4.0 mm\(^2\). The initial percent diameter stenosis and lesion length were similar in both groups (51 ± 8% and 24 ± 12 mm, respectively, in the FFR group versus 52 ± 8% and 24 ± 13 mm, respectively, in the IVUS group). However, the IVUS-guided group underwent stenting significantly more often (91.5% versus 33.7%, \(P < 0.001\)) with no significant difference in major adverse cardiac event (MACE) rates between the two groups (3.6% and 3.2% in FFR-guided and IVUS-guided PCI, respectively; Figure 24.20). Although both FFR- and IVUS-guided PCI strategies for intermediate coronary artery disease were associated with favorable outcomes, the FFR-guided PCI reduces the need for revascularization of many of these lesions.

**Physiologic Lesion Assessment for Coronary Interventions**

For intermediately narrowed stenoses, FFR or CFR values above the ischemic thresholds have been used to safely defer coronary interventions with adverse clinical event rates of <10% over a 2-year follow-up period. FFR can be used to determine the appropriateness of angioplasty. For example, the DEFER study randomized 325 patients scheduled for PCI into three groups and reported the 5-year outcomes. If FFR was ≥0.75, patients were randomly assigned to the deferral group \((n = 91, \text{ medical therapy for CAD})\) or the PCI performance group \((n = 90, \text{ PCI with stents})\). If FFR was <0.75, PCI was performed as planned and patients were entered into the reference group \((n = 144)\). The event-free survival was not different between the deferred and the performed
**Figure 24.19** Scatterplot of the reference diameter of the coronary artery (vertical axis, in mm) against the percent diameter stenosis (horizontal axis). What should be appreciated is that the relationship between these two variables is not linear.

**Figure 24.20** Depiction of the incidence of performing PCI when assessing intermediate stenoses with fractional flow reserve (FFR) versus intravascular ultrasound (IVUS) in the study performed by Nam et al.66 As can be seen, when intermediate lesions were assessed with IVUS, there was a significantly higher rate of PCI performed in this cohort.

Multivessel CAD

Early nonrandomized studies demonstrated the benefit of FFR guidance in patients with multivessel CAD. Berger et al.76 showed a reduction in major adverse cardiac events in 102 patients with multivessel CAD with planned PCI of
at least two vessels. In 113 coronary arteries with baseline FFR of $0.57 \pm 0.13$ PCI was performed, and in 127 coronary arteries with an FFR $>0.75$ (FFR $0.86 \pm 0.06$), PCI was not performed. Overall, MACE occurred in 9% of patients after 12 months and in 13% after 36 months. In the non-treated vessels eight cases (6.3%) of MACE were reported, whereas 14 cases (12.3%) of MACE were related to any one of the initially PCI treated coronary arteries. Similarly, in another nonrandomized, single-center trial, FFR-guided PCI (FFR-PCI) was compared to angiographic guided PCI (Angio-PCI) in 137 patients with multivessel CAD. PCI was performed for all stenoses with FFR <0.75. As compared to the FFR-PCI group, there were more vessels per patient treated in the Angio-PCI group (2.27 versus 2.57, $P=0.02$), had lower procedure cost ($5,332 versus $6,007, P<0.001$), and shorter hospital stay (3.4 versus 3.7 days, $P=0.05$). More importantly, at 2-year follow-up, the FFR-PCI group presented with fewer MACE (13.2% versus 18.4%, $P=0.04$), fewer combined death or MI (7.3% versus 11%, $P=0.02$), and a lower total number of MACE (76 versus 113, $P=0.02$) as compared with the Angio-PCI group (Figure 24.22).

In a larger prospective randomized, multicenter trial, Tonino et al., on behalf of the FAME (FFR versus Angiography for Multivessel Evaluation study) investigators, tested the outcomes for two PCI strategies in patients with multivessel CAD: a physiologically guided PCI approach (FFR-PCI) as compared to the conventional angiographic guided PCI (Angio-PCI). After identifying which of the multiple lesions required treatment, 1,005 patients undergoing PCI with drug-eluting stents were randomly assigned to one of the two strategies; 496 patients were assigned to the Angio-PCI, and 509 to the FFR-PCI. For the FFR-PCI group, all lesions had FFR measurements and were only stented if the FFR was <0.80. The primary endpoints of death, MI, and repeat revascularization (CABG or PCI) were obtained at 1 year. Clinical characteristics and angiographic findings were similar in both groups. The Syntax (Synergy between PCI with Taxus and Cardiac Surgery) scores for gauging risk in multivessel disease involvement were identical at 14.5, indicating low- to intermediate-risk patients.

As compared to the Angio-PCI group, the FFR-PCI group used fewer stents per patient (1.9 ± 1.3 versus 2.7 ± 1.2, $P<0.001$), less contrast (272 versus 302 mL, $P<0.001$), had lower procedure cost ($5,332 versus $6,007, P<0.001$), and shorter hospital stay (3.4 versus 3.7 days, $P=0.05$). More importantly, at 2-year follow-up, the FFR-PCI group presented with fewer MACE (13.2% versus 18.4%, $P=0.02$), fewer combined death or MI (7.3% versus 11%, $P=0.04$), and a lower total number of MACE (76 versus 113, $P=0.02$) as compared with the Angio-PCI group (Figure 24.22).

The precise mechanisms of reduced endpoints in the FFR-guided arm of FAME are not known, but are likely associated with fewer implanted stents having fewer procedure-related early (e.g., side branch occlusion, additional troponin release) and late stent complications (e.g., subacute thrombosis, restenosis). This study is a substantial clinical validation of the preceding FFR outcome studies in single- and multivessel disease patients from single centers and has important implications for managing CAD patients by integrating physiology for best long-term results. The FAME study also demonstrated that not all cases of angiographic 3v (3-vessel) CAD are physiologic 3v CAD. A functional syntax score (syntax grading excluding any vessel that has FFR of $>0.80$) adds prognostic value of FFR to angiographic grading in patients with multivessel CAD. The economic impact of the FFR-guided strategy produces superior results at lower cost (Figure 24.23). An example of a patient with multivessel disease treated based on an FFR-guided PCI strategy can be seen in Figure 24.24.
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**Figure 24.22** Graphical representation of the results from the FAME trial at 2 years. The patients randomized to the angiographically guided treatment strategy had a significantly higher rate of death or MI (periprocedural and late) (12.7% versus 8.4%, *P* = 0.03) and a higher rate of myocardial infarction, MI (9.5% versus 6.1%, *P* = 0.03).

**Left Main Stenosis**

The correct clinical assessment of left main stem CAD lesions is of pivotal importance. Decisions based on angiography alone, especially in the absence of ischemia, are questionable and can be supported by adjunctive lesion assessment modalities. Nonischemic FFR values (>0.80) in left main lesions are associated with excellent long-term outcomes. For example, in their prospective single-center follow-up studies, Bech et al.\(^7^9\) and Courti\(s\) J et al.\(^8^0\) respectively, and in a multicenter trial, Hamilos et al.\(^8^1\) all found low incidence of MACE including cardiac death or MI in groups with FFR >0.80 (treated medically) as compared to those undergoing CABG when FFR was <0.80. Hamilos et al.\(^8^1\) reported on 5-year outcome of the use of FFR to triage patients with LM narrowing to medical or surgical therapy based on the criterion of FFR <0.80 (Figure 24.25). FFR can identify the physiologic significance of intermediate left main disease and the suitability of surgical revascularization or continued medical therapy with excellent survival and low event rates. Figure 24.26 shows an example of a patient with moderate left main disease evaluated physiologically.

**Figure 24.23** Economic data from the FAME trial showing that almost all patients treated in the trial by FFR guidance had better outcomes and a reduction in costs.
A. Patient with multivessel CAD undergoing PCI with an FFR-guided approach. The LAD lesion (1) is judged to be severe and matched with stress test result and symptoms. The mid LAD lesion (2) is clearly intermediate, as is the lesion in the circumflex (3). B. FFR is obtained in the LCX, with the wire positioned as shown, and is 0.88. This lesion is physiologically insignificant and is not treated with PCI. C. A stent is placed in the proximal LAD lesion and then FFR is performed to assess the significance of the more distal LAD lesion originally judged to be intermediate. The FFR of the LAD is 0.68 and the more distal lesion is subsequently stented as well, secondary to this significant FFR finding. D. Final angiogram, showing the treated proximal and mid-LAD lesions with the intermediate LCX lesion left untreated.

An accurate LM FFR reflects flow through both the LAD and the CFX. Understanding the LM FFR in the setting of LAD and/or CFX disease requires further explanation. To compute FFR, maximal flow in the bed supplied by the target vessel is required. The LM transmits flow to the majority of left ventricle through the LAD and CFX. Thus the myocardial bed for the LM is the summed territories of both the LAD and the CFX (Figure 24.27). The LM bed can be even larger if the RCA is occluded and there is collateral supply from the left coronary system. In this case, the flow through the LM would involve supply to the inferior LV as well as the anterior LV. An isolated LM narrowing with no LAD, CFX, or RCA stenoses (top left, Figure 24.27) reflects the physiologic significance of just the LM narrowing. However, an LM narrowing plus LAD stenosis (top right, Figure 24.27) could produce a higher LM FFR because the LM bed is reduced in size owing...
Finally, in the setting of LM narrowing plus totally occluded RCA with collaterals from LCA and no LAD or CFX disease (bottom left, Figure 24.27), the LM FFR would reflect the flow through the entire left and right ventricular myocardium. After recanalization of the RCA with resolution of collateral flow, the LM FFR would increase since LM myocardial bed size is reduced (bottom right, Figure 24.27), as illustrated by Sachdev et al. in a case example shown in Figure 24.28, and Iqbal et al. The overestimation of the LM FFR in the presence of a second lesion downstream depends on the severity of the additional lesion and on the mass of myocardium distal to this second lesion.

Fractional Flow Reserve and Ostial Branch Assessment

Ostial narrowings, especially in side branches within stents (called “jailed” branches), are particularly difficult to assess by angiography because of the overlap orientation relative to the parent branch, stent struts across the branch, and image foreshortening. Koo et al. compared FFR to QCA in 97 “jailed” side branch lesions (vessel size >2.0 mm, percent stenosis >50% by visual estimation) after stent implantation (Figure 24.29). No lesion with <75% stenosis had FFR <0.75 (Figure 24.29). Among 73 lesions with ≥75% stenosis, only 20 lesions (27%) were functionally significant. Koo et al. also reported the 9-month outcome of FFR-guided side branch PCI strategy for bifurcation lesions. Among 91 patients, side branch intervention was performed in 26 out of 28 patients with FFR <0.75. In this subgroup FFR increased to >0.75 despite residual stenosis of 69 ± 10%. At 9 months, functional restenosis was 8% (5 out of 65) with no difference in events as compared to 110 side branches treated by angiography alone (4.6% versus 3.7%, \( P = 0.7 \)). Measurement of FFR for ostial and side branch assessment identifies even the minority of lesions which are functionally significant. An example of assessing a newly created ostial lesion after stenting is shown on Figure 24.30.

Fractional Flow Reserve and Saphenous Vein Graft Assessment

Considerations regarding use of FFR in assessing lesions in the SVG involve three sources of coronary blood flow to the distal myocardial region: the competing flows (and pressure) from (i) the native and (ii) conduit vessels and (iii) the collateral flow induced from long-standing native coronary occlusion (Figure 24.31). In the most uncomplicated situation of an occluded native vessel with minimal distal collateral supply, the theory of FFR should apply just as much to a lesion in a saphenous vein graft to the right coronary artery feeding a normal myocardial bed as to a lesion in the native right coronary. For more complex situations, the FFR will reflect the summed responses of the three supply sources and yield a net FFR, with a value <0.80 indicating potential ischemia in that region and vice versa.
Figure 24.26 LAO and RAO angiograms of a 72-year-old patient undergoing coronary angiography for angina. As can be seen in the left panel, it appears as though the ostial and proximal left main coronary artery is narrowed as compared to the body. As is the case with many angiograms, this is not seen in the RAO projection. There was damping of the diagnostic catheter waveform noted upon engaging the left main. To assess the ostial left main significance, a 6F JL4 guide was used and a 0.014 inch pressure wire was zeroed and advanced to the tip of the guiding catheter left in the ascending aorta. The signals were equalized at that point and then the guiding catheter was advanced to engage the left main. The pressure wire was advanced to the midportion of the LAD and the guiding catheter withdrawn back into the ascending aorta and flushed. Intravenous adenosine was administered at 140 μg/kg/min, and at maximal hyperemia, the FFR was found to be 0.94. The operator also chose to perform IVUS in the left main, and this showed that the left main was heavily calcified with an elliptical orifice originating from the aorta, with a mean luminal area of 10 mm². No intervention was performed, and the patient was treated medically.

Figure 24.27 Schematic demonstration of how the perfusion bed supplied by the left main coronary artery may play a large role in determining the physiological significance of a severe left main coronary lesion. (See text for further details.)
Figure 24.28

A. Right anterior oblique caudal view showing left coronary artery with chronic total occlusion (CTO) of the left circumflex artery (LCx). B. Left anterior oblique view showing stenoses in proximal and mid segments, and CTO of distal segment of the right coronary artery (RCA). C. Anterior–posterior cranial view showing mild stenoses in mid and distal left anterior descending artery (arrows). D. Anterior–posterior cranial view showing grade 3 collaterals to right posterior descending artery. (From Sachdeva R, Uretsky BF. The effect of CTO recanalization on FFR of the donor artery. Cathet Cardiovasc Interv 2011;77:367–369.)

FFR provides insight into the fate of SVG conduits implanted distal to hemodynamically insignificant lesions. Surgeons and cardiologists recognize that in such vessels late patency is reduced and native CAD can be accelerated. Even though most surgical consultations recommend “bypass all lesions with >50% diameter narrowing in patients with multivessel disease,” the patency rate of saphenous vein grafts on vessels with hemodynamically nonsignificant lesions has rarely been questioned. Botman et al. found that there was a 20% to 25% incidence of graft closure in 450 coronary artery bypass grafts when placed on arteries with hemodynamically insignificant stenoses (preoperative FFR >0.80) at 1-year follow-up (Figure 24.32). While the precise mechanisms of graft closure remain under study, it is postulated that coronary blood flow favors the lower resistance path through the native (relatively) nonobstructed arteries rather than through vein grafts, with slower or competitive graft flow promoting premature graft closure. In patients requiring CABG for multivessel revascularization, angiographic lesions of uncertain significance would benefit by FFR, providing prognostic information regarding potential of future bypass graft patency. FFR has serious implications for best long-term CABG outcomes.

Assessment of Diffuse Atherosclerosis

A diffusely diseased atherosclerotic coronary artery can be viewed as a series of branching resistance units diverting and gradually distributing flow, thereby reducing perfusion pressure along the length of the conduit. Diffuse atherosclerosis,
in contrast to a focal narrowing, is characterized by a continuous and gradual pressure recovery as the sensor moves from the distal to proximal arterial region without a localized abrupt increase in pressure related to an isolated stenosis. De Bruyne et al. examined FFR in normal and diffusely atherosclerotic nonstenotic arteries (Figure 24.33). FFR in the normal group was $0.97 \pm 0.02$ and was significantly lower, $0.89 \pm 0.08$, in the diffuse disease group. In 8% of arteries in the diffuse disease group without a focal narrowing, FFR was <0.75, a value below the ischemic threshold. For diffuse atherosclerosis, mechanical therapy to treat impaired flow would be futile.

**Serial Epicardial Lesions**

An essential prerequisite for the calculation of FFR is the achievement of maximum trans-stenotic flow. In the case of two consecutive stenoses, the blood flow interaction between the stenoses limits the applicability of the simple FFR ratio ($P_1/P_2$) derived for a single stenosis. When a second stenosis

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**Figure 24.29** Physiologic assessment of jailed side branch lesions using FFR. All patients had main branch stenting and then underwent FFR evaluation of the “jailed” sidebranch. This graph shows the association between percent stenosis of the sidebranch and the FFR findings. Of particular interest are the number of points reflecting angiographic stenoses of >80% with FFR values of >0.80 (upper right portion of the graph). Thus, despite a significant correlation of these values, often the angiographic stenosis overestimated the physiologic significance of that stenosis in these patients. (From Koo BK, et al. JACC 2005;46:633–637.)

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**Figure 24.30** Patient example in which a significant lesion in the mid-to-distal portion of the LAD was found (A). This lesion was successfully stented and follow-up angiography shows a change in the appearance of the ostium of a moderate-sized diagonal branch which is now “jailed” by the LAD stent (B). Subsequent to this angiogram, a pressure wire was advanced into the diagonal branch and an FFR was obtained of the ostial diagonal after administering intravenous adenosine. As seen in C, the FFR was 0.86, indicating that the ostial lesion was not flow limiting, and no further treatment was performed.
is present in the same epicardial vessel, flow through one stenosis will be submaximal because of the second stenosis. The extent to which both stenoses influence each other is somewhat unpredictable. In this case, the simple FFR does not predict to what extent a proximal lesion will influence myocardial flow until complete relief of the second stenosis and restoration of maximal hyperemia. However, the simple FFR can assess the summed effect across any series of stenoses, but individual lesions in the series will be more difficult to appreciate without special calculations.\(^{89,90}\)

The most practical technique to assess serial lesions involves two steps with two different measurements:

1. Pass the pressure wire distal to the last lesion and measure the summed FFR across all lesions. For example, if the FFR = 0.84 then none of the lesions would need treatment and nothing further needs to be done.

2. If the summed FFR in step 1 is <0.80 the next step is to determine which of the lesions contributes the maximum resistance to flow (i.e., the largest pressure gradient).

Figure 24.31  
Schematic depiction of a proximal LAD stenosis (yellow) in which there is a bypass graft anastomosed to the more distal portion of the LAD. If a pressure wire is used to assess the FFR of the LAD, the resultant FFR may well be >0.80 as the distal bed receives blood flow from at least two separate sources: (1) antegrade flow down the LAD, which may be compromised secondary to the presence of the proximal lesion and (2) flow down the bypass graft. The same situation can be incurred if significant collateralization to a vessel is seen.

Figure 24.32  
A. Percentage of occluded bypass grafts seen on follow-up plotted against percentage angiographic stenosis in the coronary artery prior to bypass surgery, showing the highest proportion of occluded grafts when they are placed on arteries with <50% stenosis. B. Percentage of occluded grafts seen on follow-up in the same patients as in (A) plotted against FFR values prior to bypass surgery. There is a much more striking association between non-physiologically significant stenosis (i.e., FFR >0.80) and the presence of an occluded graft than there was for the angiographic prediction. (From Botman CJ, Schonberger J, Koolen S, et al. Does stenosis severity of native vessels influence bypass graft patency? A prospective fractional flow reserve-guided study. Ann Thorac Surg 2007;83:2093–2097.)
This is accomplished by performing a pressure pullback during IV adenosine hyperemia. The pressure gradient (∆P) between lesions indicates the degree of lesion severity (Figure 24.34). Treatment with stenting should then start with the lesion exhibiting the most significant gradient (largest ∆P). After treating this lesion, the remaining lesion(s) should be reassessed by repeating the standard FFR technique. If the FFR still remains ischemic, then treatment should progress to the next largest ∆P.

Individual FFR of each stenosis can be separately predicted by different equations using $P_a$, pressure between the two stenoses ($P_{a1}$, $P_{a2}$, and $P_{a3}$) recorded during maximum hyperemia, thus reducing the error of FFR calculation in the presence of a second stenosis (Figure 24.35). The serial FFR formula requires $P_a$ obtained during coronary balloon occlusion and thus is not applicable for purely diagnostic studies.

In the examination of a single stenosis out of several in a series, the worst stenosis, as indicated by the largest pressure drop during hyperemia, may not occur where it would have been expected from angiography. In that case, the equations for FFR\(_{pred}\) can be applied to each stenosis rather than the simple ratio $P_a/P$ to determine the severity of each. In clinical practice, the measurements of $P_a$, $P_{a1}$, and $P_{a2}$ can be obtained during a simple pullback of the pressure sensor from the distal to the proximal part of the vessel under maximum hyperemia.

Fractional Flow Reserve and Acute Coronary Syndrome

The pathophysiology of the infarct-related artery and microvascular bed after MI is complex. Because of the dynamic nature of patients with ACS, particularly MI, the predictive ability of FFR has some theoretic limitations. In ACS the microvascular bed in the infarct zone may not have uniform, constant, or minimal resistance. The stenosis may also evolve as thrombus and vasoconstriction abate. FFR measurements are not meaningful when angiographic reperfusion (i.e., TIMI 3 flow) has not been achieved in the artery. FFR has limited utility in the infarct-related artery in the acute setting. However, FFR has value in lesion assessment in the recovery phase of MI and in the assessment of lesions in the remote non-infarct related vessels.

The size of the myocardial bed is related to the FFR and accounts for many of the visual functional mismatches of angiography, especially in the post-MI patient. FFR represents the percentage of normal flow across a stenosis. Flow is determined by the myocardial bed beyond the stenosis. For example, a small diagonal branch with an 80% stenosis supplying a tiny territory of muscle needs little flow and hence an FFR of 0.84 might be just fine and certainly be considered clinically insignificant. Since the perfusion bed is related to flow and to FFR, a severe angiographic lesion supplying a territory that is infarcted and does not need much flow can produce a high FFR, not corresponding to the visual estimate of narrowing.

To address the utility of measurements days after MI, DeBruyne et al.\(^1\) compared SPECT myocardial perfusion imaging and FFR obtained before and after PCI in 57 MI patients >6 days (mean 20 days) prior to evaluation. Patients with positive SPECT before PCI had a significantly lower FFR than observed in patients with negative SPECT (0.52 ± 0.18 versus 0.67 ± 0.16; $P = 0.0079$), but a significantly higher left ventricular ejection fraction (63% ± 10% versus 52% ± 10%; $P = 0.0009$) despite a similar percentage diameter stenosis (67% ± 13% versus 68% ± 16%; $P = NS$). The sensitivity and specificity of FFR of <0.75 to detect a defect on SPECT were 82% and 87%, respectively. When only truly positive or negative SPECT imaging was considered, the corresponding values were 87% and 100% ($P < 0.001$). The best FFR cutoff for determining peri-infarct ischemia was 0.78. Of note, a significant inverse correlation was found between left ventricular ejection fraction and FFR ($r = 0.29$, $P = 0.049$) suggesting a relationship between FFR and the mass of viable myocardium. For patients who are assessed >6 days after an infarction, FFR accurately reflects the hemodynamic severity of a lesion and its impact on myocardial perfusion despite the damaged microvasculature in the infarct bed.

In a similar study and relevant to clinical practice in the United States, where AMI patients often present early for angiographic evaluation (day 1 to 4 postinfarction), McClish et al.\(^2\) found similar FFR in 43 vessels subtending recent infarct beds as compared to 25 control vessels, matched by
lesion length and minimal luminal diameter, in patients without infarcts (0.67 ± 17 versus 0.68 ± 17, \( P = \text{NS} \)). However, noninvasive physiologic evaluation was not performed. Therefore, in a subsequent study, Samady et al.\(^5\) compared FFR to SPECT and myocardial contrast echo (MCE) in 48 patients 3.7 ± 1.3 days after infarction. To identify true reversibility, follow-up SPECT was performed 11 weeks after PCI. The sensitivity, specificity, and concordance of FFR ≤0.75 for detecting true reversibility on SPECT were 88%, 93%, and 91% (chi-square \( P < 0.001 \)), respectively, and for detecting
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Figure 24.35 Top graphic shows 2 serial lesions with regions of pressure gradient changes that a detectable on pressure wire pull back. Individual FFR values cannot be computed without using the coronary balloon occlusion pressure, $P_w$, as shown on the equation for the FFR of lesion A as it would be predicted from the equations with and without use of $P_w$. A Plot of true vs predicted FFR not incorporating the use of $P_w$ into the calculation. $P_a$, arterial pressure; $P_m$, interlesional pressure; $P_d$, distal vessel pressure. B. Formula that can be used to calculate the individual effect of each stenosis on FFR. $P_w$, distal coronary wedge pressure.
The use of FFR to reduce cost in ACS patient management was reported by Leesar et al.\textsuperscript{99} who randomized 70 patients with recent unstable angina or NSTEMI with intermediate single-vessel stenosis to one of two strategies: angiography followed by SPECT the next day or FFR-guided revascularization at the time of angiography. As compared with the SPECT strategy, the FFR-guided approach had a reduced hospital duration (11 ± 2 hours versus 49 ± 5 hours, \( P < 0.001 \)) and cost ($1,329 ± $44 US dollars versus $2,113 ± $120 US dollars, \( P < 0.05 \)), with no increase in procedure time, radiation exposure time, or clinical event rates at 1-year follow-up. Similarly, Potvin et al.\textsuperscript{96} evaluated 201 consecutive patients (62% with unstable angina or myocardial infarction) in whom revascularization was guided by FFR. At 11 ± 6 months of follow-up, cardiac events occurred in 20 patients (10%), and no significant differences were observed between patients with unstable angina or MI and those with stable angina (9% versus 13%, \( P = 0.44 \)). Finally, Fischer et al.\textsuperscript{99} found similar MACE rates at 12 months in patients with \( n = 35 \) and without \( n = 85 \) ACS in whom revascularization was guided by FFR (15% versus 9%, \( P = NS \)).

### Quantitative Assessment of Collaterals in the Cath Lab

There are four methods for assessing collaterals in the living patient in the cath lab: angiography; sensor-tipped flow and pressure angioplasty; guidewire measurements; and noninvasive perfusion imaging techniques. Angiography and noninvasive perfusion techniques are discussed elsewhere.\textsuperscript{97–99}

Coronary back pressure during coronary occlusion reflects the degree of collateral filling. Collateral flow contribution to overall myocardial blood flow has been described by Pijls et al.\textsuperscript{100} The FFR calculations account for coronary, myocardial, and collateral blood flow. Collateral FFR is determined as follows:

**Compute myocardial FFR (FFR\textsubscript{myo}):**

\[
FFR\textsubscript{myo} = 1 - \frac{\Delta P}{P_a - P_w} = \frac{P_d - P_w}{P_a - P_w}
\]

**Compute coronary fractional flow reserve (FFR\textsubscript{cor}):**

\[
FFR\textsubscript{cor} = 1 - \frac{\Delta P}{P_a - P_w}
\]

**Calculate collateral fractional flow reserve (FFR\textsubscript{coll}):**

\[
FFR\textsubscript{coll} = FFR\textsubscript{myo} - FFR\textsubscript{cor}
\]

where \( P_d \) is distal coronary pressure; \( \Delta P \), mean translesional pressure gradient; \( P_a \), mean right atrial pressure; \( P_w \), mean coronary wedge pressure or distal coronary pressure during balloon inflation; and \( P_a \), mean aortic pressure. All measurements except \( P_a \) are made during hyperemia.

For FFR\textsubscript{coll}, a coronary balloon is used to occlude the vessel and the mean coronary occlusion or wedge pressure (\( P_w \), distal coronary pressure during balloon occlusion) is measured and divided by the mean aortic pressure (\( FFR\textsubscript{coll} = P_a/P_w \)). If the central venous pressure is abnormal, then it should be subtracted from both the wedge and aortic pressures. A FFR\textsubscript{coll} \( \geq 0.25 \) suggests sufficient collaterals to prevent ischemia during PCI.\textsuperscript{83,84} FFR\textsubscript{coll} has also been studied in patients with acute myocardial infarction and shown to be the major determinant of left ventricular recovery after primary PCI. The study of collateral flow and function in patients is thus facilitated to a great extent by the use of sensor-wire measurements.

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Angiography remains the clinical standard for coronary and peripheral vascular imaging to identify significant arterial narrowing and to guide both catheter-based and surgical interventions. Although angiography provides a highly useful picture of the vessel lumen, it offers only indirect information about the arterial wall. The advanced catheter-based imaging tools described in this chapter—intravascular ultrasound, optical coherence tomography, angioscopy, and spectroscopy—provide supplemental and unique insights into vascular disease and the mechanism of therapeutic intervention.

**INTRAVASCULAR ULTRASOUND**

Intravascular ultrasound (IVUS) catheters use reflected sound waves to visualize the arterial wall in a two-dimensional, tomographic format, analogous to a histologic cross section. They utilize significantly higher frequencies than utilized in noninvasive echocardiography (20 to 45 MHz as compared with 2 to 5 MHz). This provides high resolution (100 to 200 μm for the coronary catheters) at the expense of beam penetration (limited to 4 to 8 mm from the catheter tip). Since the initial clinical experience with IVUS in 1988, this technique has gained acceptance both as a research method and as a clinical tool for situations in which the angiogram is unclear or unable to make precise measurements via visual estimate or computer-assisted techniques.

**Imaging Systems**

There are two approaches to IVUS imaging: solid state dynamic aperture and mechanical scanning. Both approaches generate a 360°, cross-sectional image plane perpendicular to the catheter tip. In the solid state approach, the individual elements of a circumferential array of multiple transducers mounted near the tip of the catheter are activated with different time delays to create an ultrasound beam that sweeps the circumference of the vessel. As the number of elements has increased, there have been progressive improvements in lateral resolution. Complex miniaturized integrated circuits in the catheter tip control the timing and integration of the transducer activation and route the resulting echo information to a computer where cross-sectional images are reconstructed and displayed in real time. In the mechanical approach, a single transducer element is rotated inside the tip of a catheter via a flexible torque cable spun by an external motor drive unit attached to the proximal end of the catheter. Images from each angular position of the transducer are collected by a computerized image array processor, which synthesizes a cross-sectional ultrasound image of the vessel.

The latest solid state coronary catheter system (Volcano Corp., San Diego, CA) has 64 transducer elements arranged around the catheter tip and uses a center frequency of 20 MHz. The current coronary catheters in a rapid-exchange configuration are 3.5F at the largest dimension (transducer assembly) and thus compatible with a 5F guide catheter. Larger peripheral imaging catheters are produced in both over-the-wire and rapid-exchange configurations. A 10F phased-array catheter for intracardiac echo (ICE) imaging (Siemens Medical Solutions USA, Inc., Malvern, PA) uses a unique technology adapted from transesophageal echocardiography, providing a sector ultrasound image with color and spectral Doppler capabilities. The catheter is compatible with multiple-frequency imaging (5.0 to 10 MHz) so that the operator can determine the desired trade-off between resolution and penetration (up to 15 cm).

Mechanical IVUS systems are available from several manufacturers in slightly varying configurations (Volcano Corp.; Boston Scientific Corp., Natick, MA; Terumo Corp., Tokyo, Japan). The current coronary catheters use a 40 or 45 MHz transducer and are 3.2F to 3.5F at the largest dimension, compatible with a 6F guide catheter. Larger catheters with lower center frequencies are also available for peripheral and ICE imaging. The catheters are advanced over a guide wire using a short rail section at the catheter tip, located
beyond the imaging-window segment within which the spinning transducer may be advanced or withdrawn. To improve the trackability and pushability, one manufacturer provides an imaging catheter with a second long rail section located proximally in addition to the standard short rail section at the catheter tip (Terumo Corp.). In mechanical systems, the fact that the guide wire runs outside the catheter parallel to the imaging segment results in a shadow artifact in the image.

In head-to-head comparisons, mechanical systems have traditionally offered advantages in terms of image quality, as compared to the solid-state systems, owing to their higher center frequencies and the larger effective aperture of the transducer element. Particularly, near-field resolution is excellent with mechanical catheters so that digital subtraction of the ring-down artifact is not required. In addition, a stationary outer sheath of mechanical catheters allows the transducer to be moved through a segment of interest in a precise and controlled manner. On the other hand, the longer rapid-exchange design of the solid-state catheter may track better than the short rail design of mechanical systems in complex coronary anatomy. The distance from the transducer to the catheter tip is shorter than that of mechanical systems, which may also be beneficial in IVUS-guided intervention of chronic total occlusion (CTO) lesions. The solid-state catheter includes no moving parts, and thus is free of non-uniform rotational image distortion (NURD). This artifact can occur with mechanical systems when bending or friction of the drive cable interferes with uniform transducer rotation, causing a wedge-shaped, smeared image to appear in one or more segments of the image (Figure 25.1). With both systems, serial cross-sectional images can be reconstructed into a longitudinal display mode, and both still frames and video images can be digitally archived on local storage memory or a remote server using Digital Imaging and Communications in Medicine (DICOM) Standard 3.0. Both systems can be installed directly into the cine angiogram system, enabling operators to quickly and easily incorporate IVUS interrogations into their interventional procedures.

### Image Acquisition Procedures

The image integrity of the IVUS system should be checked before inserting the catheter. Mechanical catheters require flushing with saline to remove air bubbles from inside the catheter. This preparation should be performed before inserting the IVUS catheter to avoid air embolism in the coronary artery. Residual microbubbles within the protective sheath can result in poor image quality once the catheter is inserted (Figure 25.1). Solid state catheters require an extra step to mask “ring down” artifact prior to being inserted into the coronary artery. This masking process is accomplished while positioning the catheter tip free in the aorta.

IVUS examination should be performed with intravenous administration of heparin (5,000 to 10,000 unit) or equivalent anticoagulation (an activated clotting time of > 250 seconds is recommended). Intracoronary nitroglycerin (100 to 200 μg) should also be routinely administered prior to the delivery of the IVUS catheter in order to induce maximal vasodilation and to prevent vasospasm. Using standard interventional techniques with a 0.014 inch angioplasty guide wire, the imaging probe is advanced at least 10 mm distal to the area of interest under fluoroscopic guidance. The length of the target vessel is then scanned by retracting the transducer within a stationary outer sheath (mechanical IVUS) or by moving the catheter itself (solid state IVUS). Unless the patient complains

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**Figure 25.1** Common IVUS image artifacts. **Air bubbles** can cause a high echoic noise around the imaging catheter with image deterioration. **Ring-down** artifacts seen as a series of bright rings around the mechanical IVUS catheter (arrow) can also be caused by air bubbles, which need to be flushed out. **Non-uniform rotational distortion (NURD)** results in a wedge-shaped, smeared appearance in one or more segments of the image (between 9 and 4 o’clock in this example). **White cap** artifacts caused by side lobe echoes (arrows) originate from a strong reflecting surface, such as metal stent struts or calcification. Smearing of the strut image can lead to the mistaken impression that the struts are protruding into the lumen. **Radiofrequency noise** (arrows) appears as alternating radial spokes or random white dots in the far-field. The interference is usually caused by other electrical equipment in the cardiac catheterization laboratory.
of chest discomfort or myocardial ischemia is suspected, the image acquisition is recommended to include distal vessel, lesion site, and the entire proximal vessel, back to the aorta. For comparison with repeated studies, identifiable landmarks such as major side branches may be used as a fixed starting point of imaging. Accurate evaluation of the aorto-ostial segment requires that the guide catheter be disengaged slightly from the ostium.

**Image Interpretation**

Interpretation of the images begins with the identification of two key landmarks: the blood/intima (luminal) border and the media/adventitia interface (Figure 25.2). The luminal border is the first bright interface beyond the catheter and is generally easy to locate on IVUS images. However, blood within the lumen exhibits a speckled low-intensity pattern, which is more prominent at higher ultrasound frequencies and may make recognition of the intimal border more difficult. Signal-processing software can color code or subtract the blood signal so that it does not obscure the intimal interface. If the blood signal is still confusing, saline can be injected through the guide catheter to reduce blood speckle and help delineate the true lumen border.

The second key IVUS landmark is the media/adventitia border. In muscular arteries such as the coronary tree, the media may stand out as a thin dark band since it contains much less echo-reflective material (collagen and elastin) than contained by the neighboring intima and adventitia. This provides a characteristic three-layered (bright–dark–bright) appearance on IVUS images. However, the stronger echo reflectivity of the intimal layer often causes a spillover effect, known as blooming, resulting in a slight overestimation of the intimal thickness with a corresponding underestimation of the medial thickness. Also, this three-layered appearance may be undetectable in truly normal coronary arteries wherein the intimal thickness is below the effective resolution of IVUS.

In atherosclerotic disease where the media has been destroyed, the media may not appear as a distinct layer around the full circumference of the vessel. In the proximal vessel segments and at branch points, the media contains relatively high amounts of collagen and elastin, frequently causing it to blend with the surrounding layers. Even in such cases, however, the boundary between the outer media and adventitia (the outer perimeter of plaque-plus-media zone) is generally identifiable owing to a step-up in echo reflectivity at this boundary without blooming. In most cases, the IVUS beam penetrates beyond the arterial wall, providing images of perivascular structures such as the cardiac veins, myocardium, and pericardium (Figure 25.3). These structures have characteristic appearances when

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**Figure 25.2** Cross-sectional format of a typical IVUS image. The bright–dark–bright, three-layered appearance is seen in the image with corresponding anatomy as defined. “IVUS” represents the imaging catheter in the blood vessel lumen. Histologic correlations with intima, media, and adventitia are shown. The media has lower ultrasound reflectance owing to less collagen and elastin as compared with the neighboring layers. Because the intimal layer reflects ultrasound more strongly than does the media, there is a spillover in the image, which results in a slight overestimation of the thickness of the intima and a corresponding underestimation of the medial thickness.
viewed from different positions within the arterial tree and can provide useful landmarks regarding the position of the imaging plane.

**Quantitative Assessment**

Unlike coronary angiograms, IVUS has an intrinsic distance calibration, provided as a grid on the image or tag information of DICOM files. Electronic caliper (diameter) and tracing (area) measurements can be performed at the tightest cross section (maximum stenosis), as well as at reference segments located proximal and distal to the lesion. In general, the reference segment is selected as the most normal-looking (largest lumen with smallest plaque burden) cross section within 10 mm from the lesion with no intervening major side branches.

Vessel and lumen diameter measurements are important in everyday clinical practice where accurate sizing of devices is needed. The maximum and minimum diameters (the major and minor axes of an elliptical cross section) are the most widely used. The ratio of maximum to minimum diameter defines a measure of symmetry. Area measurements are performed with computer planimetry. Lumen area is determined by tracing the leading edge of the blood/intima border, whereas total vessel (or external elastic membrane, EEM) area is defined as the area enclosed by the outermost interface between media and adventitia. Plaque area (or more accurately, the plaque plus media area) is calculated as the difference between vessel and lumen areas; the ratio of plaque area to total vessel area is termed the percent plaque area, plaque burden, or percent cross-sectional narrowing.

Metal struts of stents are seen as bright, focal points in a circular-arrayed pattern on the IVUS scan, and the stent measurement is performed at the leading edge of stent struts in the same way as done in non-stented segments. Neointimal hyperplasia within the stent has low echo-reflectivity at follow-up IVUS imaging, and the area is calculated as the difference between stent area and lumen area. Area measurements can be added to calculate volumes using Simpson’s rule with the use of motorized pullback. For standardized data expression, the volume is presented as a volume index or average area, calculated as the absolute volume divided by the length of the analyzed segment.

Arterial remodeling, originally described by Glagov et al. for necropsy specimens, is a bidirectional vessel response represented as the increase or decrease in vessel size that occurs during the development of atherosclerosis. In clinical settings, direct evidence of remodeling can be derived from serial changes in the EEM cross-sectional area (CSA) in two or more IVUS measurements obtained at different times. In single time-point studies, measurements of reference sites are used as a surrogate for the original vessel size before the artery became diseased. The reference segment(s) used for such purpose should be measured without any major intervening side branches. Classification of arterial remodeling includes positive (or adaptive), no or intermediate, and negative (or constrictive) remodeling. A remodeling index (the ratio of EEM CSA at the lesion site versus the reference site) as a continuous variable may also be used, in combination with the categorical classifications (positive
Chapter 25 Intravascular Imaging Techniques

Quantitative IVUS measurements for non-stented (upper) and stented (lower) segments. Area measurements are performed with computer planimetry. External elastic membrane (EEM) area is defined as the area enclosed by the outermost interface between media and adventitia, while lumen area is determined by tracing the leading edge of the blood/intima border. Plaque + media area is calculated as the difference between EEM and lumen areas. Stent area is measured by tracing the leading edge of the stent struts, and neointimal area is calculated as the difference between stent and lumen areas. For EEM, lumen, and stent, the maximum (solid arrows) and minimum (dotted arrows) diameters are determined. For plaque + media and neointima, the maximum (solid arrows) and minimum (dotted arrows) thickness are measured.

remodeling = remodeling index >1.0 or 1.05; negative remodeling = remodeling index <1.0 or 0.95).6

Figure 25.4

Qualitative Assessment

Plaque Characterization

In gray-scale IVUS, atheromatous plaques are classified into soft (echogenicity less than the surrounding adventitia), fibrous (intermediate echogenicity between those of soft plaques and highly echogenic calcified plaques), calcified (echogenicity higher than that of the adventitia with acoustic shadowing), and mixed plaques (more than one subtype contained within the plaque) (Figure 25.5). Calcium deposits are described qualitatively as superficial or deep according to the location of the leading edge of acoustic shadowing within the inner versus outer half of the plaque-plus-media thickness. The shadowing precludes determination of the thickness of a calcific deposit as well as visualization of vessel structures behind the calcium. Ultrasound reverberation (multiple ghost images of the leading calcium interface spaced at regular intervals radially) should not be misinterpreted as true vessel structures.

Since visual interpretation of conventional gray-scale IVUS images has limitations in the precise detection and quantification of specific plaque components, several advanced signal analysis techniques have been developed and introduced into both research and clinical arenas. To date, three different systems have been commercialized based on computer-assisted analysis of raw radiofrequency (RF) signals in the reflected ultrasound beam: Virtual Histology™ IVUS, the iMap™ system, and the Integrated Backscatter system. The Virtual Histology™ (VH) IVUS system (Volcano Corp.) employs spectral radiofrequency analyses with a classification tree algorithm developed from ex vivo coronary datasets and classifies plaques as four types: fibrous, necrotic, calcific, and fibro-fatty. The iMap™ system (Boston Scientific Corp.) identifies and quantifies four different types of atherosclerotic components (fibrotic, necrotic, lipidic, and calcified tissues) based on the degree of spectral similarity between the backscattered signal and a
Plaque characterization by gray-scale IVUS. The brightness of the adventitia can be used as a gauge to discriminate between predominantly fatty and fibrous plaque (plaque that appears darker than the adventitia is considered fatty). Regions of calcification are strongly echo-reflective and create a dense shadow peripherally from the catheter, known as acoustic shadowing, with reverberation (arrow in the middle image). Large plaque burden with deep ultrasound signal attenuation despite absence of bright calcium and plaques with a large low-echoic region suggesting a lipid pool (arrow in the right image) are susceptible to distal emboli during balloon dilatation or stenting.

Abnormal Lesion Morphology

Thrombus
Thrombus is usually recognized as an intraluminal mass, often with a layered, lobulated, or pedunculated appearance (Figure 25.7). Acute thrombus may appear as a relatively echo-dense mass with speckling or scintillation, while old organized thrombus often has a darker ultrasound appearance. Thrombus is also more likely than soft plaque to have the appearance of blood flow in microchannels. However, none of these IVUS features is pathognomonic for thrombus, and slow blood flow, air bubbles, stagnant contrast, or an echolucent plaque should be considered as differential.

Virtual Histology

Thrombus is usually recognized as an intraluminal mass, often with a layered, lobulated, or pedunculated appearance (Figure 25.7). Acute thrombus may appear as a relatively echo-dense mass with speckling or scintillation, while old organized thrombus often has a darker ultrasound appearance. Thrombus is also more likely than soft plaque to have the appearance of blood flow in microchannels. However, none of these IVUS features is pathognomonic for thrombus, and slow blood flow, air bubbles, stagnant contrast, or an echolucent plaque should be considered as differential.
Diagnosis. Injection of contrast or saline may disperse the stagnant flow from the lumen, often allowing differentiation of stasis from thrombus.

**Dissection**

Dissection appears as a fissure or separation within intima or plaque (Figure 25.7). The severity of a dissection can be quantified based on its depth (intimal, medial, or adventitial) and extent (circumferential or longitudinal). Intra-stent dissection is another type of dissection, characterized as separation of neointimal hyperplasia from stent struts.

**Hematoma**

Intramural (intravascular) hematoma is recognized as an accumulation of blood within the medial space, displacing the internal elastic membrane (IEM) inward and EEM outward (Figure 25.7). On the IVUS image, it is observed typically as a homogenous, hyperechoic, crescent-shaped area, but may present with a heterogeneous and/or layered appearance when contrast dye or saline is trapped in the false lumen. Entry and/or exit points may or may not be observed. Extramural (extravascular) hematoma is visualized outside the arterial wall in the adventitial tissue. It presents as irregularly shaped with an echo-dim pattern owing to the dilution of red blood cell concentration and dissemination throughout an echogenic adventitia. Extramural hematoma is more often realized after an interventional procedure, such as atherectomy or recanalization of CTO lesions, and requires careful attention in antithrombolytic and/or antiplatelet treatment.

**Aneurysm**

By IVUS, true aneurysm is defined as having an intact vessel wall and a maximum lumen area 50% larger than proximal reference. In contrast, pseudoaneurysm shows a loss of vessel wall integrity and damage to adventitia or perivascular tissue.

**Vulnerable Plaque**

Hypoechoic plaques without a well-formed fibrous cap are presumed to represent potentially vulnerable atherosclerotic lesions. Plaque rupture is diagnosed when a hypoechoic cavity within the plaque is connected with the lumen and a remnant of the ruptured fibrous cap is observed at the connecting site. Ruptured plaques are often eccentric, less calcified, large in plaque burden, positively remodeled, and associated with thrombus. In patients with acute coronary syndromes (ACS), multiple plaque ruptures are frequently detected by three-vessel IVUS examination, suggesting that ACS are associated with pan-coronary destabilization. However, lumen compromise and clinical symptoms likely depend on the severity of the original or coexisting stenosis or on thrombus formation, not solely on plaque rupture.

Among the IVUS characteristics suggesting plaque instability, extensive positive remodeling represents the most consistent feature reported in gray-scale IVUS.
Interventional Applications

Angiographic Intermediate Lesions

A considerable number of angiographic intermediate lesions referred for elective percutaneous coronary intervention (PCI) are in fact hemodynamically insignificant and can be successfully managed with medical treatment alone. In early studies of proximal coronary lesions, minimum lumen area (MLA) measured by IVUS demonstrated reasonable correlation with results from physiologic assessment. The ischemic MLA threshold was identified as 3.0 to 4.0 mm² for major epicardial coronary arteries based on physiologic assessment with coronary flow reserve, fractional flow reserve, or stress scintigraphy. Patients with intermediate coronary lesions in whom PCI was deferred based on IVUS findings (MLA >4.0 mm²) had target lesion revascularization in only 2.8% with a composite event rate of 4.4%. More recent studies expanded the study population into a wide variety of lesions, and indicated that the diagnostic accuracy and the optimal cut-off values of the MLA can vary depending on the location or the amount of myocardium supplied by the target segment. Nevertheless, the consistently high negative predictive values of the MLA in these studies suggest that interventions can still be safely deferred at least in lesions with an MLA larger than the proposed cut-offs.

Calcified Lesions

It is important to identify calcified plaque since the presence, degree, and location of calcium within the target vessel can substantially affect the delivery and subsequent deployment of coronary stents. One important advantage of IVUS guidance is its ability to assess the extent and distance from the lumen of calcium deposits within a plaque. For example, lesions with extensive superficial calcium may require rotational atherectomy prior to stenting to avoid underexpansion. Conversely, lesions with deep calcium may be successfully treated by stenting alone, even with severe calcification seen on fluoroscopy, to achieve lumen expansion large enough for drug-eluting stents (DESs).

High-Risk Lesions for Distal Embolization

Evaluation of plaque composition by preinterventional IVUS may predict the occurrence of distal emboli during balloon dilatation or stenting that may result in the “slow-flow” or “no-reflow” phenomenon leading to peri-procedural myocardial infarction. In gray-scale IVUS, predictive findings include large plaque burden with (non-calcium related) signal attenuation, a large low-echoic region suggesting a lipid pool, and thrombus-containing plaque (Figure 25.5). Recent studies with VH-IVUS or IB-IVUS have also demonstrated that the amount of lipid or necrotic core at preintervention was related to findings suggesting distal emboli. Identification of high-risk plaques may help in selecting lesions suitable for distal protection devices.

Left Main Lesions

In the assessment of left main coronary disease, angulations, calcification, or spasm in this location can lead to poor catheter engagement and confound angiographic interpretation. Several studies have shown that high percentages of patients with angiographically normal left main coronary artery had disease when assessed by IVUS. Conversely, only less than half of patients with angiographically ambiguous left main stenosis had a significant stenosis. This was especially true for ostial left main coronary disease where only 36% of the lesions had a significant stenosis and 41% had plaque burden <50% when assessed by IVUS. Plaque distribution in left main bifurcation lesions can also be evaluated more accurately with IVUS as compared with conventional angiographic classifications.

The ischemic MLA threshold for the left main coronary artery is considered 6 mm² based on physiologic assessment with fractional flow reserve as well as theoretical calculation using Murray’s law. This cut-off value has recently been validated in a prospective multicenter study (LITRO) where the predefined IVUS criterion of an MLA ≥6 mm² was used for deferred revascularization in patients with intermediate left main disease. In a 2-year follow-up period, both cardiac death and event-free survivals were comparable between the deferred and the revascularized groups. Another study
has also shown the safety of IVUS-guided deferral of revascularization for intermediate left main disease, but using a larger MLA cut-off (7.5 mm²) predetermined based on the lower range of normal left main MLA from their clinical database. In practice, however, the judgment should be made in conjunction with other information, such as the presence of diabetes and plaque burden at the MLA site.

**Bifurcation Lesions**

At bifurcation lesions, the extent of side-branch involvement can be difficult to assess by angiography alone. The combination of plaque and carina shift following balloon dilatation or stenting may cause severe narrowing or occlusion of a side branch, particularly in the presence of preexisting ostial disease. Such anatomical situations are responsible for the majority of creatine kinase elevations following stent implantation. Plaque deposition in the ostial lesion of a side branch can often be appreciated by looking across from the parent artery into the ostium of the branch, although accurate assessment requires direct imaging of the side branch. After PCI on bifurcation lesions using the two-stent technique, both inadequate postprocedural minimum stent area (MSA) and increased neointimal hyperplasia represent the major mechanisms of increased restenosis rate in the side-branch ostium.

**Chronic Total Occlusion Lesions**

IVUS is useful in several aspects during intervention on CTO lesions. In lesions with abrupt-type occlusion, the entry point at the CTO ostium is often difficult to identify by angiography. If there is a side branch located near the entrance of the CTO, the IVUS catheter can be inserted into the side branch to examine the target for wire penetration. In addition, the IVUS catheter can possibly be inserted into the subintimal space to determine the direction of the true lumen. A true lumen is surrounded by all three layers of the vessel. Side branches may offer another clue since they should communicate with the true but not with the false lumen. It is important to note, however, that insertion of the IVUS catheter into the subintimal space has the potential risk of enlarging the subintimal space. Finally, as in the case of other PCI procedures, proper balloon and stent sizes as well as acute complications can accurately be evaluated by IVUS. Particularly, intramural or extramural hematoma (or perforation) can occur, not infrequently, during the CTO procedure. Early detection and precise assessment of these conditions are crucial for safe and effective treatment of patients with CTO.

**Restenotic Lesions**

The primary mechanism of restenosis can be accurately identified by IVUS, which significantly affects the treatment strategy in patients with restenotic lesions. An IVUS study of in-stent restenosis (ISR) lesions following bare metal stent (BMS) implantation demonstrated that 20% of lesions had an MSA of <5.0 mm² and an additional 4.5% had other mechanical problems that contributed to restenosis. In another IVUS study of DES restenosis, 21% of lesions had an MSA of <5.0 mm², 38% of which were not associated with significant neointimal hyperplasia. For this type of ISR, mechanical optimization is the first priority, and IVUS can differentiate mechanical issues from exaggerated neointimal proliferation that may truly require DES implantation within the original restenotic stent.

For DES treatment of ISR, early clinical studies suggested a hypothesis that full DES coverage of the original stent might be important for the prevention of recurrent restenosis. This aggressive optimization strategy, however, can be associated with several clinical issues, and thus, may not be feasible in every case. In a retrospective IVUS study of BMS restenosis treated with sirolimus-eluting stents, 77% of the uncovered BMS segments maintained adequate lumen patency at follow-up. Therefore, as long as the original BMS is well expanded and has a segment with sufficient lumen area, conservative coverage with DES can be a clinical option—the so-called “spot stenting” strategy. Another study from the TAXUS trials evaluated IVUS findings of patients who did not require revascularization at the time of 9-month angiography. At 3 years, revascularization was required in 4.9% of paclitaxel-eluting stents and 6.7% of BMS. Multivariate analysis identified MLA at 9 months as a significant predictor of later revascularization for both stent types.

**IVUS-Guided Selection of Device Size and Length**

When assessed by IVUS, angiographically “normal” reference segments for PCI have 35% to 51% of plaque burden. Precise measurement of vessel size and lesion length by IVUS can guide the optimal sizing of devices to be employed. IVUS-guided balloon sizing was first systematically pursued by the Clinical Outcomes with Ultrasound Trial (CLOUT), followed by a randomized multicenter study (Balloon Equivalence to Stent study: BEST) in which the nominal balloon size chosen was the closest size to the media-to-media diameter measured at the lesion site, and inflation pressure was determined based on the compliance curve to attain the target diameter. In a contemporary DES trial of complex lesions (Angiography versus IVUS Optimization: AVIO), the size of the postdilatation balloon was selected based on the average of the media-to-media diameters at multiple sites within the stented segment. The precise vessel size measurement is also critically important for size selection of self-expanding or fully biodegradable stents because undersizing of these devices is not amendable once deployed in the lesion.

Assessment of true lesion length by IVUS dictates the exact length of stent necessary to appropriately scaffold a lesion. Several IVUS studies of DES have identified higher reference plaque burden as an independent predictor of subsequent stent edge restenosis or thrombosis. The STTLLR (The Impact of Stent Deployment Techniques on Clinical Outcomes of Patient
Treated with the CYPHER Stent trial also demonstrated that geographic miss had a significant negative impact on both clinical efficacy and safety at 1 year following DES implantation.44 Therefore, complete coverage of the reference disease is currently recommended. Importantly, however, longer stent length has also been reported to be independently associated with DES restenosis and thrombosis.45,46 Online IVUS guidance can facilitate the determination of appropriate stent length for anchoring the stent ends in relatively plaque-free vessel segments while minimizing the stent length for complete lesion coverage. One practical approach has recently been proposed in a single-center registry, where stepwise IVUS criteria (plaque burden <50% as the primary target zone) determined the optimal landing zone for DES.47

**IVUS Guidance for Optimal Stent Expansion**

The most consistent IVUS risk factor for DES restenosis and thrombosis is underexpansion of stent, the incidence of which has been reported as 60% to 80% of current DES failures. In the BMS era, the predicted risk of restenosis was reported to decrease 19% for every 1 mm² increase in MSA.46 In the Can Routine Ultrasound Improve Stent Expansion (CRUISE) trial, IVUS guidance by operator preferences increased MSA, leading to a 44% relative reduction in target vessel revascularization at 9 months as compared with angiographic guidance.49 A subsequent randomized trial (Angiography Versus IVUS-Directed Stent Placement: AVID) also demonstrated larger acute dimensions achieved with IVUS-guided stent implantation that resulted in lower 12-month target lesion revascularization rates in complex lesion subsets.50

In the DES era, the relationship between postimplantation MSA and ISR can further be enhanced when variability of the biologic response (neointimal proliferation) is reduced. In the SIRIUS trial, a significant positive correlation was observed between baseline MSA and 8-month MLA with a stronger correlation with a higher regression coefficient in sirolimus-eluting stents than in control BMS.43 In another clinical IVUS study of sirolimus-eluting stents, the only independent predictors of angiographic restenosis were postprocedural final MSA of <5.5 mm² and IVUS-measured stent length of >40 mm.43 In a series of restenotic BMS lesions treated with sirolimus-eluting stents, 82% of recurrent lesions had an MSA of <5.0 mm² versus 26% of nonrecurrent lesions (P = 0.003).52 A pooled analysis of paclitaxel-eluting stent trials has also identified baseline MSA as an independent predictor of subsequent in-stent restenosis in both paclitaxel-eluting stents and control BMS.52

In general, the relative benefit of further obtaining larger MSA to ensure a higher “safety margin” for an unexpected amount of neointima (the so-called bigger-is-better theory) can significantly vary among DES, depending on variability of subsequent neointimal proliferation.44 Given the wide variety of clinical backgrounds, patient risk factors, lesion morphologies, and disease complexities in clinical practice, one single pre-specified MSA endpoint could unlikely be effectively applied to all target lesions. Nevertheless, the ability of IVUS to assess the results of stent implantation more precisely than assessed by angiography significantly contributes to enhanced clinical judgment for individual patients. The utility of IVUS to ensure adequate stent expansion cannot be overemphasized, particularly if there are clinical risk factors for DES failure (e.g., diabetes, renal failure).

**IVUS Assessment of Acute Stent Problems**

Postinterventional IVUS can identify several stent deployment issues. Incomplete expansion occurs when a portion of the stent is inadequately expanded as compared with the distal and proximal reference dimensions, especially when dense fibrocalcific plaque is present (Figure 25.7). Incomplete stent apposition (or malapposition) occurs when part of the stent structure is not fully in contact with the vessel wall. After stent implantation, tears at the edge of the stent (marginal tears or pocket flaps) can occur, which may be recognized as haziness by angiography. The stent edge tears have been attributed to the shear forces created at the junction between the metal edge of the stent and the adjacent, more compliant, tissue, or to the effect of balloon expansion beyond the edge of the stent.

When investigated by IVUS, angiographic hazy lesions can represent a spectrum of anatomic morphologies, such as calcium, dissection, thrombus, hematoma, spasm, and excessive plaque burden with extreme remodeling at the reference segment (Figure 25.7). In addition to the diagnosis of the etiology, IVUS can also demonstrate the precise location and severity of these findings. For example, the location of the dissection can be important for risk of extension. Dissections on the free wall (same side as pericardium) may have a higher likelihood of propagating through to the vessel wall as compared with dissections on the mural wall, where the surrounding muscle constrains further propagation. Other criteria of vulnerable dissection are large, moving flaps and extensive medial tears occupying >50% of the vessel circumference (onion skin-like appearance). Identification of these patients at high risk of abrupt closure, who require preventive treatment such as additional stent implantation, is often possible and augments the angiographic findings.

**IVUS Assessment of Chronic Stent Problems**

Several IVUS studies have demonstrated that late-acquired incomplete stent apposition (LISA) is frequently observed in lesions of late DES thrombosis (Figure 25.8). A literature-based meta-analysis also suggested a significantly higher risk of late or very late DES thrombosis in patients with incomplete stent apposition at follow-up (OR 6.51, P = 0.02).53 The main mechanism of LISA after DES is often focal, positive vessel remodeling, whereas plaque regression or thrombus resolution is the predominant mechanism of LISA after BMS.56 In LISA with positive vessel remodeling, incompletely apposed struts are seen primarily in eccentric plaques, and gaps develop mainly...
on the disease-free side of the vessel wall. Thus, the combination of mechanical vessel injury during stent implantation and biologic vessel injury with pharmacological agents or polymer in the setting of little underlying plaque may predispose the vessel wall to chronic, pathologic dilation. It remains controversial, however, whether this morphologic abnormality independently contributes to the occurrence of stent thrombosis.

Other IVUS-detected conditions that may be of importance in DES include non-uniform stent strut distribution and stent fractures after implantation. Theoretically, both abnormalities can reduce the local drug dose delivered to the arterial wall as well as affecting the mechanical scaffolding of the treated lesion segment. By IVUS, strut fracture is defined as longitudinal strut discontinuity and can be categorized based upon its morphological characteristics: (1) strut separation, (2) strut subluxation, or (3) strut intussusceptions. Another proposed classification focuses on potential mechanisms of the strut fracture, categorizing them based upon the presence and absence of aneurysm at the fracture site (Type I and II, respectively). Angiographic or IVUS studies have reported the incidence of DES fracture as 0.8% to 7.7%, wherein in-stent restenosis or stent thrombosis occurred in 22% to 88%. The exact incidence and clinical implications of strut fractures remain to be investigated in large clinical studies.

**Long-Term Clinical Impact of IVUS-Guided Stent Implantation**

In the BMS era, multiple studies have indicated the long-term benefits of IVUS in stent implantation, whereas controversial results were also reported in some IVUS-guided stent trials. This may be, in part, owing to inconsistent procedural endpoints for IVUS-guided stenting as well as various adjunctive treatment strategies that were used in these trials in response to suboptimal results. Overall, a meta-analysis of nine clinical studies (2,972 patients) demonstrated that IVUS-guided stenting significantly lowers 6-month angiographic restenosis (OR 0.75, \( P = 0.01 \)) and target vessel revascularizations (OR 0.62, \( P = 0.00003 \)), with a neutral effect on death and non-fatal myocardial infarction, as compared to an angiographic optimization.

The impact of IVUS guidance during DES implantation on long-term clinical outcomes has also been assessed in several large studies. In a single-center study of IVUS-guided DES implantation versus propensity score matched control with angiographic guidance alone, a higher rate of definite stent thrombosis was seen in the angiography-guided group at both 30 days (0.5% versus 1.4%, \( P = 0.046 \)) and 12 months (0.7 versus 2.0%, \( P = 0.014 \)). In addition, a trend was seen in favor of IVUS guidance in 12-month target lesion revascularization (5.1% versus 7.2%, \( P = 0.07 \)). Several other large registries have also demonstrated improved long-term clinical outcomes by IVUS-guided DES implantation in the treatment of unprotected left main (Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty versus Surgical Revascularization: MAIN-COMPARE) and bifurcation lesions. Finally, the real-world clinical impact of IVUS guidance for DES implantation in an unselected patient population has recently been investigated in the Comprehensive Assessment of Sirolimus-Eluting Stents in Complex...
Lesions (MATRIX) registry, where IVUS guidance was associated with a reduction in both early and long-term (up to 2 years) clinical events, mostly driven by a reduction in the incidence of early myocardial infarction.

Safety and Limitations
During imaging, the most frequent acute complication is transient coronary spasm (up to 3%), although major complications are rare (dissection, thrombosis, or abrupt closure in <0.5%), careful catheter manipulation is mandatory, similar to other interventional procedures. Regarding possible endothelial injury and disease progression as a chronic complication of intracoronary instrumentation, a study of transplant patients confirmed no acceleration of coronary artery disease associated with repeated IVUS examinations.

When extensive calcification is present at the lesion site, it may be difficult to identify the exact size of the vessel owing to large acoustic shadowing. Severe calcifications can also hamper the delivery of the IVUS catheter, even if the stenosis is not severe. Similarly, severe angulation can affect the passage of the IVUS catheter, particularly with a short-monorail configuration. With mechanical IVUS systems, severely angulated lesions may also cause significant image distortions that preclude accurate quantitative analysis. Off-axis position of the IVUS catheter may alter the vessel geometry on the IVUS image in an elliptical fashion. As a result, it may cause overestimation of the vessel dimensions, which requires careful attention, particularly for the evaluation of aorto-ostial segments.

Future Directions
Current technical efforts in IVUS technology are aimed not only at further improvement of the system with enhancement in image quality, but also at the development of combined imaging or therapeutic devices. Integration of IVUS and OCT into one imaging catheter is under development to combine the advantages of the two imaging technologies. LippiScan™ IVUS coronary imaging system (Infraredx, Inc., Burlington, MA), which recently received FDA approval, combines gray-scale IVUS with near-infrared spectroscopy (NIRS) to visualize coronary lesions with simultaneous detection and localization of the lipid-rich plaque (see Spectroscopy section of this chapter). Another interesting area is “forward-looking” IVUS (FLIVUS) technology, which examines the vessel wall distal to the imaging catheter thereby having the potential to visualize the true and false lumens or entry of penetration in CTO lesions. Currently, integration of an RF ablation feature into the FLIVUS catheter is also being explored for the CTO application. These technical advances may enable us to better understand coronary pathophysiology and further enhance the new treatment strategies to benefit our patients.

OCT generates real-time tomographic images from backscattered reflections of infrared light. This use of optical echoes can thus be regarded as an optical analog of IVUS. The greatest advantage of this light-based imaging technology is its significantly higher resolution (10 times or more) than that of conventional pulse-echo, ultrasound-based approaches. The principal technology was developed and first described by researchers at the Massachusetts Institute of Technology in 1991 and has been applied clinically in ophthalmology, dermatology, gastroenterology, and urology.

Imaging Systems
The intravascular OCT imaging system consists of an optical engine emitting and receiving infrared light signals; a catheter interface unit including a motor drive; a fiberoptic imaging catheter; and a computer processor and display console for system control, image reconstruction, and digital recording. The optical engine includes a super-luminescent diode as a source of low-coherence, infrared light, with a wavelength of approximately 1,300 nm to minimize light absorption by vessel wall and blood cell components (protein, water, hemoglobin, and lipids). Unlike IVUS, which directly measures the time-of-flight of acoustic reflections, the high propagation speed of light requires OCT to use interferometric techniques to determine the depth of the reflector. In the first-generation systems, called time domain (TD)-OCT, the emitted light is split into a sample beam (that travels through the imaging catheter to the scanning tissue and is reflected back to the interferometer) and a reference beam (reflected from a moving reference mirror whose distance within the system is accurately known). When these beams are recombined, positive interference occurs only when the two paths are matched—only the tissue plane that corresponds exactly to the reference arm length is recorded for image reconstruction. The motion of the reference beam mirror allows variable tissue depths to be interrogated (A-scan). In the second-generation frequency domain (FD)-OCT systems, also known as Fourier domain OCT or optical frequency domain imaging (OFDI), interference is generated using a rapidly swept wavelength source and a stationary reference arm. Each frequency component of the detected interference signal is associated with a discrete depth location within the tissue. To generate an A-line, a technique called the Fourier transform converts the interference information to depth-resolved reflectance. In both approaches, rotation of the imaging lens allows circumferential data to be collected and passed to the processor for reconstruction of a cross-sectional image (B-scan).

Intravascular OCT catheters consist of a fiberoptic core encapsulated in an optically transparent imaging sheath. For TD-OCT, the currently available imaging probe (St. Jude Medical, Inc., St. Paul, MN) has a maximum outer diameter...
of 0.019 inch (with a standard 0.014 inch radiopaque coiled tip) and contains a single-mode fiberoptic core within a translucent sheath. For FD-OCT, the imaging probes are integrated in a short-monorail catheter (profile varies currently from 2.6F to 3.2F) compatible with conventional 0.014 inch angioplasty guide wires and 6F guide catheters (St. Jude Medical, Inc.; Terumo Corp.). The main difference between TD- and FD-OCT systems is that FD-OCT systems are capable of obtaining A-lines at much higher imaging speeds, achieving significantly higher frame rates (100 to 160 fps) than achieved by TD-OCT (15 to 20 fps). Both systems have an axial resolution of 10 to 20 μm and a lateral resolution of 25 to 30 μm at the focus. Inverse or pseudocolor OCT images are displayed in a real-time format. Pullback of the imaging core enables a longitudinal or three-dimensional image reconstruction.

Image Acquisition Procedures

The imaging procedure of intravascular OCT is similar to that of IVUS, except that blood must be displaced by an optically transparent liquid (contrast media, low-molecular weight dextrase, or lactated Ringer’s solution) while imaging, since red blood cells cause significant scattering of near-infrared light, resulting in very large signal loss. There are two approaches to clear blood from the imaging site: the occlusive technique using proximal balloon occlusion for TD-OCT and the continuous flushing technique for FD-OCT. In the occlusive technique, the occlusion balloon catheter is first advanced beyond the target site over a standard angioplasty guide wire. After replacing the guide wire with the OCT imaging probe through the over-the-wire lumen, the balloon is repositioned proximal to the target and inflated at a low pressure (0.3 to 0.5 atm) to avoid unnecessary vessel stretching. While flushing from its distal exit ports typically via a power injector at a flow rate of 0.5 to 1.0 mL/second, the length of the target site is imaged with an automatic pullback device (0.5 to 2.0 mm/second). The continuous-flushing technique is an alternative approach without using the proximal occlusion balloon. Image acquisition is performed during continuous flushing through the guide catheter typically using a power injector at a flow rate of 3 to 6 mL/second. FD-OCT utilizes this technique, since its high-speed image acquisition enables rapid pullback (20 to 40 mm/second) to scan a long coronary segment during short flushing for <5 seconds.

Image Interpretation

Similar to that seen by IVUS, the normal vessel wall is characterized by a three-layered architecture on OCT images, comprising a highly backscattering (signal-rich) intima, a media with low backscattering (signal-poor), and a heterogeneous and frequently highly backscattering adventitia (Figure 25.9). The higher resolution of OCT, however, can often provide superior delineation of each structure with visualization of IEM and EEM as separate thin high-intensity layers. The periadventitial tissues may present an appearance consistent with adipocytes, characterized by large clear structures resembling cells and/or vessels. In calcified lesions, OCT has the advantage of being able to image through calcium without shadowing, as seen with IVUS.

![Cross-sectional format of a typical OCT image. Similar to that seen by IVUS, the normal vessel wall is characterized by a three-layered architecture, comprising a highly backscattering intima, a media with low backscattering, and a heterogeneous and frequently highly backscattering adventitia. The periadventitial tissues may present an appearance consistent with adipocytes, characterized by large clear structures.](image-url)
On the other hand, signal penetration through the diseased arterial wall is more limited (up to 2 mm with current OCT devices), making it difficult to investigate deeper portions of the artery or to track the entire circumference of the media–adventitia interface.

Several common image artifacts should be noted (Figure 25.10). As seen with mechanical IVUS, NURD can occur with OCT systems caused by a defective catheter or increased friction on the rotating components. While TD-OCT systems show no guide wire artifact on the image plane (since the original guide wire is exchanged for the image wire), the rapid-exchange design at the distal portion of the FD-OCT catheter results in the guide wire always being seen as a point artifact with shadowing. Eccentric catheter position within the lumen may result in an artifact termed as “sunflower” or “merry-go-round,” where stent struts form a pinwheel pattern, appearing to face the imaging probe. If the catheter has moved significantly with respect to the vessel during the time of a single cross-sectional image acquisition (due to cardiac motion or rapid pullback), an axial discontinuity, termed a “seam line,” may appear at the location of the transition between the first and the last A-line. In FD-OCT systems, a portion of the vessel may appear to fold over in the image. This can occur when the vessel is larger than the ranging depth (8 to 9 mm in current systems) and should not be interpreted as real tissue structure. Residual blood from inadequate vessel flushing can result in significant deterioration of image quality and/or high-intensity, variable-shape structures within the lumen.

**Figure 25.10** Common OCT image artifacts. A guide wire is seen as a point artifact with shadowing (*). Suboptimal flushing can result in residual blood inside the vessel lumen (arrow) leading to deterioration of image quality. Non-uniform rotational distortion (NURD) results in a wedge-shaped, smeared appearance in one or more segments of the image (arrows). Seam line or “sew up” artifact appears as an axial discontinuity (arrow) caused by a catheter motion during the single cross-sectional image acquisition. Tangential signal dropout can occur when the optical beam is directed nearly parallel to the tissue surface, which can resemble OCT appearance of thin-cap fibroatheroma (arrows). Blood inside the catheter presents as a high-intensity area within the imaging sheath, possibly affecting image quality. Sunflower or “merry-go-round” artifacts appear as smeared stent struts (arrows) facing the OCT probe, which are usually more pronounced when the imaging catheter is off-centered within the artery. In this example, the image is also blurred owing to blood inside the catheter. Saturation artifacts are linear streaks of high and/or low intensities along the axial direction. This phenomenon can occur when a strong reflector, such as a guide wire or metal stent struts, backscatters at too high an intensity to be accurately detected by the system. Highly reflective objects can also produce a series of ghost reflections, or Reverberation, that appear as a replica at a fixed distance from the primary image of an object (arrows).
Quantitative Assessment

Diameter and area measurements by OCT can be performed in a similar fashion to quantitative IVUS analyses, whereas a few technical considerations specific to OCT should be noted. For accurate measurements, the OCT image should be correctly calibrated for refractive index and z-offset. Refractive index is a property of a material that governs the speed of light through the material. Because the speed of light is slower in flushing media and tissue than in air, the distances in the images need to be corrected for this delay. OCT manufacturers provide a correction for refractive index by dividing the distances in the axial direction in the OCT image by the estimated refractive index of the flushing media and tissue. Z-offset refers to slight variations in optical path length of the optical fiber within the catheter. Calibration can be achieved by adjusting the optical path length in the sample and/or reference arm, which can be performed automatically or manually before each OCT examination. Since the fiber length can also change during a single pullback, resulting in a varying z-offset across the OCT dataset, OCT images should be evaluated to verify the z-offset and adjust it, if necessary, before quantitative analysis.

Whereas measurements by OCT are generally performed at the leading edge of boundaries, stent measurements may require using the axial center (or the highest intensity point) of the strut image. This is because a blooming artifact can often occur at the surface of a high reflector (such as metallic stent struts), creating an enlarged or smeared appearance of the bright reflector along the axial direction (Figure 25.11). In general, a clearer delineation of intraluminal border than seen in IVUS owing to blood removal and higher image resolutions allows more precise automated determination of lumen contour with fewer errors. On the other hand, OCT is not suitable to study plaque burden or vessel remodeling, which can be well addressed by IVUS, because of its limited signal penetration through the diseased arterial wall.

Qualitative Assessment

Plaque Characterization

In OCT, fibrous plaques exhibit homogeneous, signal-rich (highly backscattering) regions; calcified plaques exhibit signal-poor regions with sharply delineated upper and lower borders; and lipid-rich plaques exhibit signal-poor regions (lipid pools) with poorly defined, diffuse borders (Figure 25.12). Artifacts such as tangential signal dropout, blood, or red thrombus may also create a lipid-pool-like appearance, thus requiring careful interpretation (Figure 25.10). A fibrous cap generally appears as a signal-rich band overlying a lipid pool (or necrotic core) or calcium as defined above. Macrophage accumulations may be found within the fibrous cap as signal-rich, distinct or

Figure 25.11 OCT assessment of metal stent struts in relation to the arterial wall. Strut apposition to the vessel wall is determined by measuring the distance from the stent strut surface to the vessel wall as compared to the nominal strut thickness. Due to a blooming effect of metal struts (arrow), the highest intensity point within the strut image should be used for the measurement. Stent struts at follow-up are classified into four categories, based upon the apposition and tissue coverage of the struts.
confluent punctate regions that exceed in intensity the background speckle noise. Cholesterol crystals appear as thin, linear regions of high intensity, usually associated with a fibrous cap or necrotic core (Figure 25.13). Microvessels in the coronary plaque present as signal-poor voids that are sharply delineated and are usually followed in multiple contiguous frames. Thrombus is recognized as a mass attached to the luminal surface or floating within the lumen. Erythrocyte-rich thrombus (red thrombus) has high backscattering with high signal attenuation, whereas platelet-rich thrombus (white thrombus) shows less backscattering and a homogeneous appearance with low attenuation (Figure 25.13).

**Vulnerable Plaque**

The unique capabilities of OCT for the assessment of a lipid pool, a thin fibrous cap, macrophage accumulations, and other detailed surface morphologies suggest OCT as a suitable research and clinical tool for vulnerable-plaque investigation. In OCT, TCFA is defined as an OCT-delineated lipid or necrotic core with an overlying fibrous cap where the minimum thickness of the fibrous cap is less than a predetermined threshold (Figure 25.14). The fibrous-cap thickness measured by OCT has been shown to correlate well with that obtained from histopathologic examination. The most commonly used threshold is 65 μm based on histopathologic studies, although this cut-off may need to be adjusted when applied to in vivo OCT images, accounting for considerable tissue shrinkage (10% to 20%) that occurs during histopathologic processing. A clinical OCT study of ACS patients reported that one-third of plaque ruptures occurred in thick fibrous caps of ≥70 μm (up to 160 μm). In this study, the broken fibrous-cap thickness correlated positively with activity at the onset of ACS, and the plaques ruptured more frequently at the shoulder in the exertion-triggered ACS (rest 57% versus exertion 93%, \( P = 0.014 \)). In another clinical study that enrolled ACS and stable angina patients, the thinnest cap thickness was <80 μm in 95% of ruptured plaques. These results suggest that the cap thickness alone may be insufficient to identify lesions at risk of plaque rupture.

In OCT diagnosis of TCFA, several investigators have used an additional parameter: the lipid or necrotic core should subtend an arc of >90° or comprise more than one quadrant of the vessel circumference. With these definitions, multiple studies have shown a correlation of OCT-determined TCFA
**Figure 25.13** Common abnormal findings detected by OCT. All images have guide wire artifact (*).
or plaque rupture with clinical presentations. OCT–TCFAs were also observed to cluster in the proximal left anterior descending artery, but were more evenly distributed throughout the left circumflex artery and right coronary artery, consistent with previous histopathological reports. As another mechanism for thrombotic events, plaque erosions can also be evaluated in vivo by OCT, typically defined as OCT evidence of thrombus, an irregular luminal surface, and no evidence of cap rupture evaluated in multiple adjacent frames. In a clinical study of acute myocardial infarction (AMI) patients examined by multimodality imaging, fibrous-cap erosion was detected in 23% by OCT but only in 0% and 3% by IVUS and angioscopy, respectively.75

To date, no large-scale natural history studies have been performed to definitively demonstrate that OCT-TCFAs are associated with future risk for a coronary event. However, one recent study of 69 nonsignificant coronary plaques demonstrated that TCFAs and intraplaque microchannels determined by OCT highly correlated with subsequent plaque progression at 7-month follow-up.76 Several other clinical studies have shown that lipid-lowering therapy with statins for 9 months significantly increased the fibrous-cap thickness as measured by OCT.77-79 Whether these OCT findings can be used as surrogate endpoints of plaque stabilization therapies remains to be investigated.

Interventional Applications

Preinterventional Plaque Assessment

In addition to the standard morphometrics on the target and reference lumens, preinterventional OCT can offer unique information on lesion characteristics, such as the thickness of superficial calcification, TCFAs, plaque rupture, or presence and type of thrombus, that may help guide the procedure. Unlike in IVUS, the OCT signal can penetrate calcium without shadowing. This allows operators to access the thickness of superficial calcification, suggesting the need for plaque modification with rotational atherectomy prior to stenting. Several studies have also shown that OCT-TCFAs were susceptible to the no-reflow phenomenon, microvascular obstruction as assessed by MRI, or periprocedural MI in patients treated with PCI.80-82 Thinner fibrous caps and larger lipid arcs were particularly associated with those unfavorable events, and thus may benefit from adjunctive pharmacologic or device therapies to protect distal microvasculature during PCI.

OCT Assessment of Acute Stent Problems

Stent geometry can be accurately measured by OCT to confirm adequate stent expansion. Semiautomatic contour detection can facilitate the lumen area measurement of the stent and reference segments as well as instant identification of MSA. Appearances of dissections and tissue protrusions are essentially similar between OCT and IVUS. However, the higher resolution as well as the higher contrast between the lumen and the vessel wall often allows OCT to visualize those entities in greater detail than possible with IVUS (Figure 25.13). Unlike IVUS, strut apposition is assessed by direct measurement of the distance between the adluminal reflection of the strut and that of the vessel wall (Figure 25.11). Incomplete apposition is then defined as a strut–vessel distance longer than the nominal strut thickness (including polymer if present),83 often with the addition of a correction factor. Some investigators have also proposed further classification of apposed struts as either embedded or protruded.84 Clinical implications of the subtle abnormalities that are detectable only by OCT remain open questions.

OCT Assessment of Chronic Stent Problems

OCT can offer unique observations of the stented vessel at a chronic phase, particularly in the context of DES. Given the precision with which OCT visualizes the stent struts and their relationships with the vessel wall, the degrees of stent strut apposition and tissue coverage at long-term follow-up are being extensively explored using OCT. Combined with the binary definitions of strut apposition described above, stent struts at follow-up are classified as (i) apposed and covered; (ii) apposed and uncovered; (iii) non-apposed (protruded) but covered; or (iv) non-apposed and uncovered (Figure 25.11). Some investigators also propose the struts jailing side branches as additional independent categories of non-apposed struts with or without tissue coverage.85-86 The neointimal healing response after stenting is considered to reduce the percentage of non-apposed and/or uncovered struts over time, and therefore, this parameter has been used as one of the OCT endpoints of multiple clinical DES studies. Indeed, several investigators have demonstrated that non-apposed and/or uncovered struts were significantly associated with the presence of OCT-detected thrombus at follow-up.87-88 On the other hand, the direct association of these findings with late adverse clinical events has not been proven by sufficiently large longitudinal studies. One relevant technical consideration is that a thin endothelial layer is beyond the image resolution even with current OCT systems. Another remaining question is whether the detected tissue on DES struts represents thrombo-protective neointima with functioning endothelium or other material such as thrombus or fibrin. One investigator group recently suggested the potential of OFDI to discriminate fibrin- versus neointima-covered struts using optical density measurements,89 which may in part address the latter concern.

Another intriguing area of OCT is characterization of neointimal tissue within or surrounding the previously implanted stent80-83 (Figure 25.13). Pathologic examinations of human specimens have demonstrated that neointimal tissue after DES implantation can be considerably different from that after BMS implantation, consisting of heterogeneous components, including proteoglycan-rich tissue, organized thrombus, smooth muscle cells, atheroma, inflammatory cells, or fibrinoid. In
particular, atherosclerotic changes and consequent vulnerability in the neointimal tissue can occur much earlier in DES than in BMS, which may contribute to late or very late thrombosis after stenting. In clinical settings, OCT reveals a variety of optical heterogeneity and neovascularization of the tissue within DES in a relatively early phase, presumably representing the pathologic changes of the neointima described above. In cases with very late thrombosis, neointimal plaque rupture has also been reported with OCT.

**OCT Assessment of Fully Biodegradable Stents**

As compared with balloon-expandable metallic stents, accurate device sizing with preinterventional imaging is more crucial for polymer-based fully biodegradable stents (or "vascular scaffolds"), since overdilation of undersized biodegradable stents can damage the polymer struts. After deployment, the optical transparency of the polymer struts allows direct assessment of the strut apposition to the vessel wall, rather than based on the distance measurement. In a chronic phase, the process of strut degradation, absorption, and interaction with the vessel wall can be monitored by OCT. In an early clinical study of a biodegradable stent, the morphological changes of the poly-L-lactic acid (PLLA) struts were described as (i) preserved box; (ii) open box; (iii) dissolved bright box; or (iv) dissolved black box as assessed by OCT.

**Safety and Limitations**

Because the biologic safety of applied energies in OCT has been well established in other medical fields, potential issues predominantly derive from the mechanical designs of intravascular devices and transient ischemia during coronary imaging. A multicenter study of 468 patients who underwent TD-OCT (55% used the proximal balloon occlusion technique) reported no case of coronary spasm or MACE related to imaging. The most common complications were transient chest pain (48%) and QRS widening/ST-change (46%), all of which resolved following cessation of imaging and were significantly more frequent in patients with the occlusive balloon technique than in those with the nonocclusive flush technique. In FD-OCT, the shorter acquisition time, no need for the occlusive balloon, and the reduced amount of flush medium significantly contribute to the reduction of ischemic complications. Initial clinical experiences with FD-OCT have reported no major complications or ischemic ECG changes in a report of 114 image acquisitions in 90 patients.

Because of the blood clearing procedure, caution is required for patients who have severely impaired left ventricular function or those presenting with significant hemodynamic compromise. The use of radiocontrast medium for flushing should also be avoided in patients with markedly impaired renal function or known allergy to the contrast. Complete visualization of lesions at the aorto-ostium or with coexisting rich collateral blood flow may not be feasible as a consequence of insufficient blood clearance.

**Future Directions**

Integration of the OCT technology into catheter-based therapeutic devices is being pursued actively. One example is a combined OCT/atherectomy catheter recently approved in Europe for the treatment of peripheral artery disease. This device has an OCT probe mounted near a corkscrew cutter at the distal tip, offering real-time imaging guidance for the CTO revascularization procedure (Figure 25.15). Other technical enhancements currently being explored consist

![Image of catheter with OCT probe and markers](image-url)
of various signal processing techniques to provide additional biochemical or functional information on the structural details of OCT. Spectroscopic analysis uses a spectrum of the infrared light reflected from the structures and color codes the information on the tomographic images, providing insights into the biochemical contents of the tissue. Polarization analysis, measuring the degree of birefringence in the tissue, may also be helpful in plaque component discrimination, since regions with highly oriented fibrous or smooth muscle cell components are more sensitive to the polarity of the imaging light than are degenerated atheromatous regions with randomly oriented cells. OCT Doppler and elastography may be accurately assessed based on its intrinsic properties using laser speckle analysis.

ANGIOSCOPY

Percutaneous coronary angioscopy is an endoscopic technology adapted from the gastrointestinal to the endovascular domain. It provides real-time, full-color images of the luminal surface of coronary arteries to visualize the surface color and superficial morphology of atherosclerotic plaque, thrombus, and intimal flaps. Since the initial clinical experience in percutaneous coronary angioscopy reported in 1985,103 significant technical improvements have been achieved with image quality enhancement, catheter miniaturization, and development of subselective catheterization systems. Even though coronary angioscopy has not become broadly incorporated into routine clinical practice, clinical investigators worldwide have been using this diagnostic modality to offer unique insights into the pathophysiology of coronary lesions, particularly in the fields of ACS and stent thrombosis.

Imaging Systems and Procedures

In general, intracoronary angioscopy consists of an external optical engine incorporating a light source and a Charge Coupled Device camera; a fiberoptic catheter for illumination and imaging; a subselective delivery catheter system; and a video monitor with an image recording system. The light source emits a high-intensity white light to illuminate the target object through the fiberoptic catheter. The imaging catheter contains a flexible fiberoptic bundle of several thousand pixels; the latest-generation catheter, incorporating 6,000 fibers, is 0.75 mm in outer diameter with a microlens providing a 70° field of view and a focused depth ranging from 1 to 5 mm. The delivery catheter system for the imaging catheter serves two roles: subselective delivery of the angioscope to the target segment, and the creation of a blood-free field for optical imaging. Conventional delivery systems were equipped with a distal balloon or cuff for occluding blood flow; an alternative system uses a smaller catheter to continuously flush an optically clear liquid in front of the tip of the angioscope for blood displacement. This approach precludes possible complications related to balloon occlusion (coronary rupture, dissection, or thrombosis) and minimizes ischemic time as blood flow is restored immediately as the flush pressure is reduced.

Prior to the procedure, “white balancing” by imaging a reference white surface is required to adjust the internal circuitry of the video camera for the correct white level. The occlusion cuff system requires an 8F guide catheter whereas the nonocclusion/flush approach is compatible with a 6F guide catheter; both delivery designs accept a standard 0.014 inch angioplasty guide wire. The angioscope with the cuff occlusion design (4.5F) is advanced to the region of interest using a double monorail technique (inner optical bundle and outer delivery catheter) under fluoroscopy. As warm Ringer’s lactate is infused (0.3 to 1.0 mL/second) through the distal guide wire lumen, the occlusion cuff is gently inflated with a saline/contrast mixture until a satisfactory blood-free imaging is obtained. The monorail optical bundle is then advanced or withdrawn along the guide wire as needed to bring the target lesion into the optimal view.

In contrast, the angioscope with the noncuff approach uses an over-the-wire technique to advance the delivery system (4.0F) to the target site. After removal of a 2.9F inner catheter together with the guide wire (a secondary guide wire may thus be required to protect the target lesion), the fiberoptic probe is advanced within the outer delivery catheter. To avoid vessel injury, the probe tip should be placed immediately proximal to the exit of the delivery catheter under real-time angioscopy. The segment of interest is then imaged by pullback of the entire system with continuous flush through the delivery catheter. Some operators experienced in this technique prefer warm low-molecular weight dextran for safe and effective irrigation.

Image Interpretation

Similar to gastrointestinal endoscopic images, coronary angioscopic images are interpreted based on the surface color and endoluminal morphology of vessel walls or structures. The normal coronary artery surface appears as grayish white and smooth in contour without any protruding structure, whereas atherosclerotic plaques can show varying degrees of yellowish color with or without visible irregularities on the luminal surface. The yellow plaque surface signifies a lipid-rich core seen through a fibrous cap, and the yellow intensity rises as the fibrous cap thins and becomes increasingly transparent (Figure 25.14). Dissections are characterized as visible cracks or fissures on the luminal surface and/or sail-like white protruding structures that can be loose or immobile inside the lumen.
Intimal flaps are visualized as thin, faint, highly mobile fronds of white tissue. Both structures are generally contiguous and of similar appearance to the adjacent vessel wall. Thrombi are recognized as masses that are red, white, or mixed in color, which adhere to the intima or protrude into the lumen. Red masses, not dislodged by flushing, are considered as fibrin/erythrocyte-rich thrombi, whereas white granular or cotton-like appearance is characteristic of platelet-rich thrombi. Subintimal hemorrhage may be detected as distinct, demarcated patches of red coloration that appear clearly within the vessel wall.

A histopathologic basis for angioscopic image interpretation has been provided by several investigators. In an ex vivo study of 70 human arterial segments postmortem,102 angioscopic findings were classified as normal artery, stable atheroma, disrupted atheroma, and thrombus. As compared with a histologic reference, angioscopy demonstrated a high sensitivity, specificity, and accuracy (each >90%) for all categories except disrupted atheroma. For this type of lesion, the sensitivity was only moderate (73%), whereas the specificity, accuracy, and predictive values were still high (>90%). Importantly, the sensitivity of angioscopy for thrombus was 100% and significantly superior to that of IVUS (57%). Other investigators validated in vivo angioscopic findings using corresponding tissue materials retrieved by directional coronary atherectomy103. This study concluded that the yellow plaque color was closely related to degenerated plaque or atheroma and was associated with unstable coronary syndromes.

To alleviate subjectivity in reporting angioscopic interpretation, several investigators have proposed classification systems for angioscopic findings with reproducibility evaluation. The Ermenonville classification was established by a European coronary angioscopy working group, featuring several parameters, such as image quality, lumen diameter, surface color, atheroma, dissection, and thrombus, graded in three to five categories.104 However, κ values for chance-corrected intraobserver and interobserver agreements of the diagnostic items were low at 0.51 to 0.67 and 0.13 to 0.29, respectively. On the other hand, the important items, such as red thrombus and dissection, were shown to have good intraobserver and acceptable interobserver agreements when recorded more simply as either present or absent. Similarly, relatively simple classifications by other investigators resulted in good reproducibility.105 Quantitative evaluation of lumen narrowing is also limited with current angioscopy, although a total occlusion and the presence or absence of lumen narrowing can be recognized.

### Diagnostic Applications

#### Acute Coronary Syndromes

Driven by the high sensitivity of angioscopy to detect intraluminal thrombus in vivo, a number of clinical studies have investigated morphologic characteristics of culprit lesions responsible for ACS. By angioscopy, most culprit lesions show occlusive or mural thrombi frequently overlying disrupted yellow plaque.103,106,107 The thrombi are predominantly white, but can turn into red or mixed once they become occlusive. In some cases, the thrombi look yellow where they are mixed with exposed material from a lipid core of disrupted plaque. One investigator group suggests that this type of culprit lesion may have a higher risk of distal embolization at PCI than found in purely thrombotic lesions with no visible plaque content protrusion.108 In a small percentage of AMI cases, neither yellow plaque nor adhering thrombus is detected after reperfusion; in these situations, secondary thrombosis after vasospasm or other mechanisms may be suspected.

The detailed healing process of infarct-related, disrupted plaques has also been evaluated in vivo by serial angioscopy. In a study of AMI patients,109 culprit lesions were examined immediately after PCI and/or thrombolysis and at 1-, 6-, and 18-month follow-up. Thrombus was detected in 93% at baseline and in 64% even 1 month after the onset of AMI, suggesting long persistent thrombogenicity at the culprit lesion. The prevalence of thrombus, however, markedly decreased at subsequent time points, accompanied by a significant reduction in visually graded yellow color intensity of the plaque. Interestingly, these stabilization processes were significantly impaired in patients with diabetes mellitus or hyperlipidemia.

### Detection of Vulnerable Plaque

To date, a number of angioscopic studies have suggested that intensive yellow surface color of plaque is associated with unstable lesion morphology or clinical presentations. An early clinical study showed that yellow plaques were more common in patients with acute coronary disorders (50%) than in those with stable angina (15%) or old myocardial infarction (8%).100 In a more recent study of 843 patients who underwent catheterization for suspected coronary disease, 1,253 yellow plaques were detected at nonstenotic (diameter stenosis <50%) segments and were graded as 1 to 3 (from light to intensive yellow) using pre-specified color samples.110 This extensive series reported that intraluminal thrombus was detected more frequently on the plaque of higher yellow color grade (15%, 26%, and 52% on plaques of color grade 1, 2, and 3, respectively, P < 0.0001).

Pathophysiologic mechanisms for this association may be partly explained by structural and mechanical characteristics of yellow plaques. An experimental study using a bovine model of lipid-rich plaque showed an inverse correlation between angioscopic percent yellow saturation and histologic plaque cap thickness.111 Similar correlations were also reported in clinical studies by comparing angioscopic surface colors and plaque cap thickness measured by integrated backscatter analysis of IVUS signals or OCT.113 (Figure 25.14). Furthermore, another clinical angioscopic study with conventional IVUS and simultaneous intracoronary pressure measurement demonstrated...
that yellow plaques had higher distensibility and higher remodeling ratio (more compensatory enlargement) than those of white plaques, both suggesting increased vulnerability of angioscopic yellow plaques.

On the other hand, yellow surface color of individual plaques alone may not have a sufficiently high predictive value for future clinical events, presumably owing to the presence of “silent” plaque rupture as well as the need of additional factors for triggering the events. An early natural course study with prospective 12-month follow-up reported that ACS occurred more frequently in patients with yellow plaques than in those with white plaques. Particularly, the events occurred more frequently in patients with glistening yellow plaques than in those with nonglistening yellow plaques. A more recent prospective study extended this initial observation in a large number of patients, and demonstrated that patients with ≥2 yellow plaques per vessel had a 2.2-fold higher incidence of ACS events as compared with those who had 1 or no yellow plaque per vessel during the mean follow-up interval of 4.8 years. The reported event rates were 15.6%, 9.0%, and 4.1% in patients with ≥5 yellow plaques, ≥2 yellow plaques, and 1 or no yellow plaque per vessel, respectively ($P = 0.02$), suggesting the estimated probability of each yellow plaque to cause ACS as 0.3% to 1% per year.

In an extensive angioscopic examination of all three major coronary arteries in patients undergoing follow-up catheterization 1 month after myocardial infarction, both infarct-related and non-infarct related coronary arteries showed equally prevalent, multiple yellow plaques (3.7 ± 1.6 versus 3.4 ± 1.8 plaques per artery, respectively), indicating a pan-coronary process of vulnerable plaque development. On this basis, the same investigator group proposed a plaque index (number of yellow plaques multiplied by maximum color grade), the predictive value of which for future clinical events remains to be explored. Although angioscopic examination of the entire coronary tree is not practical in clinical settings, angioscopic plaque characterization has the potential to offer unique complementary information in the field of vulnerable plaque/patient investigation.

### Interventional Applications

Assessment of lesions before or after coronary intervention represents another commonly reported application of coronary angioscopy. Angioscopic features of disruption, yellow color, or thrombus at the culprit lesion site can identify patients at high risk of early adverse outcome after PCI. A recent study also demonstrated that distal protection reduced microcirculation damage and left ventricular dysfunction in patients with AMI who had angioscopically defined ruptured plaque.

Coronary angioscopy can also significantly contribute to our understanding of new interventional devices or pharmacologic interventions. In coronary stenting, a number of studies have evaluated in vivo the vessel response to BMS or DES implantation by serial angioscopy. In the assessment of the healing process of the stented segment, angioscopic evaluation primarily focuses on the degree of neointimal coverage over stent struts and the existence of red or white thrombi. Neointimal coverage is usually classified into three or four grades (Figure 25.16) based upon the visibility of stent struts (higher grades indicate more complete coverage), and incomplete neointimal coverage is often accompanied by thrombus. In one animal study comparing angioscopic findings and histologic measurements, neointimal thickness of grade 0 (uncovered) or 1 (covered by a thin layer) was 80.2 ± 40.0 μm, whereas neointimal thickness of grade 2 (buried under neointima) was 184 ± 59.4 μm. In clinical angioscopic studies, the degree of neointimal coverage, the incidence of thrombus, and the heterogeneity of these findings within the stented segment at any given point in time can significantly vary among different stent types. In general, the healing process assessed by angioscopy is often delayed in DES than in BMS, although this appears to be improved in newer-generation DES with more biocompatible or bioabsorbable polymers (Figure 25.16). It remains controversial whether these angioscopic parameters can be utilized as safety measures of late thrombotic events following stenting.

Plaque surface color assessed by angioscopy offers another unique insight into the vessel response to interventions. In studies of acute or recent MI patients, serial angioscopy demonstrated that the plaque color of culprit lesions turned from yellow into white within 6 months in the majority of patients treated with BMS, suggesting that BMS implantation may lead to sealing of unstable plaque with neo-intimal proliferation. Similar changes in plaque color have also been reported with plaque stabilization by lipid-lowering interventions. In contrast, the effects of DES implantation on unstable plaques remain controversial. While one angioscopic study showed significantly promoted neointima coverage after sirolimus-eluting stent implantation in patients with ACS, another study demonstrated that preexisting yellow plaques were associated with decreased neointimal coverage of sirolimus-eluting stents.

During several years following BMS implantation, the white neo-intima observed at mid-term follow-up can often change into yellow plaque, representing atherosclerotic transformation of the in-stent tissue. A recent serial angioscopic study demonstrated that this phenomenon can progress more rapidly in DES, presumably owing to an impaired endothelial barrier allowing accelerated infiltration of lipid as well as monocyte adherence and sub-endothelial migration. In this study, even in lesions with no yellow plaque at baseline, yellow color had newly developed in 94% of lesions at 10-month follow-up. An unknown percentage of very late stent thrombosis might be explained by sustained exposure of yellow plaque or accelerated atherosclerosis of the tissue within DES.
Safety and Limitations

The light source of angioscopy provides a high-intensity but "cold" light (low infrared content) to avoid thermal damage to the illuminated vessel wall. On the other hand, mechanical design of the angioscope and its delivery catheter can significantly affect the safety profile of this invasive imaging tool. To date, several complications have been reported, related to the occlusion cuff of the delivery catheter or transient ischemia owing to flow obstruction during imaging. Another complication is the so-called wire-trapping caused by a loop formation of the guide wire between the two monorail wire channels of a certain angioscopy system. With the new over-the-wire system with no occlusion cuff, one experienced group reported a complication rate of <1% during 1,200 procedures, but no comprehensive report of a large multicenter experience is available yet.

Despite recent technical advances, angioscopy still has limitations in evaluating small vessel segments or imaging across tight stenoses. Also, in the presence of protruding structures, only the proximal aspect of the target may be visualized. Other technical limitations include its limited capability to assess inner tissue structures and the subjectivity of qualitative interpretation, which potentially results in relatively large intraobserver and/or interobserver variability.

Future Directions

One technical solution to the subjective color interpretation is a quantitative colorimetric analysis of angioscopic images. In addition to the variability of human color perception, hardware-induced chromatic distortions can occur depending on the angioscopic system used, individual catheters, illuminating light settings, and spatial location of the object within the view field. Quantitative colorimetric methods can overcome these limitations, and excellent measurement reproducibility with this technique has been reported in experimental studies.136

Another interesting area of technical advancement is molecular or cellular targeting imaging using fluorescence angioscopy. Visualization of cholesterol and cholesteryl esters within human coronary plaques has been reported both ex vivo and in vivo by near-infrared fluorescence angioscopy.137 Color fluorescence angioscopy is also being explored for the detection of tissue components and substances related to plaque progression or destabilization such as oxidized low-density lipoprotein and lysophosphatidylcholine.138,139
SPECTROSCOPY AND OTHER OPTICAL IMAGING

Spectroscopy determines the chemical composition of plaque substances, based on the analysis of spectra induced by interaction of electromagnetic radiation, or light, with the tissue materials. To date, several forms of photonic spectroscopy have been adapted for characterization of atherosclerotic plaques, including diffuse reflectance near-infrared, Raman, and fluorescence spectroscopy. When tissues are exposed to a light beam containing a broad mixture (spectrum) of wavelengths, wavelengths absorbed by the illuminated molecules will be missing from the spectrum of the original light after it has traversed the tissue. Diffuse reflectance near-infrared spectroscopy (NIRS) analyzes the amount of this absorbance as a function of wavelengths within the near-infrared window (700 to 2,500 nm). In contrast, Raman spectroscopy uses a light beam of a single wavelength and monitors shifts in wavelength as some of the incident photons interact with the molecules so as to gain or lose energy (i.e., shift in wavelength). Raman spectroscopy measures this inelastic scattering, or the so-called Raman scattering, since it contains unique information on the substance with which the photons interacted. Under a certain condition, the photons can excite molecules to a higher energy level, the decay from which releases the energy difference in the form of light. Fluorescence spectroscopy utilizes this photoluminescence or luminescent emission to identify the properties of the tissue being illuminated. Fluorescence molecular imaging is another optical imaging technique to visualize molecules that have been labeled with a fluorescent compound.

Imaging Systems and Procedures

Among the several different optical techniques, the diffuse reflectance NIRS is the frontrunner, showing the ability to identify the lipid component of atherosclerotic plaques in clinical settings. The commercially available coronary spectroscopy system incorporates a dual-modality imaging catheter that provides simultaneous IVUS and NIRS imaging for co-registered acquisition of structural and compositional information (Infraredx, Inc., Cambridge, MA). The 3.2F imaging catheter contains, within a protective outer sheath, fiberoptic bundles for delivery and collection of light. The catheter with a rapid-exchange design is compatible with a 6F guide catheter and can be advanced to the coronary segment of interest using a standard interventional technique. Unlike other light-based imaging techniques, this system does not require removal of blood from the imaging field. The catheter directs the light to the vessel wall with a mirror located at the tip to acquire spectra within 20 milliseconds, through flowing blood. This configuration allows not only circumferential data collection but also a complete longitudinal scan of the target segment using controlled pullback of the probe. The collected light is analyzed by a spectrometer; using a diagnostic algorithm, the processed data are color coded and displayed in a two-dimensional map of the vessel called a “chemogram” with the spatial (circumferential and longitudinal) information (Figure 25.17). The current system is specifically designed for the detection of lipid-rich plaque, which is seen in yellow color on the chemogram. A color scale from red to yellow indicates increasing algorithmic probability of a lipid component in the vessel wall.

Figure 25.17 Example images obtained with a dual-modality IVUS/NIR spectroscopy system. A color scale from red to yellow indicates increasing algorithmic probability of lipid content. The spectroscopy data are laid in a halo surrounding the cross-sectional IVUS image in a real-time manner (left). In a two-dimensional map of the vessel called a chemogram (upper right), the x-axis represents millimeters of pullback in the artery and the y-axis represents degrees of rotation. A summary of the results for each 2 mm section of artery is displayed as a block chemogram, which is portrayed in the central catheter artifact of the cross-sectional (left) and longitudinal IVUS images (lower right).
40 MHz IVUS transducer is mounted adjacent to the NIRS probe, and the chemogram data are laid in a halo surrounding the cross-sectional IVUS image in a real-time manner. A summary of the results for each 2 mm section of artery is displayed as a block chemogram, which also is portrayed in the central catheter artifact of the cross-sectional IVUS image. In addition, a lipid core burden index (LCBI) is computed as the fraction of valid pixels within the scanned region that exceed a lipid probability of 0.6, multiplied by 1,000.

Validation and Initial Clinical Experience

A number of studies have reported the ability of biospectroscopy to identify the basic chemical components of atherosclerotic plaques in animal models or human arterial samples. An early experimental study using diffuse reflectance NIRS examined 199 human aortic samples and compared the findings with corresponding histology. The sensitivity and specificity of NIRS for histologic plaque vulnerability were 90% and 93%, respectively, for lipid pool, 77% and 93%, respectively, for thin fibrous cap (<65 μm), and 84% and 89%, respectively, for inflammatory cell infiltration. Similar promising results were then reported using an intravascular NIRS through blood. In this in vivo rabbit aortic model, the catheter-based system identified lipid areas of >0.75 mm² exhibiting 78% sensitivity and 75% specificity.

Prototype validation of the intracoronary NIRS system was performed through blood in 212 coronary segments from 84 autopsy hearts. A diagnostic algorithm was constructed with the first 33 hearts used as a reference set; blinded predictions of lipid-rich plaques (defined as fibroatheroma with a lipid core of >60° in circumferential extent and >200 μm in thickness, with a fibrous cap having a mean thickness of <450 μm) were then performed on the remaining samples. The algorithm identified localized lipid-rich plaques with an area under the receiver-operating characteristic curve of 0.80 (95% CI: 0.76 to 0.85) in vessels ≤3.0 mm in diameter. The LCBI also well correlated with the fibroatheroma volume measured by histology. In parallel with this ex vivo autopsy study, the clinical feasibility of the intracoronary NIRS system was tested in the SPECTACL (SPECTroscopic Assessment of Coronary Lipid) trial. This first-in-human multicenter study compared the clinically obtained NIR spectra with those obtained from the autopsy specimens. Predetermined criteria for spectral similarity were met in 83% of spectrally adequate pullbacks (95% CI: 70% to 93%), satisfying the primary end point of this feasibility study. Other clinical studies also demonstrated high intra- and intercatheter reproducibility of the intracoronary NIRS for the in vivo detection of lipid core coronary plaques as well as the measurement of lipid core plaque length and LCBI.

In direct comparison with other intravascular imaging techniques in clinical settings, larger plaque area, ultrasound signal attenuation, and echoluent plaques obtained by gray-scale IVUS were associated with increased detection of lipid-rich components by NIRS. A positive relationship between VH-IVUS (%necrotic core) and NIRS findings has also been reported in noncalcified plaques. Comparison of NIRS–IVUS and OCT findings is currently being conducted in an ongoing clinical study.

Interventional Applications

Aside from the possible utility of NIRS as a diagnostic tool of vulnerable plaque or as a surrogate endpoint of plaque stabilization therapy, preinterventional NIRS imaging may offer unique guidance for PCI. In particular, multiple clinical studies have suggested that detection of lipid-rich plaques by intracoronary NIRS may identify an increased risk of periprocedural MI. The COLOR (Chemometric Observations of Lipid Core Plaque of Interest in Native Coronary Arteries) registry is an ongoing prospective observational study to evaluate the long-term significance of lipid-rich plaques detected by the NIRS system in 1,000 patients. A substudy of the COLOR registry demonstrated that PCI of lesions with a large lipid core (defined as ≥500 maxLCBI per 4 mm by preinterventional NIRS) was associated with a 50% risk of periprocedural MI (95% Cl: 28% to 62%), compared with only a 4.2% risk (95% Cl: 0.8% to 11%) for lesions without a large lipid core (P = 0.0002). This preliminary finding is being further evaluated in a prospective multicenter trial (CANARY: Coronary Assessment by Near-infrared of Atherosclerotic Rupture-prone Yellow) randomizing PCI patients with NIRS-determined high-risk lipid-rich plaques to standard predilation versus stent implantation with an embolic protection device in place prior to any angioplasty. Several other potential applications of NIRS are also under active investigation, including determination of the optimal stent length to avoid residual lipid-rich plaques at the treatment margins and risk stratification for side branch compromise during PCI based upon NIRS findings of plaques located in proximity to the side branches.

Safety and Limitations

The SPECTACL study that examined 106 patients with the standalone NIRS catheter showed no major adverse events related to NIRS imaging. One patient experienced chest pain during the imaging, which was attributed to temporary occlusion of the vessel by positioning of the device across a narrow stenosis. No distal embolization, no-reflow, or thrombus formation was seen in the imaged target vessels. On the other hand, a relatively high rate of failure (16%) to obtain adequate data was reported in this early clinical experience. The safety and performance of the newer dual-modality NIRS–IVUS system are being evaluated in the SAVOIR (Simultaneous Acquisition of Intravascular Ultrasound and Near Infrared Spectroscopy Data in the Coronary Artery) study.

At present, the ability of this approach to detect and differentiate various other plaque components or pathological features of plaque vulnerability (such as thrombus, intraplaque hemorrhage, and inflammation) remains to be determined. One investigator group recently developed a new algorithm for the
current NIRS system to differentiate the cap thickness of lipid core plaque by the amount of collagen signal contribution.

**Future Directions**

As compared with diffuse reflectance NIRS, Raman spectroscopy has a theoretical advantage in direct quantification of individual plaque components. The main technical challenge in intravascular application is that only a small percentage of photons are recruited into the Raman shift, resulting in a low signal-to-noise ratio and poor tissue penetration. However, a newer technique has been shown to significantly reduce the background signals by utilizing the high wavenumber Raman region (2,400 to 3,800 cm\(^{-1}\)) instead of the fingerprint Raman region (400 to 1,800 cm\(^{-1}\)). Accordingly, a prototype of intravascular Raman spectroscopy catheter system and diagnostic algorithms for high wavenumber Raman spectra have been developed and are under preclinical evaluation.

Several encouraging ex vivo studies with fluorescence spectroscopy, including fluorescence lifetime imaging microscopy and time-resolved laser-induced fluorescence, are yet to be translated into successful in vivo applications of this technique. Recently, combined approaches using fluorescence and other optical techniques have been proposed.

Ongoing efforts are also aimed at application of fluorescence molecular imaging to catheter-based imaging techniques. In particular, intravascular near-infrared fluorescence (NIRF) imaging has demonstrated the potential for in vivo molecular imaging of arterial inflammation. Instead of operating in the visible region, NIRF utilizes imaging agents with emission wavelengths of 650 to 1,000 nm. This shift in wavelength offers technical advantages over conventional fluorescence imaging (such as an increase in the penetration depth and a reduction in the detected tissue autofluorescence), leading to a significant increase in the signal-to-noise ratio of the NIRF imaging agents. In ex vivo and in vivo experiments, a recently developed dual-modality optical imaging catheter system incorporating OFDI and NIRF has successfully visualized molecular-level functional details (such as fibrin and inflammation-associated enzymatic activity) precisely co-registered.

**Figure 25.18**

In vivo dual-modality images of a rabbit iliac artery obtained with a combined OFDI–NIR fluorescence catheter system. **Top panels** show 3D rendering of the stented artery. Structural components are color coded in OFDI images (artery wall in red; stent in white; thrombus in purple; NIRF fibrin in yellow). **Middle panels** show OFDI–NIRF fusion images of atherosclerosis microstructure and inflammatory enzyme activity. A strong NIRF signal is observed in a focal lipid-containing (L) atherosclerotic lesion (arrowheads) on the OFDI image (a–c). In the corresponding histology sections (bottom), RAM 11–stained image (d) shows a plaque with a dense accumulation of macrophages (arrowheads). Fluorescence microscopy image (e) reveals strong protease activity–induced NIRF signal (red) detected at the luminal surface of the plaque, subtending an arc similar to that of the elevated NIRF signal obtained in vivo. Immunoreactive cathespin B is also detected in the macrophage-rich plaque region (f). (Yoo H, et al. *Nat Med* 2011;17:1680–1684.)
onto the microscopic architectural morphology of the artery wall [157] (Figure 25.18). In addition to FDA-approved NIR fluorescence-imaging agents, such as indocyanine green, several molecular-activity agents in the regulatory approval pipeline are anticipated to be available for human coronary imaging in the near term.

ACKNOWLEDGMENTS

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observed changes after coronary stent implantation. 


Disorders of the myocardium remain one of the most challenging areas in modern cardiology. Although echocardiography and MRI can noninvasively provide substantial amounts of information on various causes of heart failure, right heart catheterization can define the severity of congestion, depression of cardiac output, and response to therapy, and left heart catheterization and angiography can confirm or identify specific causes of heart failure (e.g., coronary artery, valvular, and pericardial disease), more than half of the patients presenting with new onset heart failure remain classified as idiopathic. It stands to reason that myocardial biopsy should allow more precise characterization of the underlying primary myocardial pathology in such patients, provide prognostic guidance, and monitor therapy. Unfortunately, in reality these benefits have been established for relatively few myocardial pathologies (such as transplant rejection and doxorubicin toxicity). However, as more precise molecular and genetic analyses are now applied to myocardial biopsy specimens (beyond the standard histologic, immunohistochemical, and electron microscopic analysis), the prognostic value of myocardial biopsy should improve. This chapter reviews the history of endomyocardial biopsy, available devices, biopsy techniques and complications, guidance for postprocedure care, indications for endomyocardial biopsy in the current era, and its utility and findings in specific disease states.

HISTORICAL PERSPECTIVE

In 1958, Weinberg, Fell, and Lynfield performed biopsies through an incision in the left intercostal space at the costochondral junction. The pericardium was identified after dissection of the cartilage and the pleura, and partially resected to allow an incisional biopsy of the epicardium and myocardium. In reality, the pericardial biopsy was of as much or greater value than myocardial biopsy revealing inflammatory, tuberculosis, and traumatic causes of pericardial constriction, but two of the patients displayed myocardial pathology (lupus myocarditis and nonamyloid restrictive heart disease). Because of the need for an open incision and surgical extraction, however, this technique was not widely adopted.

In 1960, Sutton and Sutton reported their experience with percutaneous heart biopsy performed at the left ventricular apex or peristernal region in the fifth intercostal space, using a modified flexible thin-walled Terry needle. One hundred and fifty biopsies were performed in 54 patients with myocardial disease of unknown cause. With this technique, 13 of 54 patients had inadequate specimens for diagnosis, 13 of 54 had no abnormality, and 16 displayed nuclear enlargement and/or fibrosis compatible with idiopathic cardiomyopathy. But 12 of the 54 patients had specific etiologic findings including myocarditis, sarcoidosis, rheumatic heart disease, and fibroelastosis. One patient died 11 days after biopsy, and frequent ventricular premature contractions were reported.

Shirey and colleagues used a percutaneous Vim-Silverman or Menghini needle in 20 dogs, using electrocardiographic monitoring via the needle to signal epicardial contact. Whereas diagnostic material was obtained in 60.5% of the attempts, these animals developed signs and symptoms suggestive of pneumothorax or hemopericardium, and most displayed an inflammatory pericarditis within 2 weeks of the puncture. Even so, in 1965 Timmis and colleagues reported similar use of a Silverman needle to obtain specimens percutaneously from 198 patients with heart disease, of whom 36% had primary myocardial disease whereas the others had coronary or valvular heart disease. The needle was inserted at the left ventricular apex under fluoroscopy until premature beats and pulsation through the needle indicated contact with the left ventricular wall. With the cannula held in position, the obturator was replaced with a
cutting stylet or cutting needle and the elongated specimen obtained was then sectioned for appropriate examination. Nearly all (192 of 198) of these patients had tissue recovered, with half of them showing nonspecific hypertrophy and interstitial fibrosis, 13% small vessel disease, and the rest showing nonspecific basophilic degeneration, amyloidosis, rheumatic heart disease, or myocarditis. The validity of the percutaneous biopsy was confirmed in 11 patients who later died, allowing full postmortem examination of the heart. Complications of this technique included pericardial tamponade in eight and postpericardiotomy syndrome in an additional four patients.

In 1965, Bulloch introduced the concept of percutaneous insertion of a heart biopsy needle through the right external or internal jugular vein to allow sampling of the right interventricular septum. In this technique, cutting blades were inserted through a 16-gauge, 50-cm-long curved shaft positioned in the right ventricle through a large-bore radiopaque catheter. Although this technique is no longer used, it established several principles that are still used today: (1) percutaneous access, (2) use of the right internal jugular vein, (3) definition of right heart boundaries by right heart catheterization before an endomyocardial attempt, (4) rotation of the curved biopsy sheath counterclockwise (anteriorly) to avoid the coronary sinus or tricuspid valve, and (5) advancing the tip of the biopsy forceps toward the interventricular septum (posterior medially). Although the 20 human specimens revealed no specific diagnosis, the authors reported no serious complications.

The Konno biopsy techniques were introduced by Sakakibara and Konno. Their original device consisted of a 100-cm shaft equipped at its tip with two sharpened cups (diameter either 2.5 or 3.5 mm). The cups were opened and closed under the control of a single wire, activated by a sliding assembly attached to the proximal end of the catheter. This flexible biopsy thus allowed endomyocardial sampling by pinching rather than advancement of a cutting needle. The authors demonstrated the relative ease of obtaining samples in five patients, with establishment of a specific diagnosis in three. Because of the large size of the catheter head, however, it was usually introduced by a cutdown technique through a vein or artery. The Konno biopsy is currently used infrequently because of its relatively large size, stiff shaft, and lack of durability with repeated usage.

In 1972, Caves modified the Konno biopsy for use through the right internal jugular vein. This modification allowed the biopsy to be inserted percutaneously, but the large diameter of the biopsy head required use of a large (nonvalved) sheath that placed the patient at risk for bleeding or air embolization at the time of biopsy insertion or removal. The technique did allow several advantages including percutaneous insertion, use of local anesthetic allowing minimal discomfort to the patient, rapid performance, direct passage of the biopsy to the right ventricular apex, and repeated entry and exit through the same sheath.

Caves subsequently introduced the Stanford modification to the previous Konno biopsy (Figure 26.1). The Stanford (or Caves–Shulz) biopsy served as the industry standard from approximately 1975 to 1995. It was 50 cm long and had a moderately flexible coil shaft fabricated from stainless steel wire coated by a clear plastic tubing (Scholten Surgical Supply, Palo Alto, CA). Two hemispheric cutting jaws with a combined diameter of 3 mm (9F) were mounted on the catheter tip. One of the jaws remained stationary while the other opened and closed under the control of a mosquito-like clamp at the proximal end of the catheter. The degree of curvature of the biopsy probe could be modified between 45° and 90° by preshaping the shaft and adjusting the degree of closure of the handle ratchet mechanism. Spring-loaded adjustable nuts allowed the operator to adjust the amount of force applied with opening and closing of the surgical-like clamp. Because this biopsy was reusable, it required careful cleaning after each use and ultimately needed retooling and sharpening of the cutting edges of the jaws after 50 procedures.

Richardson of Kings College Hospital in London introduced a smaller-diameter (1.8 mm) biopsy in 1974 that was more flexible and could be inserted percutaneously into jugular, femoral, or even subclavian veins. In 1977, Kawai and Kitaura designed a biopsy probe with a more flexible tip controlled by rotation of a knob on the operating handle (Figure 26.2). A modification of this biopsy probe allowed intracardiac electrocardiographic monitoring (1980). Although the biopsy probe allowed easy maneuverability through the vasculature and across the tricuspid or aortic valve, the flexible tip required a stylet to be advanced into the biopsy shaft before an endomyocardial biopsy could be performed.
MODERN BIOPTOMES

Currently used biopsy forceps draw heavily on the early instruments described above. They are, however, single-use and disposable devices that eliminate the risk of patient-to-patient disease transmission, pyrogen reaction, need for retooling and resharpening of the cutting edges, and mechanical malfunction sometimes seen in the earlier reusable devices. They follow either a preshaped or a flexible (long-sheath) format (Figure 26.3).

The unshaped flexible biopsy forceps are inserted through a preformed sheath that directs the head of the instrument toward the desired portion of the right ventricular septum or left ventricular wall. The preformed sheath is generally advanced over an angled pigtail or balloon flotation catheter and remains in the ventricular cavity throughout the biopsy procedure. This increases the risk for ventricular arrhythmia or perforation and reduces the operator control of the site and direction of the biopsy’s path.

In contrast, the preshaped biopsy forceps are introduced through a short venous sheath and maneuvered as independent catheters to access the right ventricle. They are stiffer and allow greater control of the course and direction of the instrument by the operator. The degree of curvature of the preshaped biopsy forceps can be modified by the operator to suit the angulation required to traverse the tricuspid valve. For the rare patient in whom the relatively stiff preshaped biopsy forceps fail to enter the right ventricle, biopsy can still be performed by advancing a preformed sheath into the ventricle over either a guidewire or a ballooned-tipped catheter. Disposable biopsy forceps and sheaths are available for use from the right or left jugular vein, subclavian vein, femoral vein, or femoral arteries and vary in length, shape, jaw size, and diameter.

VASCULAR ACCESS FOR ENDOMYOCARDIAL BIOPSY

Right ventricular heart biopsy can be performed percutaneously from the right internal jugular vein, left internal jugular vein, right subclavian, or right or left femoral vein. Left ventricular biopsy is usually performed from the right or left femoral artery; however, it can also be accomplished from the right or left brachial artery. The necessary equipment is listed in Table 26.1.
Internal Jugular Access

Right ventricular endomyocardial biopsy procedures are most commonly performed via the right internal jugular vein. Patients usually fast for 8 hours prior to the procedure, but sedative premedications are generally not required for this outpatient procedure. Monitoring during the procedure includes continuous electrocardiogram, pulse oximetry, and blood pressure. For patients who are in decompensated heart failure, continuous arterial pressure monitoring (using a small-bore catheter or a commercially available noninvasive instrument) is recommended.

The patient's head is turned 30° to 45° to the left to facilitate evaluation and preparation of the venous cannulation site. The internal jugular is located lateral to the carotid artery, within the anterior triangle formed by the sternal and clavicular head of the sternocleidomastoid muscle and top of the clavicle (Figure 26.4). These anatomical features can be identified more easily by having the patient briefly lift his or her head just off the table. Internal jugular venous cannulation should be attempted in the middle third of the triangle outlined by the landmarks noted above. This allows compression of venous or arterial structures should bleeding persist after the procedure or if carotid artery puncture

<table>
<thead>
<tr>
<th>Table 26.1 Equipment for Endomyocardial Biopsy</th>
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<tbody>
<tr>
<td>Continuous electrocardiographic monitor</td>
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<tr>
<td>Automatic intermittent cutaneous or invasive blood pressure monitor</td>
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<tr>
<td>Continuous oxygen saturation monitor</td>
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<tr>
<td>Ether screen or drape support</td>
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<tr>
<td>Povidone-iodine, alcohol, or both</td>
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<tr>
<td>Plastic or cloth drape set</td>
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<tr>
<td>Two 20-mL syringes</td>
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<tr>
<td>One 10-mL syringe</td>
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<tr>
<td>One 25-, one 22-, and three or four 18-gauge needles</td>
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<tr>
<td>250 mL of flush solution (with heparin)</td>
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<tr>
<td>18-gauge Amplatz needle or 22-gauge micropuncture needle</td>
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<tr>
<td>7F, 8F, or 9F self-sealing introducer with 0.038-inch guidewire</td>
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<tr>
<td>Micropuncture wire, 0.021 inch</td>
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<tr>
<td>4F or 5F micropuncture sheath</td>
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<tr>
<td>No. 11 surgical blade and handle</td>
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<tr>
<td>Mosquito clamp or small-tipped instrument</td>
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<tr>
<td>Tissue preservative</td>
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<tr>
<td>Formalin</td>
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<tr>
<td>Glutaraldehyde</td>
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<tr>
<td>Dry ice</td>
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<td>Lidocaine: 1 or 2%, 15 mL</td>
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<td>Emergency equipment</td>
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<tr>
<td>Defibrillator</td>
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<tr>
<td>Pacemaker and wire</td>
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<tr>
<td>Pericardiocentesis set</td>
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<td>Resuscitation drugs and equipment</td>
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</tbody>
</table>

(From Baughman KL. History and Current Techniques of Endomyocardial Biopsy. Philadelphia: W.B. Saunders; 2002:269, Figure 25.1.)
Regional anatomy for internal jugular puncture. With the patient's head rotated to the left, the sternal notch and clavicle, as well as the sternal and clavicular heads of the sternocleidomastoid muscle are identified. A skin nick is made between the two heads of this muscle, and two fingerbreadths above the top of the clavicle (near the top of the anterior triangle). The needle is inserted at an angle of 30–40° from vertical, at 20–30° right of sagittal, aiming the needle away from the more medially located carotid artery.

Figure 26.4

Two-dimensional echo of the carotid artery (c) and the internal jugular vein (ij) at rest (left) and during Valsalva maneuver (right), showing the marked enlargement in jugular venous caliber with increased distending pressure.

Figure 26.5
a no. 11 surgical blade. The incision is then expanded with the tip of a mosquito clamp to ensure that the skin will accommodate the 7F venous sheath. In a classic approach, the 22-gauge anesthesia needle is directed toward the anticipated venous pathway at an angle of approximately 30° to 40° from vertical and 20° right of the sagittal plane and is advanced in small increments, aspirating before infiltration of small amounts of lidocaine to provide local anesthesia. Excess lidocaine infiltration should be avoided, since it may result in venous compression or infiltration of vocal cords or carotid sheath resulting in transient hoarseness or Horner syndrome.

Once venous blood is aspirated, indicating entry into the internal jugular vein, the operator notes the position and direction of the needle, and a second 18-gauge single-wall puncture needle with syringe is advanced parallel to the “finder” needle. Continuous aspiration is applied as the needle is advanced in small increments, particularly in individuals with small internal jugular veins or a low central venous pressure. Usually the “give” of the vein wall is palpable, even before blood return is evident. A J-tip guidewire is then introduced, followed by the necessary sheath.

If the initial attempts at venous entry are unsuccessful, the probing needle is retracted to just beneath the skin level and redirected more laterally. If venous return is still not achieved, the needle may be directed more medially (toward the plane of the carotid artery). Should arterial puncture occur, the probing needle and syringe will spontaneously fill with well-oxygenated blood, and the needle must be removed and compression applied for 5 minutes or until hemostasis is achieved. As described above, this problem can be avoided by using echo guidance when the initial puncture attempt is unsuccessful.

An alternative approach is to use a 21-gauge micropuncture needle and a micropuncture kit (Figure 26.6) as the deep anesthesia, probing, and definitive entry device for internal jugular vein cannulation. The needle is very atraumatic and accepts a 0.018-inch stainless steel or nitinol guidewire over which a special 4 or 5 French coaxial hydrophilic-coated double dilator is advanced. Once this has entered the jugular vein and superior vena cava, the inner cannula and 0.018-inch guidewire are removed and a conventional 0.035-inch guidewire is inserted through the outer cannula. The cannula is then removed, and a 7 or 8 French self-sealing sheath is inserted over the guidewire. This is facilitated by passing the wire from the superior vena cava, across the right atrium, and into the inferior vena cava, avoiding runs of ventricular ectopy seen when the wire tip enters the right ventricle. Once the sheath is in the appropriate position, the guidewire and the dilator are removed, the sheath is aspirated and flushed, and the heart biopsy procedure can proceed. To minimize blood losses and the risk of air aspiration, the needle hub and the hub of the dilator sheaths should be occluded with a gloved finger during guidewire and sheath exchanges. A further alternative is to use a micropuncture vascular access Glidesheath kit, which includes a 21-gauge needle, a 0.021-inch hydrophilic-coated or nitinol guidewire, and a 6F sheath (Terumo Interventional Systems, Ann Arbor, MI). After insertion of the sheath, the biopsy can be performed using a 6F biopsyome. The use of sheaths with hemostatic valves is preferred, as they reduce the risk of air aspiration.

Figure 26.6 Micropuncture apparatus: 21-gauge micropuncture needle, 0.018-inch guidewire, 5F guided sheath, and obturator. (Courtesy of Terumo Interventional Systems, Ann Arbor, MI.)
Right Subclavian Vein Access

Rarely, the right subclavian vein is used when patient’s anatomic factors make the internal jugular and femoral veins inappropriate for access.\(^\text{16}\) The entry site into the subclavian vein should be somewhat more lateral than is routinely the case for subclavian venous catheterization, as too acute a superior vena cava/subclavian vein angle will prevent the relatively stiff biopmtome from negotiating this angle into the right heart. The standard site of entry for subsequent heart biopsy is the infraclavicular region, lateral to the area of the bend of the clavicle. The preceding recommendations regarding anesthesia application and vein entry apply in this case as well. The needle is directed medially in a plane virtually parallel to the surface of the x-ray table toward the region of the supraclavicular notch. If this is unsuccessful, approaches more inferior or at a steeper angle to the chest wall can be attempted. The standard single-wall or micropuncture technique is used, as noted above. All intravascular catheters should move without obstruction. In both the internal jugular and subclavian techniques, fluoroscopy should be used to ensure that the guidewire is directed downward toward the inferior vena cava or right atrium rather than upward toward the head.

Femoral Vein and Femoral Artery Access

Although entry into the femoral vein is technically less challenging, biopsy from the femoral vein is more difficult. In a series of biopsy patients reported by Anderson and Marshall,\(^\text{17}\) the internal jugular vein could not be cannulated in 12% of patients, whereas all had successful femoral vein insertion. The femoral vein is located just medial to the femoral artery, and the site of entry should be inferior to the inguinal ligament. The femoral artery can serve as a constant landmark for orientation. The Amplatz, Seldinger, or micropuncture techniques are all used for the femoral venous approach. Ultimately, a guiding sheath of variable length is inserted in the inferior vena cava from the femoral venous site.

The femoral artery is approached in a fashion very similar to the approach adopted for the femoral vein. Left ventricular biopsies are occasionally indicated in patients with specific left ventricular masses or local pathology, isolated ventricular dysfunction, or an infiltrative process specific to the left ventricle.\(^\text{18}\) The risks of embolization and perforation are somewhat higher for patients submitted to left ventricular endomyocardial biopsy as evidenced by higher incidence of pain, low blood pressure, and pericardial effusions after left, as opposed to right, ventricular endomyocardial biopsy. After femoral sheath insertion, a constant infusion drip should be maintained through the sheath to avoid clot formation within the lengthy catheters and air embolization.

BIOPSY METHODS

Fluoroscopic guidance has proven most beneficial in the performance of endomyocardial biopsies. Nonetheless, some investigators\(^\text{19}\) have described the use of two-dimensional echocardiography, as opposed to fluoroscopy, which the authors believe reduces the risk of perforation. Visualization of the biopsy forceps is technically difficult and requires considerable operator and technician experience. We and others\(^\text{20-21}\) have used echocardiography to biopsy intracardiac masses in the right or left heart, but routinely perform endomyocardial biopsy under fluoroscopy.

Right Internal Jugular Venous Approach—Preshaped Biopmtome

The preshaped 50-cm biopmtome is inserted through the venous sheath with the tip of the biopmtome pointing toward the anterior wall of the right atrium. In the mid-right atrium, the biopmtome is advanced slowly as it is turned counterclockwise. This is facilitated by the fact that the direction of the biopmtome head is concordant with that of the handle; nevertheless, free motion and the desired orientation should always be confirmed fluoroscopically. The anterior rotation of the biopmtome head allows the tip to cross the tricuspid valve while it avoids the coronary sinus and tricuspid apparatus. Continued advancement and counterclockwise rotation then allow the biopmtome to advance farther into the right ventricle and orient toward the septum (Figure 26.7). Extreme care must be exercised during this maneuver to avoid perforation of the vena cava, right atrium, or right ventricular free wall by the relatively stiff biopmtome. If resistance is encountered, the biopmtome should be pulled back and a different angle of entry attempted—the biopsy forceps should never be forced or prolapsed into the ventricle. If entry into the right ventricle remains difficult, a Swan–Ganz catheter or other balloon flotation device may be used to define the pathway across the tricuspid valve into the right ventricle.

Once in the right ventricle, the biopmtome should lie against the midpoint of the interventricular septum. On fluoroscopy, the biopmtome should lie across the patient’s spine and is usually directed inferiorly below the plane of the tricuspid valve. If there is any question as to the biopmtome’s position, fluoroscopy in the 30° right anterior oblique (RAO) and 60° left anterior oblique (LAO) projections will confirm whether the catheter is on the ventricular side of the atrioventricular groove and pointed toward the septum. The correct position is also marked by ventricular ectopy; absence of such ectopy and fluoroscopy showing the catheter as lying in the atrioventricular groove suggest that the biopmtome has entered the coronary sinus or the infradia-phragmatic venous system. It must be withdrawn and repositioned before the jaws are opened and an attempt is made to retrieve tissue.
Figure 26.7  Cineangiographic frames obtained during right ventricular endomyocardial biopsy using the Stanford biop tome. From left to right, the top row shows A. the biop tome in the right atrium and B. then in the right ventricle after crossing the tricuspid valve. In the middle row, C. the jaws are open and D. then are closed against the septum. In the bottom row, E. the jaws are closed and the biop tome is withdrawn from the septum and F. across the tricuspid valve with the sample contained.
Even within the right ventricle, it is important to avoid the relatively thin right ventricular free wall (Figure 26.8) by directing the head of the biopsy forceps toward the interventricular septum. The interventricular septum lies in a plane approximately $45^\circ$ diagonal to the plane of the patient's chest wall and corresponds to orientation of the instrument handle leftward and posteriorly. In patients with cardiomyopathy, especially those with elevated pulmonary pressure or right ventricular enlargement, the orientation of the handle may be straight posterior.

Contact with the interventricular septum is confirmed by the appearance of premature ventricular contractions. The biopsy forceps are then withdrawn 1 to 2 cm, opened, and advanced slowly to engage the septum. The biopsy head is slowly closed to encapsulate the endomyocardial specimen. Because of the trabeculated nature of the endomyocardial surface, gentle forward pressure should be maintained while the jaws are being closed, to ensure myocardial contact. Patients with restrictive heart disease or following transplant often demonstrate a pulsatile transmission of ventricular contraction through the course of the bioptome, whereas those with idiopathic dilated cardiomyopathy are often “soft” and engagement of the ventricular septum is confirmed only by premature ventricular contractions.

After the biopsy has been secured, the operator must maintain pressure on the forceps closure device to make sure the jaws remain closed while the specimen is withdrawn from the right ventricle, right atrium, and superior vena cava. There may be some slight “give” as the specimen is released from the myocardium. Specimens that require excessive force to remove suggest entrapment of the tricuspid apparatus, transmural biopsy, or biopsy of a scar focus. In these circumstances, the bioptome head is released by opening the jaws, the bioptome is withdrawn, and another biopsy site selected. Once removed, the specimen must be scooped from the forceps and placed in an appropriate preservative.

Patients not infrequently experience a pulling or tugging sensation as the specimen is withdrawn from the heart surface. Sharp chest pain during bioptome insertion or during the performance of an endomyocardial biopsy implies cardiac perforation. Other clues to possible perforation include persistent premature ventricular contractions, excessive retraction of the ventricular wall during biopsy withdrawal, and a biopsy specimen that floats in formalin (suggesting epicardial fat content). Any of these markers should prompt blood pressure checks and fluoroscopy of the heart borders to detect signs of pericardial tamponade. This risk is lowest in patients with prior cardiac surgery or advanced cardiomyopathy and highest in nonsurgical patients with relatively normal chamber size and systolic function.

Patients with heart transplantation who undergo repeated heart biopsies may require variation in the direction of the biopsy forceps to avoid scarred areas of prior biopsy. This may include some anterior or posterior angulation or alteration of the degree of curvature in the bioptome. The number of specimens taken per biopsy procedure is variable and depends on the patient's clinical status. The operator must balance the pathologist's desire to have adequate tissue and the risks involved with performance of the procedure. We usually take three to five samples to yield adequate tissue for examination and to detect focal pathology that might not be evident in a single sample.

At the conclusion of the procedure, the heart border should be examined fluoroscopically to exclude tamponade before the venous sheath is removed and the puncture site is dressed. Patients who have had serial biopsies (e.g., transplant patients) can be discharged home within 10 minutes of uncomplicated biopsy.

**Right Internal Jugular—Preformed Sheath**

The disposable preformed sheath technique can also be used from the internal jugular approach. It differs from the preformed bioptome technique as described above in that the sheath (rather than the bioptome itself) is advanced into the right ventricle. This directs the bioptome, which is very flexible and lacking in inherent shape. A 7-French 45-cm preformed sheath can be inserted into the superior vena cava and right atrium through a short 9-French self-sealing sheath. Insertion of a smaller sheath through a larger sheath allows better torque control and decreases the risk of biopsy sheath kinking. The preformed sheath is guided into the right ventricle by use of a guidewire or a balloon-tipped flotation catheter. Once the sheath is in the right ventricle, the catheter or wire guide is removed while the sheath remains in position. If there is any question as to the right ventricular placement, the side arm of the guiding sheath can be attached to a pressure...
monitor and right ventricular pressure demonstrated, or a gentle contrast injection can be performed. The tip of the preformed sheath should be free floating rather than positioned against the ventricular myocardium or trabeculated portion of the right ventricle muscle. Once in a stable position, the sheath should be aspirated and flushed with heparinized solution. The sheath should be connected to a constant-infusion port to maintain patency and avoid clot formation.

The flexible biopsy catheter is then inserted through the disposable sheath. The distal portion of the biopsy forceps can be manually curved before entry into the sheath to avoid straightening of the sheath during insertion of the biopsy and thus disturbing the appropriate angle for biopsy performance. The jaws of the biopsy should be opened immediately on exiting the sheath to increase cross-sectional area and thereby reduce the risk of perforating the myocardial wall. The biopsy is directed posteriorly and perpendicular to the plane of the septum. Gentle pressure is applied as the jaws are slowly closed. Once the biopsy has been removed from the sheath, the jaws are opened and the specimen removed. The biopsy jaws are flushed with saline, and repeated biopsies are taken as indicated clinically. Repeated biopsy attempts may require alteration in the direction of the sheath or angulation of the biopsy.

Left Internal Jugular Vein Approach—Flexible Sheath
This technique differs from the right internal jugular approach in the type of sheath used. After the 6-French 10-cm sheath is introduced in the left internal vein in the regular fashion, the sheath is exchanged over a 0.035-inch wire for a 6-French flexible-destination 45-cm sheath. Under careful fluoroscopy guidance, the 45-cm sheath is placed in the right atrium, the wire is removed, and then the biopsy is advanced into the right ventricle.

Femoral Vein Approach—Preformed Sheath
As with the right internal jugular venous approach, we prefer to insert a 9-French self-sealing sheath in the femoral vein through which a 7-French guiding sheath is inserted. All guiding sheaths have an angle of curvature, which varies from a 135° straight angle to a gentle 180° curvature or multiaxial curved (Baim guiding sheath). Each of these types is inserted into the right ventricular cavity with the assistance of an internal dilator, wire guide, pigtail catheter, or flotation balloon-tipped catheter. Rarely, the femoral venous approach is used to biopsy the left ventricle in children via a transseptal approach. The femoral approach allows the operator less control over the site and location of the endomyocardial biopsy, which may increase the risk for perforation.

The 130°-angle femoral sheath must be evaluated before insertion to ensure that the length of the sheath extension from the right atrium to right ventricular biopsy site does not exceed the anatomic distance from the right atrial border to the right ventricular apex. This can be done by placing the sheath on the exterior portion of the patient’s chest under fluoroscopy. If the postangled portion of the biopsy is too long, it should be shortened before insertion.

As with the internal jugular approach using a preformed sheath, insertion of the biopsy may straighten the sheath, altering the ideal angle for performance of the biopsy. If this is the case, the distal portion of the otherwise unformed 104-cm biopsy can be manually preshaped before insertion, into a curve similar to that of the sheath to decrease the chance of losing the ideal biopsy angle. Out-of-plane posterior angulation of the tip of the biopsy relative to the broad, more proximal curve can help direct the tip toward the ventricular septum as it exits the sheath.

Once the preformed sheath is inserted, it should be continuously flushed to avoid clot formation, thromboembolic complications, and air embolism. If there is a question as to the biopsy sheath tip location, a hand flush of contrast dye may be helpful (Figure 26.9). The 104-cm biopsy is inserted through the disposable sheath. The biopsy jaws should be opened just as the biopsy exits the preformed sheath, decreasing the potential for perforation by the biopsy. The biopsy forceps are advanced to the myocardial border with the jaws open. The jaws are slowly closed while gentle pressure is maintained against the septum. If the tip of the preformed sheath lies against the septum, the biopsy forceps can be unsheathed by retracting the sheath while maintaining the biopsy forceps in a stable position. This decreases the potential for perforation. After the specimen is obtained, as the biopsy forceps are withdrawn, the sheath is advanced slightly to restore its original position in the ventricle. Once the biopsy specimen has been removed from the preformed sheath, the forceps are opened and the specimen is scooped from the jaws and placed in an appropriate preservative.

Left Ventricular Biopsy—Femoral Artery Preformed Sheath
As with the femoral venous approach, the femoral artery approach requires insertion of a larger preformed short sheath to maintain artery patency and allow biopsy sheath manipulation. Both the short and the long (98-cm) femoral artery disposable sheaths must be maintained under constant pressurized infusion with a heparinized solution to maintain patency and avoid embolic phenomenon. The preformed sheath is inserted into the left ventricular cavity using a guidewire and a pigtail catheter. The wire, pigtail catheter, and preformed sheath are gently manipulated to cross the aortic valve and enter the left ventricular cavity. Once in the left ventricle, an area of acceptable irritability is established. The inferior posterior portions of the left ventricular cavity as well as areas of previous myocardial infarction should be avoided to reduce the risk of perforation because of the relatively thin muscle in these sites.
The sheath is cleared of debris by aspirating and flushing before the 104-cm biopette is inserted through the sheath and into the left ventricular cavity. The biopsy forceps should be directed away from the mitral valve apparatus. The jaws are opened and directed to the left ventricular wall, the specimen is encapsulated, and the jaws are closed firmly with extraction of the sample. Because of the increased contraction of the left ventricle, less forward pressure is applied while performing the biopsy. The sheath is maintained in the left ventricular cavity and its position adjusted to ensure sampling from several sites.

**Left Ventricular Biopsy—Femoral Artery Guiding Catheter Approach**

A retrograde left ventricular biopsy can also be performed using a 7-French JR4 guiding catheter which is passed through the aortic valve into the left ventricle using a standard J-tip guide wire. To reach the inferior, posterior, lateral, and apical walls the JR4 guiding catheter is the best option. For the anterior segments the recommended guiding catheter is the AL1, and for the left ventricular septum, the JL4. The disposable 105-cm biopette is advanced through the guiding catheter into the left ventricle under biplane-fluoroscopic or echocardiographic guidance.

Another option, instead of using the guiding catheter, is to use a 7F-long guiding sheath with a straight tip.

After each biopsy, aspiration of blood from the guiding catheter and rinsing with heparinized sodium chloride are performed to prevent clotting. Anticoagulation with heparin during the procedure (target ACT 150 second) has also been recommended.

**Perforation**

The greatest risk to patients from the performance of endomyocardial biopsy is ventricular perforation, which may result in pericardial tamponade and potential death. Patients with an International Normalized Ratio (INR) of >1.5 or who have received heparin without reversal within the preceding 2 hours should probably not be submitted to endomyocardial biopsy. Perforation is usually a complication of
injury to the right ventricular free wall, which is only 1 to 2 mm thick. Patients with pulmonary hypertension, a bleeding diathesis, or right ventricular enlargement may be at increased risk for right ventricular perforation. Any patient complaining of sharp pain during the performance of the endomyocardial biopsy should be considered to have experienced cardiac perforation. Patients in whom perforation occurs immediately complain of a visceral pain and within 1 to 2 minutes may develop bradycardia and hypotension. This is in part owing to an exaggerated vagal response, but it is our preferred method for assessing and monitoring may include fluoroscopy of the heart border, measurement of pericardioce ntesis tray should always be available in the procedure room where biopsies are performed.

Heart Block
Patients with pre-existent left bundle branch block may be at risk for complete heart block during manipulation of catheters or biopthomes in the right heart. Pressure against the septum near the tricuspid apparatus may stun the right bundle, delay conduction through the interventricular septum (a new right bundle branch block), or cause progression of prior left bundle branch block to complete heart block. Removal of the offending biopsy or catheter usually resolves the complete heart block. If this is not the case, a temporary pacing catheter can be inserted after removal of the biopsy forceps. Particularly for patients with pre-existing bundle branch block, a temporary pacemaker and pacemaker wire should be immediately available in the catheterization laboratory for emergency use if needed.

Malignant Ventricular Arrhythmias
Premature ventricular contractions are anticipated when the right or left ventricular cavities are entered, and in fact are an indication of appropriate placement of the biopthome or sheath. Occasionally, ventricular couplets or triplets may be seen. Rarely, in patients with cardiomyopathy and pre-existent ventricular arrhythmias, sustained malignant ventricular arrhythmia may occur. This can usually be terminated by removing the biopsy sheath or forceps from the ventricular cavity. If this does not stop the ventricular ectopy, medical therapy with antiarrhythmic agents or cardioversion may be necessary.

Supraventricular Arrhythmias
During cannulation of the right atrium, the atrial wall may be stimulated, causing atrial arrhythmias, particularly in those who have had a history of these rhythm disturbances in the past. Atrial arrhythmias are more likely to occur in patients with elevation of right atrial pressure. In patients with high filling pressures or a history of arrhythmia, right atrial wall contact should be avoided if possible. Occasionally, atrial tachycardia can be mechanically interrupted by touching the right atrial wall with the biopthome, interrupting the circus rhythm. This may increase the risk of perforation, however.

Pneumothorax
Laceration of the lung pleura during performance of right internal jugular or right subclavian venous entry may result in a pneumothorax. This risk can be minimized by performing the internal jugular approach in the midneck region and by continuously aspirating during every attempt at venous entry. Patients who complain of shortness of breath should be investigated immediately with fluoroscopy of the lung margins and urgent pneumothorax evacuation performed if needed.

Puncture of the Carotid Artery or Subclavian Artery
The internal jugular and subclavian veins lie adjacent to both the carotid and the subclavian arteries. Even with sonographic guidance, occasional arterial puncture may occur. Puncture of an artery caused by the guiding needle, micropuncture needle, or even an 18-gauge needle can be addressed by immediate recognition of the complication, withdrawal of the needle, and compression until hemostasis is obtained. Even though this does not preclude performance of a safe venous approach, bleeding in and around the site of arterial puncture may tamponade the venous system in the carotid sheath and make this site unusable. Cannulation of an artery with a large (7 to 9 French) sheath is a more serious error that requires urgent surgical consultation.
Pulmonary Embolization

Patients undergoing biopsy with preformed sheaths may develop clot within the sheath during the performance of the endomyocardial biopsy if not continuously flushed. This may result in recurrent thromboembolic phenomena (pulmonary embolization or potentially paradoxical embolization into the systemic arterial circuit). In addition, patients who develop a clot in the sheath not infrequently have that clot pushed forward and wedged against the endomyocardial surface of the heart by the bioptome resulting in a clot biopsy as opposed to endomyocardial tissue. Air embolism has also been described, with the risk enhanced by a low right atrial pressure. It can be prevented by meticulous management of the sheath and by asking the patient to hold breath while inserting the bioptome into the sheath or during sheath exchanges.

Nerve Paresis

Excessive or ill-directed infiltration of lidocaine in and around the jugular vein and carotid sheath may result in Horner syndrome, vocal cord paresis, and, though rarely, diaphragmatic weakness. These complications are short lived, lasting 1 to 2 hours, if owing to lidocaine infiltration rather than direct nerve trauma.

Venous Hematoma

A venous hematoma may form as a result of excessive movement of the venous sheath during the procedure, inadequate compression of the venous entry site after the procedure, or late venous bleeding owing to a transient or sustained increase in right atrial pressure or coagulopathy. This may result in local bleeding, but rarely results in long-term complications that prevent subsequent use of this site for venous entry. Nonetheless, proper attention to the site of venous entry cannot be overemphasized, particularly in those patients who must return repeatedly for endomyocardial biopsies.

Arterial Venous Fistula

Occasionally, arterial fistulas develop between small branches of the coronary artery and the right ventricle in a heart transplant patient. These are caused by biopsy of a septal coronary branch with subsequent arterial communication into the cavity from which the biopsy was performed. A multitude of long-term studies have demonstrated that such coronary AV fistulae are of no hemodynamic or clinical consequence and can be followed up conservatively.

POSTPROCEDURE CARE

After the biopsy sheath is removed, appropriate pressure should be applied to avoid local bleeding complications. Patients undergoing biopsy by jugular venous access can usually be discharged from the biopsy suite or recovery room immediately if no bleeding occurs within 5 to 10 minutes. Patients with femoral venous entry require 2 to 3 hours of supine bed rest before attempted ambulation. Patients with arterial entry require several hours of bed rest with or without arterial closure devices.

Patients should be monitored for bleeding and any change in hemodynamics. (We do not routinely obtain postprocedure chest radiographs unless there is a suggestion of pneumothorax during the procedure.) The Band-Aid® applied to their entry site can be removed after 12 hours, and patients can have oral intake within minutes of the completion of their biopsy procedure if they can sit up.

TISSUE PROCESSING

The operator has the responsibility to obtain adequate tissue for analysis and for performing the initial preparations that permit subsequent pathologic evaluation. It is generally recommended that at least five separate specimens be obtained to minimize sampling error. Most myocardial diseases affect both ventricles, so either chamber may be sampled, depending on operator experience and preference. Selective left ventricular involvement may be present in certain diseases (endomyocardial fibrosis, scleroderma, left heart radiation, and cardiac fibroelastosis of infants and newborns). Left ventricular biopsy may be performed in these conditions or in patients in whom right ventricular biopsy has been unsuccessful or nondiagnostic. In the remaining patients, we generally prefer right (rather than left) ventricular biopsy because of greater ease and speed and less likelihood of morbidity.

The safest and most eloquent techniques of endomyocardial biopsy and sample preparation are useless without expert pathologic interpretation. The availability of a cardiac pathologist who is fully trained in the evaluation of biopsy-obtained tissue and conversant with the latest classification schemes is mandatory in any biopsy program. Artifacts such as crushing or contraction bands are frequently present in endomyocardial biopsy specimens and may be overinterpreted by an inexperienced pathologist or one used to evaluating only postmortem specimens. The operator may assist the pathologist by appropriate handling of the tissue in the catheterization laboratory. The specimen should be removed gently from the jaws of the bioptome with a fine needle and placed immediately in an appropriate fixative. Frozen specimens may be prepared in the catheterization laboratory by placing the samples in a suitable fluid-embedding medium and immersing them in a liquid nitrogen and dry ice isopentane mixture to allow immediate interpretation. Additional special sample preparation or staining (iron, amyloid) may be indicated for evaluation for specific disease states (Table 26.2).

It is the operator’s responsibility to ensure that the heart biopsy specimens obtained are delivered to the appropriate laboratory for analysis. Preferably, the operator should review
Table 26.2  Myocardial Biopsy Processing

<table>
<thead>
<tr>
<th>Clinical Indication</th>
<th>Stain</th>
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<tr>
<td>Amyloidosis</td>
<td>Congo red, thioflavinT, methyl violet, modified sulfated Alcian blue</td>
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<tr>
<td>Endocardial fibroelastosis</td>
<td>Movat pentachrome, Verhoff–Van Gieson</td>
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<tr>
<td>Fibrosis</td>
<td>Masson trichrome, Azan–Mallory, or Sirius red</td>
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<tr>
<td>Glycogen storage disease</td>
<td>Periodic acid-Schiff</td>
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<tr>
<td>Hemochromatosis</td>
<td>Prussian blue</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>Lymphocyte marker CD3, CD8</td>
</tr>
<tr>
<td>Transplant</td>
<td>C4d and/or C3d staining</td>
</tr>
<tr>
<td>Tumor</td>
<td>Immunohistochemical</td>
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<tr>
<td>Viral myocarditis</td>
<td>Viral nucleic acid</td>
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Myocardium should always be collected for light microscopy and placed in room temperature in 10% buffered formalin. In certain clinical situations, tissue for electron microscopy should be placed in a glutaraldehyde fixative. Tissue for immunofluorescence should be frozen in Optimal Cutting Temperature compound or placed in Zeus solution, and tissue for viral nucleic acid studies should be frozen or placed in RNAlaterRNA stabilizing solution.

The slide material obtained and assist the pathologist with an appropriate history to ensure that special studies are conducted as needed.

Patients with idiopathic dilated cardiomyopathy display a specific pathologic pattern including myocyte hypertrophy and interstitial fibrosis. These findings may allow the clinician to rule out other entities, and help define the severity and judge the duration of the patient's cardiomyopathic condition. In large-series studies of patients undergoing myocardial biopsy, approximately 20% had a specific cause identified. Taking the biopsy and clinical information together, a diagnosis can be made on virtually all patients presenting with heart failure (Table 26.3). But the threshold for performing endomyocardial biopsy clearly depends on the operator's experience, the availability of pathology expertise, and the institutional view of how important the findings are for the diagnosis and management of individual patients. Molecular techniques are becoming increasingly available and will dramatically enhance the value of endomyocardial biopsy performance, above and beyond the simple histologic, immunohistochemical, and biochemical analyses that have been available till now. Polymerase chain reaction techniques will allow pathologists to determine whether or not the patient's myopathic process is associated with a pre-existent or ongoing viral infection. Similarly, other immune markers, such as human leukocyte antigen (HLA) upregulation and immune deposition, will help identify those patients who suffer from some form of an autoimmune process that may be perpetuating ventricular dysfunction.

Given that the presence of severe heart muscle disease reduces life expectancy by as much as many other malignancies do, we believe that it is important to attempt to obtain tissue in patients who present to the catheterization laboratory and are not found to have valvular, coronary, or pericardial disease to account for their ventricular dysfunction or heart failure. Recently, the Standards and Definitions Committee of the Society for Cardiovascular Pathology and the Association for European Cardiovascular Pathology have released a consensus statement with recommendations for processing cardiovascular surgical pathology specimens (Table 26.2).

The utility and findings of endomyocardial biopsy in specific disease states and current indications are summarized below.

**Transplant Rejection**

Endomyocardial biopsy has been the cornerstone of monitoring of antirejection therapy in patients with heart or heart–lung transplants. Biopsy allows the detection of early rejection before the clinical findings of advanced cardiac damage (arrhythmias, third heart sound, congestive heart failure) become manifest and confirms the adequacy of pulsed immunosuppressive therapy to control each acute rejection episode. Surveillance biopsies are performed frequently during the first 6 months after transplantation because of the high incidence of rejection during this early period. No methodology thus far investigated has demonstrated a sensitivity or predictive accuracy high enough to replace endomyocardial biopsy in the detection of rejection in adults, although scintigraphy following the administration...
## Table 26.3 Myocardial Biopsy Indications and Findings

<table>
<thead>
<tr>
<th>Current Indications</th>
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<tr>
<td>Cardiac allograft rejection monitoring</td>
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<tr>
<td>Cardiomyopathy of unknown cause</td>
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<td>Severe ventricular arrhythmias of unknown cause</td>
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<td>Drug-induced cardiomyopathy (anthracycline)</td>
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<td>Restrictive or constrictive heart disease</td>
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<td>Research interests</td>
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<th>Cardiac Disorders with Specific Findings (see also Table 26.5)</th>
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<tr>
<td>Immune/inflammatory disease states</td>
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<tr>
<td>Myocarditis</td>
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<td>Cardiac allograft rejection</td>
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<td>Sarcoidosis</td>
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<td>Cytomegalovirus infection</td>
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<td>Toxoplasmosis</td>
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<td>Chagas disease</td>
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<td>Kawasaki disease</td>
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<tr>
<td>Degenerative</td>
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<td>Idiopathic cardiomyopathy</td>
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<td>Anthracycline cardiomyopathy</td>
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<td>Radiation cardiomyopathy</td>
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<td>Infiltrative</td>
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<td>Amyloidosis</td>
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<td>Gaucher Disease</td>
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<td>Chronic ischemic cardiomyopathy</td>
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<td>Schönlein-Henoch purpura</td>
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<tr>
<td>Cancer</td>
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<tr>
<td>Primary cardiac cancer</td>
</tr>
<tr>
<td>Metastatic cardiac cancer</td>
</tr>
</tbody>
</table>
of indium 111-labeled antimyosin Fab fragments may correlate best with biopsy findings. Because immunologic transplant rejection is a diffuse process, sampling errors are rare. The light-microscopic histologic features of rejection include interstitial edema, inflammatory infiltration, and immunoglobulin deposition. More severe rejection is marked by myocyte death and even interstitial hemorrhage.

The original Stanford grading system (1981) defined absent, mild, moderate, and severe grades of rejection, the latter two showing both lymphocytic infiltrates and myocyte damage. The initial 1990 grading system was replaced by the newer (2004) grading scale of the International Society for Heart and Lung Transplantation (ISHLT), which distinguishes four grades of rejection (Table 26.4) (Figures 26.10–26.13). Grade 0R (no evidence of rejection) and grade 1R (focal perivascular [previously 1A] or diffuse [previously 1B] sparse infiltrate without necrosis and single focus of aggressive infiltration and/or myocyte damage [previously 2]) do not warrant active treatment. In contrast, grade 2R (multifocal aggressive infiltrates and/or myocyte damage [previously 3A]) or grade 3R (diffuse inflammation with necrosis [previously 3B] or diffuse polymorphous infiltrate with necrosis and a variable degree of edema, hemorrhage, or vasculitis [previously 4]) warrants aggressive immunosuppression even if the patient is asymptomatic. The ISHLT is working toward a pathological grading system for antibody-mediated rejection (AMR) in heart transplantation based on the results of histologic and immunopathologic studies. However, owing to technical and interpretation issues, the criteria for the pathologic diagnosis of AMR are still in evolution. Examples of AMR are illustrated in Figures 26.14 and 26.15.

### Table 26.4

<table>
<thead>
<tr>
<th>Grade (2004 nomenclature)</th>
<th>Grade (1990 nomenclature)</th>
<th>Histopathological Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>0R</td>
<td>0</td>
<td>No rejection</td>
</tr>
<tr>
<td>1R</td>
<td>1A</td>
<td>Focal perivascular and/or interstitial infiltrate without myocyte damage</td>
</tr>
<tr>
<td>–</td>
<td>1B</td>
<td>Diffuse infiltrate without necrosis</td>
</tr>
<tr>
<td>–</td>
<td>2</td>
<td>Single focus of infiltrate with associated myocyte damage</td>
</tr>
<tr>
<td>2R</td>
<td>3A</td>
<td>Multifocal infiltrate with myocyte damage</td>
</tr>
<tr>
<td>3R</td>
<td>3B</td>
<td>Diffuse infiltrate with myocyte damage</td>
</tr>
<tr>
<td>–</td>
<td>4</td>
<td>Diffuse, polymorphous infiltrate with extensive myocyte damage with edema, hemorrhage, or vasculitis</td>
</tr>
</tbody>
</table>


---

**Adriamycin Cardiotoxicity**

Doxorubicin hydrochloride (Adriamycin) is a potent anthracycline antibiotic that is active against many tumors, but the usefulness of which is limited by its tendency to cause progressive and irreversible dose-related cardiotoxicity. The incidence is 4% at doses of <500 mg/m², 18% at doses between 500 and 600 mg/m², and 36% at doses of >600/m². One approach to safe clinical use has thus been to limit the total cumulative dose to 500 mg/m², but this constitutes an unnecessary limitation in patients who can tolerate substantially higher doses without cardiotoxicity and who depend on the drug for tumor control. At the same time, this approach fails to protect patients with pre-existing heart disease, prior radiotherapy, or cyclophosphamide administration; who are older than age 70; and who may develop cardiac toxicity at substantially lower doses. Because overt impairment of cardiac function is a relatively late finding in Adriamycin toxicity, noninvasive testing may fail to disclose whether additional doses of Adriamycin can be given safely.

Bristow and coworkers, however, have demonstrated that a progressive series of histologic changes (including electron microscopic evidence of myofibrillar loss and cytoplasmic vacuolization) takes place during the development of Adriamycin cardiotoxicity. The extent of these changes can predict whether a patient is likely to develop clinical...
cardiotoxicity during the subsequent chemotherapy cycle. The 5-step grading system relates grades to the percentage of cells that show these histology changes (1 = <5%, 1.5 = 5% to 15%, 2 = 16% to 25%, 2.5 = 26% to 35%, and 3 = >35%). A biopsy score of ≥2.5 indicates that doxorubicin therapy should be terminated, whereas lower scores allow administration of the next cycle of therapy followed by rebiopsy, thus permitting maximal yet safe dosing with Adriamycin while substantially decreasing the incidence of morbidity and mortality from Adriamycin cardiotoxicity.

**Dilated Cardiomyopathy**

Dilated cardiomyopathy—primary myocardial failure in the absence of underlying coronary, valvular, or pericardial disease—has an age-adjusted prevalence of 36 per 100,000 population in the United States and causes approximately 10,000 deaths each year. The prevalence is 2.5 times higher in blacks and males. The clinical syndrome, which includes
advanced congestive heart failure with dilation of both ventricles, chest pain, and arrhythmias, can be owing to a variety of toxins, metabolic abnormalities, inflammatory or infectious causes, neuromuscular diseases, or familial syndromes. The classification scheme was updated by the World Health Organization in 1995.50

By the time of clinical presentation, most patients with dilated cardiomyopathy already have well-established cardiac damage. Although the course is highly variable and may include transient periods of improvement, the 1-year mortality may be as high as 25% to 30%.49 Since dilated cardiomyopathy carries a substantial mortality, our approach to any young or middle-aged patient who presents with dilated cardiomyopathy consists of an invasive evaluation that includes both coronary angiography and endomyocardial biopsy. The former may be helpful, because clinical signs and symptoms (chest pain or a history of myocardial infarction) are neither sensitive nor specific for distinguishing idiopathic dilated from ischemic cardiomyopathy—both factors may be present in patients with classic dilated cardiomyopathy (with angiographically normal coronaries)—or may be absent in up to half of patients with ischemic cardiomyopathy (despite a high incidence of triple vessel disease). Since some patients with a myopathic presentation of extensive coronary artery disease do well with revascularization, coronary angiography is an important part of the evaluation.

Unfortunately, endomyocardial biopsy in patients with dilated cardiomyopathy generally displays only the monotonous histologic findings of myocyte hypertrophy, interstitial and replacement fibrosis, and endocardial thickening.37,49 Occasional small clusters of lymphocytes (<5 per high-power [300× to 400×] field) may be present, without meeting the criteria for diagnosing myocarditis. The amount of collagen—particularly rigid type I collagen—is increased, potentially accounting for an increase in diastolic stiffness.51 As such, the histologic findings in dilated cardiomyopathy generally do not aid in establishing cause, long-term prognosis, or appropriate specific therapy. However, clearly there are patients with otherwise garden-variety dilated cardiomyopathy, in whom specific processes can be diagnosed by endomyocardial biopsy (Tables 26.3 and 26.5). The yield of endomyocardial biopsy findings that will significantly alter either therapy or long-term prognosis in dilated cardiomyopathy, however, is admittedly low.12,35,37

Myocarditis
In contrast to the “burned-out” condition of the myocardium in dilated cardiomyopathy, myocarditis is an acute or subacute inflammatory illness in which there is variable lymphocytic infiltration in conjunction with myocardial cell damage49,52,53 (Figure 26.16). Epidemiologic studies suggest that approximately 5% of a Coxsackie B virus-infected population showed some evidence of cardiac involvement,49 and replicating enteroviral RNA may be recovered from myocardial samples.38,54-56 Infection and inflammation may resolve spontaneously or may become chronic with perpetuation of an autoimmune process that causes ongoing myocardial damage.57,58 Similar processes can result from various viral, protozoal, metazoal, or bacterial infections. Patients with myocarditis typically present with symptoms of chest pain, arrhythmias, or heart failure, with a clinical course that may vary from days to months. Newer noninvasive tests such as scintigraphy after administration of indium 111-labeled antimony Fab (where a ratio of counts over the heart to counts over the lung in the anterior view of >1.6 is positive) may help identify cases of myocarditis, but it has a low sensitivity (66%) as compared with endomyocardial biopsy.53,59 In patients in whom myocarditis is strongly suspected but not confirmed by scintigraphy, biopsy should still be performed.
### Table 26.5 Final Clinical Plus Biopsy Diagnosis from 1,278 Patients with Dilated Cardiomyopathy

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic dilated cardiomyopathy</td>
<td>654</td>
<td>51.2</td>
</tr>
<tr>
<td>Myocarditis (2/3 active, 1/3 borderline)</td>
<td>117</td>
<td>9.2</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>98</td>
<td>7.7</td>
</tr>
<tr>
<td>Peripartum cardiomyopathy</td>
<td>58</td>
<td>4.5</td>
</tr>
<tr>
<td>Hypertension</td>
<td>54</td>
<td>4.2</td>
</tr>
<tr>
<td>Human immunodeficiency virus infection</td>
<td>46</td>
<td>3.6</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>41</td>
<td>3.2</td>
</tr>
<tr>
<td>Connective tissue disease (mostly scleroderma/lupus)</td>
<td>40</td>
<td>3.1</td>
</tr>
<tr>
<td>Drug-induced (mostly adriamycin)</td>
<td>30</td>
<td>2.3</td>
</tr>
<tr>
<td>Chronic alcohol abuse</td>
<td>30</td>
<td>2.3</td>
</tr>
<tr>
<td>Familial cardiomyopathy</td>
<td>25</td>
<td>2.0</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>19</td>
<td>1.5</td>
</tr>
<tr>
<td>Sarcoid</td>
<td>16</td>
<td>0.9</td>
</tr>
<tr>
<td>Endocrine (mostly thyroid)</td>
<td>11</td>
<td>0.9</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>9</td>
<td>0.7</td>
</tr>
<tr>
<td>Neoplastic</td>
<td>6</td>
<td>0.5</td>
</tr>
</tbody>
</table>


Much of the confusion in this field stemmed from use of various definitions for myocarditis, some of which (e.g., more than five lymphocytes per high-power field) were fairly liberal. In contrast, the Dallas criteria adopted in 1986 require that infiltrating lymphocytes be adjacent to myocyte necrosis or degeneration to diagnose active myocarditis. If lymphocyte infiltration is present without adjacent myocyte damage, the diagnosis is borderline myocarditis. Roughly 9% of biopsies done for the evaluation of dilated cardiomyopathy will show myocarditis (about two-thirds active and one-third borderline). Biopsy samples that were previously read as showing myocarditis may now be read as borderline or even frankly negative using the Dallas criteria. If the biopsy shows nondiagnostic abnormalities (particularly if borderline changes are present), the patient may still turn out to have active myocarditis on a repeat biopsy. If confirmation of active myocarditis is clinically relevant, repeat right ventricular biopsy is generally sufficient, since the incidence of right versus left ventricular discordance in myocarditis is apparently low.

Using both clinical and histopathologic criteria, the Hopkins group has classified myocarditis as *fulminant* (intense infiltration, acute onset with progression to death or recovery within 1 month, poor response to immunosuppressives);
subacute (less distinct onset, active inflammation, potentially good response to immunosuppressives); chronic active (progressive decline in cardiac function, a biopsy that shows mixed inflammation and fibrosis, and only a brief response to immunosuppressives); or chronic persistent myocarditis (histologic evidence of myocarditis, near-normal ventricular function, unaffected by immunosuppressives). Positive biopsies for myocarditis may thus be found in patients presenting with new- or recent-onset congestive heart failure, including patients with peripartum cardiomyopathy during the last month of pregnancy or within the 5 months after delivery and in survivors of cardiac arrest who have no other evident organic heart disease. Several recent studies involving series of patients with AIDS have shown serious clinical cardiac abnormalities associated with myocarditis.

Given this high apparent prevalence of myocarditis among patients with both acute and chronic illness, uncontrolled use of immunosuppressive treatment (analogous to that used for transplant rejection) was reported in the 1980s. Patients with active inflammation appeared to show histologic and some clinical improvement. However, immunosuppressive therapy also caused significant complications, and it was not clear whether the frequency of improvement exceeded that seen spontaneously in many patients with myocarditis.

This general confusion about the prevalence of and optimal treatment for myocarditis led to the conduct of the Myocarditis Treatment Trial. Between October 1986 and October 1990, 2,233 patients who underwent nontransplant endomyocardial biopsy within 2 years of symptom onset at any one of 30 participating centers were screened. Histopathologic evidence of myocarditis was found in 214 (10%), of whom 111 with a left ventricular ejection fraction of <45 and no medical contraindication were randomized to either placebo or 24 weeks of cyclosporine/prednisone (after an initial azathioprine/prednisone arm was dropped). There was no significant benefit in the primary endpoint (improvement in left ventricular ejection fraction from baseline to 28 weeks) in the patients receiving immunosuppression versus those receiving conventional stepped drug therapy for congestive heart failure. Despite initial screening by expert pathologists, only 66% of baseline biopsies met rigorous Dallas criteria for active myocarditis when over-read by the core laboratory, and the trial was seriously underpowered to detect even substantial clinical benefit. Some physicians thus still consider use of immunosuppressives in patients with biopsy-proven myocarditis and a deteriorating clinical picture, particularly in the clinical setting of active myocarditis. Of course, such patients should also be screened for cardiac transplantation, should their condition continue to deteriorate.

Studies by Martin, Wojnick, and Frustaci have raised questions as to the validity of the Dallas Criteria as the exclusive marker of myocarditis. Martin demonstrated that HLA upregulation in patients with a clinical syndrome compatible with myocarditis was a marker for patients who respond to immunosuppressive therapy, whereas Dallas criteria myocarditis was found in only 16% of this population. Frustaci, in a series of patients with dilated cardiomyopathy and presumed myocarditis that failed to improve with standard medical therapy, showed that those who responded to immunosuppressives with an improvement in ejection fraction had anti-heart antibodies and no viral persistence by PCR. Therefore, the absence of persistent virus, the presence of immune upregulation by anti-heart antibodies, and HLA upregulation may better define a population with immune-related heart dysfunction responsive to immunosuppressive therapy.

Restrictive versus Constrictive Disease

Heart failure caused by impaired diastolic functioning of a normal-sized or mildly dilated left ventricle is an uncommon but important clinical entity. In some cases, this may be owing to pericardial constriction, in which instance endomyocardial biopsy would offer no further information. A restrictive pattern may be seen in some patients with hypertrophic myopathy, associated with a pattern of myocyte fiber disarray. More importantly, diastolic dysfunction may also be caused by any one of a series of diseases that can be readily diagnosed with endomyocardial biopsy, thus sparing the patient from inappropriate medical or surgical therapy (e.g., pericardial stripping). These disorders include primary amyloidosis, sarcoidosis, Loeffler endomyocardial fibrosis, carcinoid-related damage, Fabry disease,
glycogen storage diseases,\textsuperscript{74} and tumors affecting the heart (Figure 26.19).

Of these, amyloidosis (AL type) is one of the most common (1,000 to 3,000 new cases per year in the United States).\textsuperscript{78,79} It also has one of the worst prognoses (typical survival for amyloidosis patients is 12 months, which is reduced to 5 months in patients with cardiac involvement). Recent trials suggest that treatment with melphalan, prednisone, and stem cell transplant significantly prolongs survival,\textsuperscript{78,79} so definitive diagnosis is important. Although most patients with cardiac amyloidosis have evidence on biopsy of more accessible organs or urinary light chain excretion, about 10\% do not. Cardiac biopsy should be performed in

patients with thick walls and a small hypokinetic ventricle, particularly if the myocardium has the characteristic speckled appearance on echocardiography.

Sarcoidosis is also relatively common (\textgtr10,000 new cases per year in the United States).\textsuperscript{78,80} Although serious cardiac dysfunction is detected in only 5\% to 10\% of patients, more than three-fourths have cardiac involvement on autopsy. About half of the patients have electrocardiographic abnormalities of conduction, or repolarization, whereas some have papillary muscle dysfunction, infiltrative cardiomyopathy, or pericarditis.\textsuperscript{80,81}

Hemochromatosis may present with either a dilated or a restrictive pattern. It is found in roughly 1\% of endomyocardial biopsies,\textsuperscript{37,82} but is important to identify given the benefits of iron chelation therapy.

Other infiltrative diseases that can be diagnosed with endomyocardial biopsy include Fabry’s disease, which may be responsive to enzyme replacement therapy;\textsuperscript{83,84} fibrosis of the myocardium; and eosinophilic cardiomyopathy, which can be responsive to corticosteroid therapy.\textsuperscript{85,86}

A novel set of clinical scenarios from which a practical decision to proceed with endomyocardial biopsy can be arrived at was published jointly by the American Heart Association, the American College of Cardiology, and the European Society of Cardiology, based on case-control series and expert opinion, which are summarized in Table 26.6.\textsuperscript{87}

**FUTURE DIRECTIONS**

Endomyocardial biopsy remains the gold standard for the diagnosis of transplant rejection and anthracycline cardiotoxicity, and a highly valuable tool for the diagnosis of myocarditis.

Gene expression profiling is a new noninvasive technique that may have a role as screening method in heart transplant patients at low risk of rejection.\textsuperscript{88} It can be used for a pretest assessment of the low risk and lower probability of rejection; however, the usefulness of gene expression profiling has been brought into question.\textsuperscript{89}

The recent use of highly specific molecular probes to look for virus genetic material or autoimmune activity in endomyocardial biopsy material promises to further sharpen the diagnostic potential of this technique. Although the lack of positive findings in the Myocarditis Treatment Trial dampened the enthusiasm for widespread performance of endomyocardial biopsy in patients presenting with congestive heart failure, the procedure remains safe and helpful. With newer techniques to define immune upregulation and viral persistence, there is no question that endomyocardial biopsies will again define myocarditis and its appropriate treatment. Furthermore, molecular and genetic analysis will identify patients in the current idiopathic cardiomyopathy category who have an
### Table 26.6 The Role of Endomyocardial Biopsy in 14 Clinical Scenarios

<table>
<thead>
<tr>
<th>Class of Recommendation and Level of Evidence</th>
<th>Clinical Scenario</th>
</tr>
</thead>
<tbody>
<tr>
<td>I B</td>
<td>New-onset heart failure of 2 weeks’ duration associated with a normal-sized or dilated left ventricle and hemodynamic compromise</td>
</tr>
<tr>
<td>I B</td>
<td>New-onset heart failure of 2 weeks’ to 3 months’ duration associated with a dilated left ventricle and new ventricular arrhythmias, second- or third-degree heart block, or failure to respond to usual care within 1 to 2 weeks</td>
</tr>
<tr>
<td>IIa C</td>
<td>Heart failure of 3 months’ duration associated with a dilated left ventricle and new ventricular arrhythmias, second- or third-degree heart block, or failure to respond to usual care within 1 to 2 weeks</td>
</tr>
<tr>
<td>IIa C</td>
<td>Heart failure associated with a DCM of any duration associated with suspected allergic reaction and/or eosinophilia</td>
</tr>
<tr>
<td>IIa C</td>
<td>Heart failure associated with suspected anthracycline cardiomyopathy</td>
</tr>
<tr>
<td>IIa C</td>
<td>Heart failure associated with unexplained restrictive cardiomyopathy</td>
</tr>
<tr>
<td>IIa C</td>
<td>Suspected cardiac tumors</td>
</tr>
<tr>
<td>IIa C</td>
<td>Unexplained cardiomyopathy in children</td>
</tr>
<tr>
<td>IIb B</td>
<td>New-onset heart failure of 2 weeks’ to 3 months’ duration associated with a dilated left ventricle, without new ventricular arrhythmias or second- or third-degree heart block, that responds to usual care within 1 to 2 weeks</td>
</tr>
<tr>
<td>IIb C</td>
<td>Heart failure of 3 months’ duration associated with a dilated left ventricle, without new ventricular arrhythmias or second- or third-degree heart block, that responds to usual care within 1 to 2 weeks</td>
</tr>
<tr>
<td>IIb C</td>
<td>Heart failure associated with unexplained HCM</td>
</tr>
<tr>
<td>IIb C</td>
<td>Suspected ARVD/C</td>
</tr>
<tr>
<td>IIb C</td>
<td>Unexplained ventricular arrhythmias</td>
</tr>
<tr>
<td>III C</td>
<td>Unexplained atrial fibrillation</td>
</tr>
</tbody>
</table>

(Modified from Cooper LT, Baughman KL, Feldman AM, et al. The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology. Endorsed by the Heart Failure Society of America and the Heart Failure Association of the European Society of Cardiology. J Am Coll Cardiol 2007;50:1914–1931.)

**CLASS I:** Conditions for which there is evidence for and/or general agreement that the procedure or treatment is beneficial, useful, and effective.

**CLASS II:** Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.

**CLASS II A:** Weight of evidence/opinion is in favor of usefulness/efficacy. **CLASS II B:** Usefulness/efficacy is less well established by evidence/opinion. **CLASS III:** Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective and in some cases may be harmful.

The weight of evidence in support of the recommendation is listed as follows: • Level of Evidence A: Data derived from multiple randomized clinical trials. • Level of Evidence B: Data derived from a single randomized trial or nonrandomized studies. • Level of Evidence C: Only consensus opinion of experts, case studies, or standard-of-care.

**Abbreviations:**
- DCM Dilated cardiomyopathy
- HCM Hyperthrophic cardiomyopathy
- ARVD/C Arrhythmogenic right ventricular dysplasia/cardiomyopathy
infectious or inherited cause for their cardiac dysfunction. Once we understand the pathophysiology of the patient’s cardiac condition, we will be in a much stronger position to identify appropriate therapy. Despite ongoing uncertainty of its correct place in the clinical workup, endomyocardial biopsy plays an important role in the evaluation of patients with recent-onset or rapidly deteriorating cardiomyopathy or potential cardiac involvement of certain systemic diseases, as well as in furthering our understanding of the pathophysiology and treatment of diseases of the heart muscle.

REFERENCES


Percutaneous Circulatory Support: Intra-Aortic Balloon Counterpulsation, Impella, TandemHeart, and Extracorporeal Bypass

There are many clinical scenarios in which patients require acute circulatory support. The most common condition in which such need arises is cardiogenic shock, which can be due to acute myocardial infarction, decompensated chronic heart failure, acute mitral or aortic valve regurgitation, acute myocarditis, and ventricular septal defect. Cardiogenic shock exposes patients to immediate risk of death or end-organ damage and also increases the risk of any diagnostic or interventional procedure undertaken to correct the underlying pathology. Right heart catheterization can aid in diagnosis and guide therapy by providing assessment of volume status and ruling out high-output states of failure (e.g., sepsis or other vasodilatory states). Pharmacologic therapy, including arterial and venous vasodilators, vasoconstrictors, and positive inotropes, may be helpful, but is often not sufficiently potent to normalize hemodynamics or has undesirable side effects such as tachycardia, arrhythmias, vasoconstriction with reduced tissue perfusion, and increased myocardial oxygen demand, which can worsen ischemia and lead to additional myocardial necrosis. Accordingly, various devices have been developed to provide circulatory support. Such devices are also used for prophylactic stabilization of patients with borderline ventricular function and large portions of remaining viable myocardium at risk during percutaneous coronary interventions or cardiac surgical procedures. To the extent that some of these support devices favorably alter the relationship between myocardial oxygen supply and demand (see Chapter 24), they may be the treatment of choice in medically refractory unstable angina when definitive revascularization procedure is delayed.

There are four classes of devices currently in use: aortic counterpulsation, transvalvular ventricle-to-aortic pumping (Impella), extracorporeal left atrial-to-arterial pumping (TandemHeart), and extracorporeal venous-to-arterial bypass with membrane oxygenation (ECMO). These devices have different principles of operation and impact ventricular hemodynamics and energetics in distinctly different ways. These differences are illustrated in the idealized hemodynamic tracings and left ventricular pressure-volume loops shown in Figure 27.1. Panel A shows ventricular pressure-volume loops and an aortic pressure tracing that typify a patient with acute cardiogenic shock. These are characterized by high LV end-diastolic filling pressure and volume; low stroke volume; and low peak, diastolic, and mean aortic pressures. The other panels show the impact of the different device classes on these tracings, which are reviewed in this chapter. In addition to discussing principles of operation, device descriptions, indications, contraindications, complications, and techniques for use, available clinical data are also reviewed. An overview of important device comparisons is also provided in Table 27.1.
Figure 27.1 Idealized left ventricular pressure–volume loops and aortic pressure waveforms for a patient in cardiogenic shock (CGS, panel A), and then showing (in red) the impact of intra-aortic balloon pumping (IABP, panel B), Impella 2.5 (panel C), TandemHeart (panel D), and extracorporeal membrane oxygenation (ECMO, panel E). Note that although each form of percutaneous support increases aortic pressure and cardiac output (to varying degrees), each has very different effects on the ventricular pressure–volume loops, which have implications for myocardial energetics that can be important in the setting of myocardial ischemia. Details are provided in the text.
### Table 27.1 Comparison of Percutaneous Support Devices

<table>
<thead>
<tr>
<th></th>
<th>IABP</th>
<th>ECMO</th>
<th>TandemHeart</th>
<th>Impella 2.5</th>
<th>Impella CP</th>
<th>Impella 5.0</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pump mechanism</strong></td>
<td>Pneumatic</td>
<td>Centrifugal</td>
<td>Centrifugal</td>
<td>Axial flow</td>
<td>Axial flow</td>
<td>Axial flow</td>
</tr>
<tr>
<td><strong>Cannula size</strong></td>
<td>7–9F</td>
<td>18–21F inflow 15–22F</td>
<td>21F inflow 15–17F outflow</td>
<td>13F</td>
<td>14F</td>
<td>22F Surgical cutdown</td>
</tr>
<tr>
<td><strong>Insertion technique</strong></td>
<td>Descending aorta via the femoral artery</td>
<td>Inflow cannula into the right atrium via the femoral vein, outflow cannula into descending aorta via femoral artery</td>
<td>21F inflow cannula into left atrium via femoral vein and trans-septal puncture and 15–17F outflow cannula into femoral artery</td>
<td>12F catheter placed retrograde across the aortic valve via the femoral artery</td>
<td>14F catheter placed retrograde across the aortic valve via the femoral artery</td>
<td>21F catheter placed retrograde across the aortic valve via a surgical cutdown of the femoral artery</td>
</tr>
<tr>
<td><strong>Hemodynamic support</strong></td>
<td>0.5 L/min</td>
<td>&gt;4.5 L/min</td>
<td>4 L/min</td>
<td>2.4 L/min</td>
<td>3.7–4.0 L/min</td>
<td>5.0 L/min</td>
</tr>
<tr>
<td><strong>Implantation time</strong></td>
<td>+</td>
<td>++</td>
<td>++++</td>
<td>++</td>
<td>++</td>
<td>++++</td>
</tr>
<tr>
<td><strong>Risk of limb ischemia</strong></td>
<td>+</td>
<td>+++</td>
<td>++++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td><strong>Anticoagulation</strong></td>
<td>+</td>
<td>+++</td>
<td>++++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Requires stable heart rhythm</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Post implantation management complexity</strong></td>
<td>+</td>
<td>++++</td>
<td>++++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

"++" denotes relative grade or intensity of the specified characteristic.

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**INTRA-AORTIC BALLOON COUNTERPULSATION**

The first device developed for use in all of these settings was the intra-aortic balloon pump (IABP), which uses counterpulsation to increase aortic pressure during diastole while decreasing aortic pressure during ejection (Figure 27.1B). This serves to enhance the pressure gradient for coronary artery blood flow (which occurs primarily during diastole) while decreasing the impedance for ejection of blood from the ventricle during systole. Despite the advent of other increasingly sophisticated and potent devices, IABP remains the most widely used form of acute circulatory support.

The IABP system consists of a balloon-tipped catheter connected to a console that controls the timing and volume of balloon inflation and deflation during the cardiac cycle. The concept of using timed inflation of a balloon to generate a positive pressure pulse during diastole (to improve coronary flow) followed by rapid deflation of the balloon to withdraw that volume during systole (to reduce resistance to systolic ejection) was first conceived by Claus in 1961\(^1,2\) and applied clinically by Kantrowitz in 1968.\(^3,4\) At first, the practice was confined to patients with cardiogenic shock,\(^1,2\) but this was soon followed by successful use in patients with medically refractory unstable angina.\(^5\) Insertion of a balloon catheter was initially performed surgically (the first IAB catheters measured 12F to 14F in diameter), but most insertions
today are done percutaneously, thanks to smaller diameter (7F to 8F) over-the-wire catheters. The popularity of IABP stems from its ease of use, safety, and the perception of clinical effectiveness.

**Intra-Aortic Balloon Pump Catheter**

The intra-aortic balloon (IAB) catheter consists of a long cylindrical polyurethane balloon (length roughly 20 to 30 cm, inflated volume 30 to 50 mL) mounted on a flexible shaft. The tip of the IAB is ideally positioned in the descending thoracic aorta, 1 to 2 cm distal to the origin of the left subclavian artery. This balloon is abruptly inflated with helium immediately after aortic valve closure, causing an increase in aortic diastolic pressure. Inflation is maintained until just before the beginning of systolic ejection (i.e., the opening of the aortic valve), when the balloon is abruptly deflated to rapidly deflate the balloon and thereby produce a sharp fall in systolic aortic pressure with a resultant decrease in the impedance to left ventricular ejection (Figure 27.2A and B). The inflation-deflation cycle is generally triggered relative to the R wave of the surface ECG. If use of the ECG is not possible or the ECG signal itself is inadequate, alternative triggering options are available (e.g., pacer, pressure or a fixed internal trigger for patients in ventricular fibrillation or on cardiopulmonary bypass). The console allows for adjustment of the timing of balloon inflation and deflation to optimize the hemodynamic effect, as reflected in the arterial pressure waveform (Figure 27.2B).

Most IABs are dual-lumen catheters. One lumen is used to shuttle gas to and from the balloon. The second (central) lumen allows delivery of the catheter over a guidewire and subsequent monitoring of central aortic pressure. A 40-mL balloon is used in most adults, and a 30- or 34-mL balloon is reserved for smaller patients. A 50-mL balloon is available for patients ≥6 feet tall. Pediatric balloons are also available in 2.5-, 5.0-, 12.0-, and 20-mL sizes. Early balloon consoles used CO₂ gas because of its excellent solubility in blood in the event that the balloon membrane developed a leak. As the shaft size of balloon catheters decreased, it became desirable to use a gas with a lower molecular weight (e.g., helium) to maintain the fast gas shuttle speeds needed for brisk inflation and deflation.

**Percutaneous Insertion**

With rare exceptions, such as the presence of severe peripheral vascular disease, the IAB catheter is inserted percutaneously through the femoral artery. If femoral insertion is not possible, the clinician may opt for insertion using a subclavian- or brachial-artery approach. Percutaneous IAB insertion can be performed via femoral artery grafts if special attention is paid to puncture technique. Although the reduction in the diameter of IAB catheters in recent years (7F to 8F are the predominant sizes today) has reduced the incidence of serious vascular complications, a careful preprocedure clinical evaluation can minimize the risk of complications. Clotting parameters (prothrombin time, partial thromboplastin time, and platelet count) should be checked, and a clinical evaluation to identify possible peripheral vascular disease should be performed prior to IAB insertion.

IABs are generally inserted percutaneously over a guidewire using either a small (7F to 8F) sheath or a sheathless (over-the-wire) technique. The technique for preparation and puncture of the common femoral artery is described in Chapter 6. If balloon placement is being performed as a stand-alone procedure, the artery is predilated using a 7F or 8F dilator after the wire has been advanced to the level of the diaphragm. Firm pressure is maintained over the puncture site to prevent hematoma as the dilator is removed. Next, the appropriate-size sheath is introduced over the wire. This regular guidewire is exchanged for the thinner guidewire supplied with the IAB insertion kit. The guidewire should be positioned just distal to the origin of the left subclavian artery. Prior to IAB catheter insertion, air is evacuated from the balloon, using a large (30 to 60 mL) syringe attached to the one-way valve to maintain the lowest possible IAB profile during introduction, and the guidewire lumen is flushed with a heparin–saline solution. The IAB catheter is then introduced over the wire and its radiopaque tip-marker is positioned approximately 2 cm distal to the origin of the left subclavian artery. The guidewire is removed and blood is aspirated from the guidewire lumen to ensure that no air is trapped. The guidewire lumen is then connected to a pressurized flushing device that delivers 3 mL/hour to maintain lumen patency. Special care must be taken to prevent inadvertent injection of air bubbles or thrombi through the guidewire lumen, since its tip is only a short distance below the aortic arch. The balloon shaft may be equipped with a protective plastic outer sleeve that can be advanced to mate with the hub of the introducer sheath to maintain sterility if subsequent adjustment is required. If a long (23-cm) sheath has been used to negotiate a tortuous iliac artery, the sheath must be partially withdrawn prior to initiation of counterpulsation so that the distal end of the sheath does not overlie and trap the distal end of the balloon.

**Sheathless Insertion**

Although insertion through a sheath is quite easy, most of the current balloons have a tapered nose to allow them to be inserted directly over a guidewire (i.e., without use of a sheath). Because the balloon shaft is roughly 1.5F (0.5 mm) smaller than the corresponding sheath's outer diameter, sheathless insertion results in less femoral arterial trauma and less obstruction to the limb circulation in patients with small or atherosclerotic arteries. Care must be taken to adequately predilate the soft-tissue track and to avoid kinking either the guidewire or the balloon catheter during insertion. In addition, the balloon catheter should not be rotated as it is passed through the soft tissues, as this will produce unnecessary tissue trauma. If undue resistance is encountered while advancing the catheter, consideration should be given to reverting to a sheathed insertion.
Initiation of Counterpulsation

Following connection to the console, the system is purged with helium inflation gas. The console can be set in such a way that the balloon will be inflated to approximately half its rated volume with each inflation, and counterpulsation is begun at the 1:2 or 1:3 setting (every other or every third beat) so that preliminary timing adjustments can be made (see below). Fluoroscopy can be used to confirm appropriate placement of the balloon proximally, full exit from the sheath distally, and uniform expansion without twists or kinks. Balloon volume is then increased to its full rated value, and fluoroscopy is performed again to verify that the balloon position
is appropriate and that the balloon has assumed a uniform symmetric cylindrical shape at full inflation. The balloon shaft and sheath (if used) are sewn to the skin; disinfectant solution is applied to the entrance site; a mark is placed across the balloon shaft and the skin to detect any subsequent balloon migration; and a sterile dressing is applied. If the patient is not already anticoagulated, heparin (5,000 units) should be given intravenously as soon as the balloon is inserted, followed by continuous intravenous heparin titrated to maintain an activated clotting time (ACT) of 1.5 to 2.0 times the normal.

**Timing of Inflation and Deflation During Counterpulsation**

Deriving maximal benefit depends on proper timing of balloon inflation and deflation. Classically, this timing was done by inspection of the central aortic pressure tracing through the balloon's central lumen, since any change in contour and timing of the pulse wave as it moves from the central aorta to the periphery can make accurate timing of counterpulsation difficult. Timing is best done with the console set at 1:2 or 1:3 pumping (i.e., counterpulsation of every other or every third beat) so that arterial pressure tracings from consecutive beats with and without counterpulsation can be compared. Current IABP systems, however, use tip pressure measurements to set proper timing automatically and require little, if any, manipulation of the console controls by the operator to maintain correct timing. In older systems, however, it is necessary for the operator to look at a central aortic pressure tracing and slowly adjust timing. Inflation should be moved back to the point when the inflation upstroke fuses with the central aortic dicrotic notch to form a "U" (see Figure 27.2B). Earlier inflation should be avoided, because this will increase aortic pressure during left ventricular ejection, resulting in decreased stroke volume. In case of too early onset of deflation (before the R wave), the timing of deflation is delayed progressively until the maximum reduction of aortic systolic pressure is observed in the subsequent beat. This is usually accompanied by a parallel 10 to 15 mmHg decrease in the nadir of central aortic diastolic pressure (Figure 27.2B). When appropriately timed, the intended effect of IABP is to reduce ventricular afterload and increase cardiac output.

**ECG R wave and the atrial pacing spike, or by setting the console to the mode that discriminates between the pacing spike and R wave by sensing both the height and duration of the signal. Manual adjustment of timing with today's state-of-the-art systems, however, is rarely required as these systems adapt automatically to irregularly timed beats as encountered in atrial fibrillation and other rhythm abnormalities by continuously seeking the best available trigger source and making appropriate timing adjustments.**

**Angiography During Counterpulsation**

In case of simultaneous IAB support and cardiac angiography or angioplasty, a few precautions should be taken to avoid damaging the balloon membrane if both femoral arteries are used for access. If the IAB catheter is placed first, it is advised to advance the guidewire and catheters beyond the level of the balloon with IAB operation suspended briefly. IAB therapy does not interfere with manipulation for cardiac angiography or angioplasty. However, the operator should remember to suspend balloon operation temporarily during catheter exchanges.

**Patient Management During Counterpulsation**

Patients on IAB support are maintained in an intensive care unit and therefore receive a high level of medical care and observation. During counterpulsation, it is particularly important that patients undergo specific evaluations at least daily for evidence of sepsis, thrombocytopenia, blood loss, hemolysis, vascular obstruction (i.e., distal leg ischemia), thrombus, embolus, and vascular dissection. Mild to moderate thrombocytopenia may occur owing to platelet destruction, but the platelet count rarely falls below 50,000 to 100,000/mL and should rapidly return to normal following balloon removal. The level of heparin anticoagulation should be monitored closely, with partial thromboplastin time (PTT) maintained at 50 to 70 seconds to prevent thrombosis-related complications. However, recent data have suggested that a strategy of selective use of heparin (i.e., administration of heparin only for a clinical indication) might be associated with a lower bleeding complications rate without an increase in ischemic complications when compared with routine heparin use. Thus, the use of routine full anticoagulation with heparin in low-risk patients has been questioned, as long as the IABP is maintained at 1:1 and when support is needed for a short period of time particularly in the postoperative state. Evaluation of the circulation to the involved limb should be done regularly and documented by nursing staff. Dorsalis pedis and posterior tibial pulses should be palpated at least every 6 to 8 hours. Use of Doppler probe to confirm presence of distal pulses is mandatory if these are not palpable.
as patients might develop acute limb ischemia secondary to arterial thrombosis, distal embolization, or plaque rupture in the setting of severe aorto-iliac atherosclerotic disease.

The position of the IAB can be visualized by chest radiography with the tip appropriately located at the level of the carina. Presence of the protective sheath allows for repositioning. If the IAB sits below the recommended position, renal arteries may be blocked during inflation. On the other hand, IAB positioning above the recommended position can block the subclavian artery or cause damage to the aortic arch (Figure 27.2A).

**Weaning from Counterpulsation and Balloon Removal**

Balloon counterpulsation is a temporary support measure. The balloon is usually removed once the patient’s condition has stabilized after the acute event (usually after 24 to 48 hours of pumping). Before removal of an intra-aortic balloon, patients are weaned progressively from support by decreasing the counterpulsation mode from 1:1 to 1:2 and then 1:3 counterpulsation. Once heparin has been stopped, continuous pumping in the 1:3 mode will reduce the chance of clot formation, until the clotting parameters have fallen to an ACT of <160 seconds or a PTT of <50 seconds, allowing the device to be removed safely.

At the point when the IAB is to be removed, the pump should be shut off. The balloon, usually together with the sheath, is then withdrawn. The site is then firmly compressed by hand or with a mechanical compression device for 30 to 60 minutes. The patient is kept at bed rest, avoiding hip flexion on the involved side, for the next 24 hours. If the balloon is placed only during an interventional procedure, the groin site can be managed by use of one of the vascular closure devices or by “preclose” of the puncture site with the Perclose suture device (see Chapter 8).

**Indications and Contraindications**

The overall indications and contraindications for IABP are summarized in Tables 27.2 and 27.3, respectively. Today the most frequent indications for use of IABP are hemodynamic support during or after cardiac catheterization, particularly in the case of high-risk interventions, and cardiogenic shock. The changing clinical applications of intra-aortic balloon counterpulsation have, in many ways, paralleled the advances in cardiac surgery and interventional cardiology. Based on the initial experience by Kantrowitz and others, IABP was then used as a stand-alone treatment for patients who had suffered an acute myocardial infarction and had lapsed into cardiogenic shock. Long-term survival of these patients, however, was poor. The SHOCK trial showed that a combined strategy of immediate revascularization on top of routine IAB therapy was superior to medical therapy and IAB. This has been the major supportive evidence for IAB usage in current practice. However, the

<table>
<thead>
<tr>
<th>Table 27.2</th>
<th>Indications for Intra-Aortic Balloon Pumping</th>
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<tbody>
<tr>
<td><strong>Hemodynamic compromise</strong></td>
<td></td>
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<tr>
<td>Cardiogenic shock secondary to AMI with continuing ischemia, VSD, or MR</td>
<td></td>
</tr>
<tr>
<td>Cardiogenic shock due to transient ischemia, myocarditis, sepsis, drug toxicity, etc.</td>
<td></td>
</tr>
<tr>
<td>Inability to wean from bypass after cardiac surgery</td>
<td></td>
</tr>
<tr>
<td>Hemodynamic support while awaiting transplantation</td>
<td></td>
</tr>
<tr>
<td>Severe arrhythmia owing to refractory ischemia</td>
<td></td>
</tr>
<tr>
<td><strong>Medically refractory ischemia</strong></td>
<td></td>
</tr>
<tr>
<td>Medically refractory unstable angina</td>
<td></td>
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<tr>
<td>Failed PCI with refractory ischemia</td>
<td></td>
</tr>
<tr>
<td><strong>Prophylactic high-risk intervention</strong></td>
<td></td>
</tr>
<tr>
<td>High-risk PCI owing to LV dysfunction and/or large territory at risk</td>
<td></td>
</tr>
<tr>
<td>PCI during acute myocardial infarction</td>
<td></td>
</tr>
<tr>
<td>Severe multivessel or left main CAD requiring urgent cardiac or noncardiac surgery</td>
<td></td>
</tr>
<tr>
<td>Large myocardial infarction</td>
<td></td>
</tr>
</tbody>
</table>

AMI, acute myocardial infarction; CAD, coronary artery disease; LV, left ventricle; MR, mitral regurgitation; PCI, percutaneous coronary intervention; VSD, ventricular septal defect.
studied concept in this trial was revascularization versus medical therapy rather than the effectiveness of IAB therapy. Experimental studies have shown that temporary myocardial unloading may lead to infarct size reduction in addition to early recovery. This concept is generally accepted to be the main reason for the use of IAB therapy in daily practice. Nevertheless, all recent randomized clinical trials and meta-analyses have not supported the validity of this concept for IAB therapy. The CRISP AMI randomized trial investigated the effect of IAB therapy versus normal therapy in patients with large anterior acute myocardial infarction. The primary endpoint was infarct size measured by MRI. The study showed no benefit for IAB therapy; in fact, a nonsignificant trend toward larger infarct size was observed with IAB treatment.

Most importantly, the recently completed IABP SHOCK II study revealed that routine usage of IABP in the setting of cardiogenic shock accompanying acute myocardial infarction treated with PCI did not reduce mortality at 30 days. A total of 600 patients with cardiogenic shock were randomized and 30 day mortality was 39.7% in the IABP group and 41.3% in the control group. There were no significant differences in secondary endpoints or in process-of-care measures, including the time to hemodynamic stabilization, the length of stay in the intensive care unit, serum lactate levels, the dose and duration of catecholamine therapy, and renal function. Timing of IABP insertion did also not affect clinical outcome. Various other sub-analyses are still ongoing and late follow up is awaited. Nevertheless, the results of the IABP SHOCK II study are completely in line with the meta-analyses and AMI CRISP study, all of which have put IAB usage into perspective. Although both the European and American guidelines have been changed recently before the results of the IABP SHOCK II study were published, the results are in line with the current recommendations.

Another important indication for temporary IABP therapy that has emerged over time is hemodynamic support to stabilize patients before, during, or immediately after percutaneous coronary interventions (PCI) or as a bailout measure. As stents, platelet inhibitors, and other additions to the interventional cardiologist’s armamentarium began to emerge in the 1990s, patients who only a few years earlier would have been deemed too high-risk for PCI and referred to surgery began to be treated in the catheterization laboratory. However, the randomized clinical trial BCIS-1 study investigated the use of routine IAB placement before high-risk angioplasty procedures versus IAB for bailout and found that there was no added benefit from routine IAB placement on the combined primary endpoint of death, acute myocardial infarction, cerebrovascular events, and further revascularization at hospital discharge. Even as there is no clear-cut and uniform definition for “high-risk” angioplasty and clinical conditions may differ from patient to patient as new angioplasty technologies emerge and as patient age increases, IAB is still being used for high-risk angioplasty procedure for temporary support in daily clinical practice.

Other indications for IAB therapy include failure to wean from cardiopulmonary bypass, preoperative management of high-risk surgical patients, and management of patients with refractory unstable angina (Table 27.4). These indications represented about half of the IAB usage noted in 5,495 acute MI patients in the Benchmark Registry reported by Stone et al. in 2003. A detailed analysis of IABP usage in the largest series of patients receiving balloon pump support to date (n = 16,909) was published in 2001.

### Complications

Data on 16,909 patients undergoing IABP therapy, collected by the Benchmark Counterpulsation Outcomes Registry (sponsored by Datascop e Corp.) between 1996 and 2000 and published in the Journal of the American College of Cardiology in 2001, showed the incidence of major complications resulting from the use of an IABP to be 2.8%. The incidence of minor complications was 4.2%. Major complications were defined as limb ischemia resulting in a loss of pulse or sensation, or abnormal limb temperature or pallor requiring surgical intervention; severe bleeding requiring transfusion or surgical intervention; and balloon leak and death directly

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**Table 27.3** Contraindications for Intra-Aortic Balloon Pumping

<table>
<thead>
<tr>
<th>Condition</th>
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<tbody>
<tr>
<td>Significant aortic regurgitation</td>
</tr>
<tr>
<td>Abdominal aortic aneurysm</td>
</tr>
<tr>
<td>Aortic dissection</td>
</tr>
<tr>
<td>Uncontrolled septicemia</td>
</tr>
<tr>
<td>Uncontrolled bleeding diathesis</td>
</tr>
<tr>
<td>Severe bilateral peripheral vascular disease uncorrectable by peripheral angioplasty or cross-femoral surgery</td>
</tr>
<tr>
<td>Bilateral femoral–popliteal bypass grafts for severe peripheral vascular disease</td>
</tr>
</tbody>
</table>
Table 27.4 Uses of IABP from the Benchmark Registry

<table>
<thead>
<tr>
<th></th>
<th>Total Population (n = 16,909)</th>
<th>Diagnostic Catheterization Only (n = 1,576)</th>
<th>Catheterization and PCI Only (n = 3,882)</th>
<th>Surgery</th>
<th>No Intervention or Revascularization Noted (n = 1,186)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Support and stabilization (%)</td>
<td>20.6</td>
<td>21.4</td>
<td>54.4</td>
<td>9.7</td>
<td>7.8</td>
</tr>
<tr>
<td>Cardiogenic shock (%)</td>
<td>18.8</td>
<td>33.1</td>
<td>23.7</td>
<td>12.3</td>
<td>29.4</td>
</tr>
<tr>
<td>Weaning from cardiopulmonary bypass (%)</td>
<td>16.1</td>
<td>0.4</td>
<td>0.1</td>
<td>24.9</td>
<td>7.1</td>
</tr>
<tr>
<td>Preop: high-risk CABG (%)</td>
<td>13.0</td>
<td>4.6</td>
<td>0.2</td>
<td>22.1</td>
<td>19</td>
</tr>
<tr>
<td>Refractory unstable angina (%)</td>
<td>12.3</td>
<td>15.3</td>
<td>8.3</td>
<td>15.8</td>
<td>3.0</td>
</tr>
<tr>
<td>Refractory ventricular failure (%)</td>
<td>6.5</td>
<td>9.1</td>
<td>2.5</td>
<td>5.9</td>
<td>12.7</td>
</tr>
<tr>
<td>Mechanical complication owing to AMI (%)</td>
<td>5.5</td>
<td>9.8</td>
<td>7.0</td>
<td>4.2</td>
<td>1.8</td>
</tr>
<tr>
<td>Ischemia related to intractable VA (%)</td>
<td>1.7</td>
<td>1.6</td>
<td>1.5</td>
<td>1.9</td>
<td>1.6</td>
</tr>
<tr>
<td>Cardiac support for high-risk general surgery patients (%)</td>
<td>0.9</td>
<td>2.1</td>
<td>0.2</td>
<td>0.5</td>
<td>1.1</td>
</tr>
<tr>
<td>Other (%)</td>
<td>0.8</td>
<td>0.7</td>
<td>0.2</td>
<td>0.8</td>
<td>2.0</td>
</tr>
<tr>
<td>Intraoperative pulsatile flow (%)</td>
<td>0.4</td>
<td>0.1</td>
<td>0.1</td>
<td>0.7</td>
<td>0.2</td>
</tr>
<tr>
<td>Missing indication (%)</td>
<td>3.3</td>
<td>1.8</td>
<td>1.9</td>
<td>1.2</td>
<td>28.1</td>
</tr>
</tbody>
</table>

AMI, acute myocardial infarction; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; VA, ventricular arrhythmias.


Attributable to IAB catheter insertion or failure. Minor complications included among others limb ischemia (evidenced by a diminished pulse), which resolved after catheter removal, and nonsevere bleeding involving either a minor hematoma or some degree of puncture site oozing. Independent predictors of a major complication were female gender, age (75 years or older), and peripheral vascular disease. IAB-related mortality was 0.5%. Overall complication rates associated with the use of IABP therapy appear to have declined over the course of the last 25 years. The introduction of low-profile 8 French IAB catheters in the late 1990s, no doubt, contributed to this drop. A single-center study of 240 patients receiving IABP treatment between 1985 and 1990 (10 years prior to the first publication of the Benchmark Registry data) showed a 7.5% rate of major complications and an overall complication rate of 13%. Another single-center European study of patients receiving IABP treatment between 1989 and 1996 showed the rates to be 4.7% and 10.4%, respectively. Recently, IABP treatment in the setting of high-risk ST elevation myocardial infarction (STEMI) has also been reported to be associated with an absolute 2% increase in stroke rate. Fuchs et al. also studied 9,662 patients undergoing PCI, the majority of whom presented with unstable angina. The prevalence of stroke was 0.38%;
the strongest predictor for developing stroke in this study was the emergency or prophylactic use of IABP. Despite the significant decline in balloon-related complication rates, however, complications can be serious and require careful peri procedural assessment and monitoring for prevention.

**Concluding Remarks on Intra-Aortic Balloon Pump Therapy**

As noted above, although IABP is considered the standard of care for many conditions requiring hemodynamic support,
there are no randomized studies in any setting to prove that this approach provides clinical benefit, and clinical investigators are increasingly calling into question its utility. This probably is reflected by the development and widespread adoption of IABP prior to the time when the U.S. Food and Drug Administration regulated the medical device industry. For the case of cardiogenic shock, however, it is widely appreciated that the amount of hemodynamic support provided by IABPs is not always sufficient to compensate for the impaired left and/or right ventricular pumping capacity. This has motivated development of alternate approaches to providing short-term (several days) and long-term (weeks, months, or years) circulatory support.

**Device Insertion and Initiation of Support**

Impella 2.5 is inserted using a modified monorail technique under direct fluoroscopic control. Impella uses both a pressure lumen adjacent to the motor and motor current monitoring to give positioning verification to the operator. The device must be put in place under fluoroscopic control to avoid kinking the catheter and compromising the purge lumen; echocardiography can be used as an adjunct to more precisely identify device location. After arterial access is obtained, the 13F peel-away sheath is positioned. After placing a 0.018-inch wire across the aortic valve with the use of a guiding catheter

**Device Description**

The Impella class of devices has a catheter-mounted microaxial flow pump; Impella 2.5 can pump up to 2.5 L/min and Impella 5.0 can pump up to 5.0 L/min. Impella 2.5 has a 9F catheter shaft and a 12F pump head and is placed percutaneously via a 13F femoral arterial sheath using a monorail type insertion platform (Figure 27.3). Impella 5.0 has a 9F catheter shaft with a 21F pump head, which is generally inserted by direct cutdown to the femoral artery. Recently an additional configuration, Impella CP, has been introduced which can pump 3.7 to 4.0 L/min. This configuration also has a 9F catheter shaft but a 14F pump head. Since Impella 2.5 is the percutaneous interventional device currently used by cardiologists, this chapter will focus on this configuration; the principles of operation of Impella 5.0 and Impella CP are the same except that they can provide significantly better hemodynamic support.

The Impella catheter is powered and controlled by a console that allows the user to monitor performance and adjust pump speed. The controlling console is also used to manage a purge system designed to keep the corrosive plasma from entering the motor compartment. Under normal operating conditions and typical arterial pressures, the rotor spins at 51k RPMs and pumps approximately 2.5 L/min throughout the cardiac cycle. Since the precise amount of flow through the pump depends on the pressure gradient between the inlet and outlet, there are slight variations in pump flow with the cyclic variations in ventricular-aortic pressure gradients during the cardiac cycle. Since pumping is continuous, ventricular volume decreases throughout the cardiac cycle (except for the rapid filling phase when the mitral valve opens) so that the pressure-volume loop no longer exhibits the usual isovolumic contraction and relaxation phases (Figure 27.1C); the loop becomes more trapezoidal or triangular than rectangular. As a result of direct pumping of blood from the left ventricle, there is a significant decrease in left ventricular end-diastolic pressure and volume; the ventricle is unloaded. In addition, the width of the pressure-volume loop, which normally equates with stroke volume, no longer reflects the total amount of blood being pumped to the body from the heart with each contraction, since the heart now contributes only partially to the total output. Finally, with an increase in overall cardiac output, there is an increase in aortic pressure, particularly during diastole which improves the pressure gradient of coronary flow.
Figure 27.3 Impella 5.0, Impella CP, and Impella 2.5 (shown on the left) are three models of percutaneously deployable trans-aortic valve ventricle assist devices. Each has a 9F catheter. The pumps heads are 21F, 14F, and 12F, respectively, and they have pumping capacities of approximately 5.0, 4.0, and 2.5 L/minutes, respectively. The principle of operation is the same for each, in that they continuously pump blood from the LV to the aorta. Each has a pigtail at the tip for ease of crossing the aortic valve and for ensuring secure seating of the device tip within the LV chamber as illustrated in the figure on the right.

(usually a 4 to 5F pigtail catheter), the Impella catheter is threaded over the wire into the left ventricle. The inlet area of the catheter should be positioned approximately 4 cm below the aortic valve. Once the device is positioned in the ventricle, the wire is removed and pumping is initiated at the minimum level allowed by the Impella console. Alternatively, the device can be placed passively through the valve, much like a pigtail, without requiring a wire placed first in the left ventricle. At this point, pressure waveforms displayed on the console screen can be utilized to confirm that the device placement is proper and stable. Once proper position is confirmed, pumping speed is typically adjusted to a higher performance level. It is common for Impella to move into the ventricle during the first few minutes of use. It is therefore advisable to wait 5 to 10 minutes before accepting final position. Excessive slack should be removed from the catheter system so that the catheter lies along the “lesser curve” of the aorta thus minimizing the tendency of the catheter to migrate into the LV.

Pump Adjustments
The current generation Automated Impella Controller (AIC) integrates the user interface, infusion pump, and power supply previously provided as separate components, with the previous Mobile Impella Console (MIC). The AIC incorporates user display with a fully automatic purge cassette system and uses a fast and simple on-screen setup allowing for quick support in emergency situations. The AIC monitors the
catheter for alarms and provides real-time catheter position information. The user can select a performance level (P0 to P9) or use the new Auto-Flow feature that allows the catheter to run at the maximum sustained speed while automatically avoiding suction condition. The AIC has an integrated power supply and is certified for transport.

Use During Angiography or in the Percutaneous Coronary Intervention Patient

Impella 2.5 is well suited for use during PCI. As with IABP, diagnostic and interventional procedures are generally performed from the contralateral groin from where Impella 2.5 is inserted. Unlike in IABP, no adjustments to pump settings are required while guide wires or catheters are passed from the groin or arm to the aortic root. Care should be taken to ensure that the device stays in place and does not inadvertently get pushed too far into or withdrawn from the left ventricle. The advantage of using Impella 2.5 during PCI is that the device can maintain the circulation and contribute a proportionally higher amount of total blood flow when the left ventricular function becomes compromised during prolonged occlusions of critical coronary vessels.

Weaning and Device Removal

As with IABP, the rate of weaning depends on the clinical setting. When used to support an uncomplicated PCI procedure, the device can simply be turned off and removed; thus, weaning in this application can be rapid and can take place over a few minutes. When used for treatment of a patient with hemodynamic compromise, the philosophy of weaning is similar to that used in IABP therapy. When clinical signs of sufficient recovery are observed, the pump speed can be reduced (e.g., to half that used to support the patient) and after a sufficient duration of demonstrated stability the device can be turned off and removed. As with the IABP, however, the rate of weaning (both the magnitude of and the duration between pump speed decrements) adopted is at the discretion of the physician and varies with the clinical setting. The Impella performance level should never be P0 while the device is in the left ventricle, as there is an open communication between the ascending aorta and the left ventricle that can result in functional regurgitation into the LV. This is why the device should always be run at P1 or P2 to prevent LV overload.

Complications

Data related to complications with the use of Impella 2.5 derive from studies performed in the United States and Europe. These studies report a low incidence of failure to implant or achieve support as well as a low incidence of complications. The main complications involve groin-related issues, such as hematoma formation, bleeding requiring transfusion, pseudoaneurysm formation, femoral artery occlusion or vascular damage requiring surgical intervention, and infections. Reports of hemolysis are rare, and there has been no evidence of acute or chronic issues relating to the aortic or mitral valve.

Indications and Contraindications

The Impella 2.5 circulatory support system is intended for providing partial circulatory support using an extracorporeal real bypass control unit, for periods up to 6 hours. It is also intended to be used to provide partial circulatory support (for periods up to 6 hours) during procedures not requiring cardiopulmonary bypass. Contraindications to the use of the device include mechanical aortic valve, moderate to severe aortic insufficiency (echocardiographic assessment of aortic insufficiency graded as ≃+2), left ventricular thrombus, and severe peripheral arterial obstructive disease that would preclude Impella 2.5 device placement. Though aortic stenosis was a contraindication in the early Impella experience, recent experience using Impella 2.5 during aortic balloon valvuloplasty procedures has shown that the device can be placed easily across stenotic valves with valve areas as small as 0.4 cm². However, operators should be cautioned that placement across severely calcified valves is not without risk of thromboembolic complications.

Clinical Results

The most common use of Impella 2.5 in clinical practice is in high-risk PCI (56% of general use), followed by in acute cardiogenic shock (25% of general use). Other clinical situations include prophylactic support during VT ablation procedures and balloon-assisted valvuloplasty procedures, cardiomyopathy with acute decompensation, postcardiotomy shock, off-pump CABG, and transplant rejection. The published literature regarding studies of Impella devices primarily include applications in high-risk percutaneous coronary interventions (PCI), acute myocardial infarction, and cardiogenic shock.

High-Risk Percutaneous Coronary Intervention

The feasibility of using Impella 2.5 in high-risk PCI was first demonstrated in the PROTECT I study. This was a prospective, multicenter study that included 20 patients. These patients were considered high-risk because of poor left ventricular function with ejection fraction ≤35%, and the intervention was being performed on an unprotected left main coronary artery or the last patent coronary conduit. The mean
duration of circulatory support was 1.7 ± 0.6 hours (range: 0.41 to 2.5 hours). Mean pump flow during PCI was 2.2 ± 0.3 L/min. None of the patients developed hemodynamic compromise during PCI, which was the primary efficacy objective of the study. The incidence of major adverse cardiac events at 30 days (which was the primary safety endpoint) was 20%: two patients had a periprocedural myocardial infarction and two patients died (at days 12 and 14, respectively).

Similar findings were obtained in the Europella Registry\[! visible text\] which was a retrospective multicenter registry of the use of Impella 2.5 that included 144 consecutive patients who underwent high-risk PCI. In this study, a PCI was considered high-risk if the patient had left main disease (53%), last remaining vessel disease (17%), multivessel coronary artery disease (81%), or low LV ejection fraction (35%). Mean score according to the European System for Cardiac Operative Risk Evaluation was 8.2 ± 3.4, and 43% of the patients were refused for coronary artery bypass grafting. Mortality at 30 days was 5.5%. Rates of myocardial infarction, stroke, bleeding requiring transfusion/surgery, and vascular complications at 30 days were 0%, 0.7%, 6.2%, and 4.0%, respectively.

Similarly, the USpella Registry study (O'Neill et al., Catheterization and Cardiovascular Intervention, in press) reported results from 175 consecutive high-risk PCI procedures supported with Impella 2.5. Angiographic revascularization was successful in 99% of patients overall and in 90% of those with multivessel revascularization, resulting in a reduction of the mean SYNTAX score post-PCI from 36 ± 15 to 18 ± 15 (P < 0.0001) and an improvement of the ejection fraction from 31 ± 15% to 36 ± 14% (P < 0.0001). At 30-day follow-up, the rate of MACE was 8%, and survival rate was 96% at 30 days, 91% at 6 months, and 88% at 1 year.

The results of these registry studies provided preliminary evidence of the safety and potential hemodynamic and clinical benefits of Impella 2.5 use during high-risk PCI. These studies set the stage for the prospective, randomized PROTECT II study of high-risk PCI in which patients were randomized to prophylactic use of IABP or Impella 2.5.\[! visible text\] The study was designed to randomize 654 patients at up to 150 sites. The primary endpoint was a composite of major adverse events (MAE) at 30 days including death, myocardial infarction, stroke, any repeat revascularization post index procedure, need for cardiac or vascular operation, acute renal dysfunction, increase in aortic insufficiency by more than one grade, hypotension, CPR or ventricular arrhythmia requiring cardioversion, and angiographic failure to dilate the target vessel(s). The study’s primary endpoint follow-up was assessed at 90 days. After review of the data at the interim mark (first 327 patients), the Data Safety Monitoring Board recommended termination of the study owing to futility of the 30-day primary analysis. At the time of the recommendation, the study had reached 69% of the planned enrollment (n = 447). Although there was no significant difference in outcomes at 30 days, the prespecified 90-day data showed a significant reduction in major adverse events in favor of Impella (P = 0.03). Thus, PROTECT II was terminated early on assumptions based on the first-half data. The analysis of the full cohort provides more insight into the study and suggests similar safety profiles with positive, sustainable-over-time outcomes for the Impella device over IABP. As of the date of this writing, the results have not been fully published, and it is expected that new and important information will be forthcoming from this trial.

**Acute Myocardial Infarction**

The use of Impella 2.5 to improve clinical outcomes in AMI with shock has been investigated in two clinical studies. The first study compared the hemodynamic effectiveness of Impella 2.5 to that of the IABP.\[! visible text\] This was a prospective, randomized study that included results from 25 patients with cardiogenic shock: 13 were randomized to IABP and 12 to Impella 2.5. Cardiac Index (CI) after 30 minutes (the primary efficacy endpoint) increased in patients with Impella 2.5 by 0.49 ± 0.46 L/min/m² which was significantly larger than the 0.11 ± 0.31 L/min/m² change achieved with the IABP (P = 0.02). Although not powered to demonstrate mortality benefit, the overall 30-day mortality was 46% in both groups. As with prior studies,\[! visible text\] demonstration of hemodynamic benefits of mechanical circulatory support in cardiogenic shock has not yet been shown to translate readily to a mortality benefit. Demonstration of mortality benefits will require large numbers of patients with long-term follow-up.

Another potentially important application of Impella 2.5 in AMI is for LV unloading to reduce infarct size. Unloading the LV during AMI reduces oxygen consumption and, along with restoration of blood flow by PCI, provides favorable metabolic conditions for myocardial recovery. The rationale for this application is grounded in prior preclinical studies comparing infarct size in a sheep model of AMI treated with either an IABP or Impella 2.5.\[! visible text\] Figure 27.4A compares the effects of an IABP and Impella 2.5 on ventricular and aortic pressures, ventricular volumes, and left ventricular pressure-volume loops.\[! visible text\] As discussed above and consistent with the concepts outlined in Figure 27.1, the IABP enhances blood pressure during diastole and reduces systolic ventricular pressure, but does not significantly influence ventricular volumes. In contrast, Impella 2.5 markedly reduces ventricular volumes and preload, and reduces peak ventricular pressure while increasing aortic systolic and diastolic pressures. The marked difference in the hemodynamic effects of these two types of devices is shown diagrammatically in the pressure–volume loops in Figure 27.4B. As compared with the subtle effects of the IABP, the percutaneous assist device markedly unloads the heart (decreased preload and afterload volumes and pressures), reduces the work of the LV (area inside the loop), and thereby decreases myocardial oxygen consumption.\[! visible text\] Indeed, use of this device in an experimental model of acute coronary ligation has resulted in marked reduction in myocardial infarct size.\[! visible text\] The feasibility of using Impella 2.5 for this purpose has been tested in a clinical study.\[! visible text\] This was a single-center,
Figure 27.4  A. Aortic and left ventricle (LV) pressure (top), LV volume (center), and aortic flow (bottom) measured in an animal model prior to and during support with either an intra-aortic balloon pump or an Impella 5.0 system. IABP reduces systolic aortic and LV pressures but increases aortic pressure during diastole, thus improving coronary blood flow and oxygen supply. However, there is no significant effect on ventricular load. The continuous-flow Impella system reduces systolic pressure and increases diastolic pressure, though to a lesser extent. However, LV volume is markedly reduced. B. Left ventricular pressure–volume loops corresponding to the tracing in panel A. The loops demonstrate the profound pressure and volume unloading provided by the continuous-flow system, thus markedly reducing pressure–volume area and consequently reducing oxygen demands of the LV. This contrasts with the effects of the IABP, which, on the pressure–volume diagram, provides mainly a relatively small effect on peak systolic pressure and therefore has relatively little influence on oxygen demand. (Tracing provided courtesy of Dr. FH van der Veen, PhD, Department of Cardiothoracic Surgery, Maastricht, The Netherlands.)
controlled study involving 20 consecutive patients with large anterior STEMI. Immediately following PCI, 10 patients were assigned to 3 days' support with Impella 2.5 and a concurrent group of 10 patients were assigned to standard care (which could include an IABP). All patients successfully underwent primary PCI. Placement of the Impella pump was successful in all cases, and the device did not induce or increase aortic valve regurgitation. Mean duration of follow-up of these patients was 2.9 ± 0.6 years in the Impella group and 3.0 ± 0.3 years in the control group. The relative increase in left ventricular ejection fraction (LVEF) from baseline was 23.6 ± 8.9% in the Impella 2.5 group, as compared to only 6.7 ± 7.0% in the control group \((P = 0.008)\). These preliminary data suggest that 3 days' support with Impella 2.5 is safe and appears to enhance myocardial recovery. If confirmed in prospective studies, this approach could have a significant impact on the management of AMI in reducing the subsequent development of heart failure and reducing long-term mortality.

As noted above, the Impella platform includes larger devices capable of pumping 5 L/min (Impella 5.0 and Impella LD). Impella 5.0 can be placed via a cutdown to the femoral artery, and Impella LD can be placed directly into the proximal aorta via an end-to-side anastomosed conduit. Because of the nature of their insertion and removal, these devices are mainly used by cardiac surgeons. However, they provide significantly more flow than provided by Impella 2.5 and can be effective in the setting of more severe cardiogenic shock. For some instances of severe cardiogenic shock, upgrading Impella therapy from 2.5 to 5.0 support may be an option as reported recently.\(^4^0\) The RECOVER I study (Griffith et al., \textit{J Thorac Cardiovasc Surg}, in press) was a multicenter study of these devices in 16 patients with postcardiotomy cardiogenic shock. The primary safety endpoint was the frequency of major adverse events (death, stroke) at 30 days. The primary efficacy endpoint was survival of the patient for implementation of the next therapy, which included recovery at 30 days after device removal and bridge-to-other-therapy. Hemodynamics improved immediately after device initiation, with cardiac index increasing from a mean of 1.65 to 2.7 L/min/m\(^2\) \((P = 0.0001)\), mean arterial pressure increasing from 71.4 to 83.1 mmHg \((P = 0.01)\), and pulmonary artery diastolic pressure decreasing from 28.0 to 19.8 mmHg \((P < 0.0001)\). The pump provided an average of 4.0 ± 0.6 L/min of flow for an average duration of 3.7 ± 2.9 days (range: 1.7 to 12.6). A primary safety endpoint occurred in two patients (one stroke and one death). For the primary efficacy endpoint, recovery of native heart function was obtained in 93% of the patients discharged, with bridge-to-other-therapy in 7%. Survival to 30 days, 3 months, and 1 year was 94%, 81%, and 75%, respectively. These data show that the use of Impella 5.0 or Impella LD provides rapid improvements in hemodynamics in patients presenting with postcardiotomy cardiogenic shock.

The most recent innovation with the Impella platform that deserves mention is Impella RP, which is a device designed for right ventricular support. Its pump head is 21F, and the catheter is 11F. It is introduced via the femoral vein and is shaped to conform to the path from the inferior vena cava, through the tricuspid valve, the right ventricle, the pulmonary outflow track, and into the pulmonary artery. As compared to the devices used for LV support, the pump is mounted in the opposite direction, but otherwise operates according to the same principles, with a maximum flow rate of approximately 4.7 L/min. This device is currently under investigation and, at the time of this writing, is not yet CE Marked or approved by the FDA.

### EXTRACORPOREAL LEFT ATRIAL-TO-ARTERIAL PUMP (TANDEMHEART)

Another device currently approved for short-term (6 hours) support is the TandemHeart percutaneous ventricular assist device (Cardiac Assist, Pittsburgh PA; Figure 27.5). This device consists of an extracorporeal, nonpulsatile centrifugal (continuous flow) pump that withdraws blood from the left atrium (via a 21F trans-septal cannula), introduced via the...
femoral vein. Blood is then pumped by the device (typically at approximately 3.5 to 5.0 L/min) and delivered into one or both femoral arteries through 15F to 18F cannulae. A This device thus functions in parallel with the left ventricle in pumping blood from the left atrium to the aorta. Owing to the nature of centrifugal, nonpulsatile flow of blood, the arterial line tracing may be “flat” with no evidence of the aortic valve opening or ejection from the left ventricle if the flow rate exceeds that of the native heart. The degree of pulsatility seen on the arterial waveform will therefore be mainly dependent on the amount of residual blood flow from the native left ventricle.

Since TandemHeart pumps blood from the left atrium, there are significant reductions in left atrial pressure and, therefore, reductions in left ventricular end-diastolic pressure and volume (Figure 27.1C). The increase in total flow is accompanied by increases in arterial pressure, both during systole and more significantly during diastole, because of the continuous, asynchronous pumping throughout the cardiac cycle. With the decrease in preload and the increase in afterload pressure, intrinsic cardiac output decreases, and this is reflected as a decrease in the width of the pressure–volume loop.

**Insertion Technique**

The TandemHeart system utilizes a 21F trans-septal cannula inserted percutaneously through the femoral vein to the inferior vena cava, into the right atrium, and across the atrial septum into the left atrium. Blood is withdrawn via this cannula from the left atrium by the pump. The trans-septal puncture can be made by various means, including via a Brockenbrough needle after positioning its tip in the fossa ovalis and via a radiofrequency puncture system. After puncture, a guide wire is inserted into the left atrium and a multistage dilator is used to dilate the opening from right atrium into left atrium until the trans-septal cannula can be slid into the left atrium. The cannula is then fixed by placing a suture at the femoral access site. Further fixation is provided by the curvature in the cannula which assists in securing lodgment of the cannula tip. The trans-septal cannula is backfilled with blood and clamped on the clear portion near the tubing connector. The placement of the trans-septal cannula should be verified by fluoroscopy or, when inserted in the operating room, by direct visualization.

**Initiation of Support**

The trans-septal cannula and arterial cannulae are attached to the pump’s inflow and outflow ports, respectively. The arterial cannula is inserted, backfilled and clamped, and the pump is primed with saline. Using wet-to-wet connection, the tubing and pump are connected and de-aired. Alternatively, in view of the low volume required for priming, the pump is first connected to the arterial cannula and primed with blood, and a wet-to-wet connection is then made to the left atrial cannula. After ensuring that all air is removed from the system, the clamps are released and the “start” button on the controller is pressed to initiate pumping.

**Pump Adjustments**

The only parameter that can be controlled on the system is pump speed, and change of speed will cause a change of flow as indicated in the controller display screen. Though maximum support is often desirable, there are conditions that result in reduced supply of blood to the left atrium (and therefore reduced left atrial pressure) that necessitate a reduction in pump speed. Examples of such conditions include hypovolemia; reduced right ventricular output (e.g., primary RV dysfunction as can occur in dilated cardiomyopathy or RV infarction); obstructed right heart outflow (e.g., saddle pulmonary embolism); primary or secondary lung diseases with increased pulmonary vascular resistance; cardiac tamponade; and arrhythmias that compromise right ventricular output. If reduced left atrial filling is traced to one of these conditions, pump speed can be reduced until that condition is corrected, with the understanding that optimal pump performance occurs with left atrial pressure (LAP) or pulmonary capillary wedge pressure (PCWP) in the range between 10 and 20 mmHg. Specific signs of inadequate blood supply to the pump from the left atrium include unusual vibrations of the trans-septal cannula or the pump, low infusion pressures or infusion pressure alarms, and kinking of the trans-septal cannula. If patient factors can be excluded, another factor to consider in low-flow conditions is inflow or outflow cannula kinks, especially at the skin exit sites. The general practice is to adjust the pump speed to a level that still allows a minimum of pulsatile flow across the native aortic valve in order to prevent stasis of blood in the left ventricle, which could result in thrombus formation and subsequent embolization.

**Management During Support**

Patients on the TandemHeart system typically undergo standard ICU monitoring, including EKG and measurement of arterial blood pressure, pulmonary artery pressures (PAP), pulmonary capillary wedge pressure (PCWP), central venous pressures (CVP), and cardiac output (CO). Arterial and mixed venous blood gases and other laboratory values are monitored according to hospital policy.

The flow displayed on the controller display panel is a measured value if the controller is used in conjunction with the TandemHeart flow sensor or is an estimated value based on parameters measured in the pump. Since the TandemHeart system pumps in parallel to the native heart, the total cardiac output is the summation of TandemHeart flow and native heart output. Total flow (the sum of TandemHeart and native heart flows) can be measured as usual by standard thermodilution methodology.
The TandemHeart system requires that the patient be anticoagulated. It is recommended that the ACT should be 400 seconds for insertion of the device but only after puncture of the septum in the catheterization lab or operating room. The ACT should be > 200 seconds during the support period. If ACT is unavailable, PTT can be used. During support, PTT should be maintained between 65 and 80 seconds (2½ to 3 times normal range).

### Weaning and Device Removal

Initiation of weaning is accomplished by reducing pump speed. Typically, flow rate can initially be reduced by approximately 50% for approximately 1 hour; however, physician discretion in the rate of speed reduction should always prevail. In any event, however, flow rate should never be reduced to <1 L/min because of the increased risk of pump thrombosis and stoppage. If the patient tolerates weaning, the device can be removed. Device removal can be accomplished at the bedside, in the catheterization lab, or in the operating room at the physician’s discretion. The femoral access site is usually managed by compression. Management of the arterial site depends on the caliber of cannulae used and may involve manual compression, use of preclose techniques, or surgical repair. In any event, management of anticoagulation must be considered and is similar to that described above for IABP removal.

### Complications

The main complications associated with use of the TandemHeart system include bleeding, complications associated with trans-septal puncture (e.g., accidental puncture of aorta, myocardial perforation, arrhythmias), dislocation of the trans-septal cannula, stroke, vascular access complications, dislocation of the arterial cannulae, leg ischemia, and hemolysis. Bleeding is a potential risk for all circulatory support devices, particularly when these devices are used to support patients with postcardiomyotomy shock, or after revascularization procedures. These risks are increased in the presence of prolonged anticoagulation which is required during the period of support. ACT values of 200 seconds are typically adequate for proper pump operation. Antiplatelet therapy following coronary interventions may also contribute to bleeding complications. Minimized manipulation of cannulae at the insertion sites reduces risk of bleeding as well as vascular complications.

The trans-septal cannula is positioned across the atrial septum and, once in place, should be promptly secured to the skin so as not to allow migration. Signs of cannula dislocation include change in color of blood in the pump from bright red to dark red (indicating that desaturated venous blood is being pumped), decreased arterial oxygen saturation, or an echocardiogram or chest x-ray indicating dislocation.

Development of leg ischemia is a potential hazard for all percutaneous vascular access procedures, and appropriate arterial cannula size for a patient should be selected prior to initiation of support. Distal flow cannulation is also available for use in situations requiring additional flow to be delivered distally. Usual measures should be taken for early detection of an impending problem, such as monitoring pulses (using Doppler if necessary), temperature, and capillary refill to check for changes in peripheral flow. If distal leg ischemia develops while a patient is on TandemHeart system support, there are several measures that can be considered to reestablish perfusion to the lower extremity. A single large arterial cannula can be replaced with one or even two smaller-bore cannulae; for the latter, a “Y” connector can be used on the outflow tubing. Finally, an additional small-gauge antegrade catheter can be inserted to directly perfuse the distal limb using the side port of the arterial cannula. The practice of inserting an antegrade sheath distally to the arterial cannula and connected via the side arm to the arterial cannula can also be instituted as a preventive measure at the time of initial arterial access. If distal perfusion cannot be established by any of these means, consideration should be given to surgical intervention to provide distal perfusion or removal of the TandemHeart system. Dislocation of the arterial cannula is another extremely rare complication, which unfortunately can be fatal as it is associated not only with bleeding at the arterial site but also with bleeding from the pump if the pump is not shut off immediately. Right-to-left shunting following removal of the left atrial cannula resulting in systemic desaturation, and requiring percutaneous closure of the iatrogenic atrial septal defect, has also been described.44

### Indications and Contraindications

The TandemHeart system is generally indicated to provide temporary circulatory support in conditions such as cardiogenic shock in the setting of acute myocardial infarction or decompensated chronic heart failure, pulmonary edema, and postcardiomyotomy shock. It has been used successfully as a bridge to recovery or as a bridge to a bridge in patients with cardiogenic shock secondary to myocardial infarction, acute myocarditis, or end-stage cardiomyopathy. The system is generally contraindicated for patients with any of the following: primary right heart failure, high-grade aortic valve regurgitation, or any condition that prevents extracorporeal blood circulation. As with any extracorporeal support system, caution should be exercised in cases of mitral or aortic mechanical heart valves.

### Clinical Results

Early studies showed that this device can improve hemodynamics in patients with cardiogenic shock caused by myocardial infarction and other causes. Studies also showed a reduction in serum lactate levels, an indication that there is improved tissue perfusion and oxygenation, and thus reversal of the cardiogenic shock state.45 In a more recent study, 41 patients with cardiogenic shock owing to acute myocardial infarction failing medical treatment were randomized...
to treatment with either an IABP or the TandemHeart assist device. In both groups, patients were supported for an average of approximately 3.5 days. The IABP had almost no effect on hemodynamics, but the TandemHeart device significantly increased cardiac output and blood pressure while significantly decreasing pulmonary capillary wedge pressure and serum lactate. Despite these clear improvements in multiple clinically important parameters, however, short-term (i.e., death during support) and 30-day mortality rates were comparable: approximately 45% and approximately 43%, respectively, in both groups. Also, as compared with IABP, use of the TandemHeart device was associated with a higher incidence of certain adverse effects (such as lower limb ischemia and bleeding); however, none of these adverse events appeared to contribute importantly to mortality.

This improvement of hemodynamic conditions without clear improvement of survival deserves further comment. As Hochman has suggested, reversal of the hemodynamic derangements of cardiogenic shock may not address all the critical underlying pathophysiologic abnormalities. Other abnormalities, such as elevated inflammatory cytokines and elevated inducible nitric oxide synthase (iNOS), with consequent increased levels of NO and peroxynitrite, could contribute importantly to morbidity and mortality in cardiogenic shock and do not appear to be reversed with restoration of a more normal hemodynamic state. This suggests that addition of other treatments in combination with effective hemodynamic support may yield better results.

Another factor that should be taken into account is the experience with the device used. It is clear that TandemHeart improves cardiac output but can be associated with more complications than IABP, and it has the added complexity of requiring a trans-septal approach. This could impede easy world-wide adoption. However, in experienced hands, TandemHeart has been shown to be an excellent tool. Kar et al. reported their 5-year experience, including a cohort of 117 severe shock patients treated with TandemHeart with a 30-day mortality rate of 40%.

The hemodynamic effects of TandemHeart have been studied in patients undergoing high-risk PCI, and several small studies have addressed the clinical efficacy of TandemHeart in high-risk patients undergoing PCI. In a single-center report of 68 patients undergoing high-risk PCI using either TandemHeart or Impella Recover 2.5, success rates (>90%) and vascular complications (7%) were similar. These findings are acknowledged in the 2011 guidelines for PCI.

Percutaneous cardiopulmonary support (CPS) is the final form of mechanical circulatory assist to be discussed here, which has been available for many years (Figure 27.6). It is analogous to the heart–lung machine used during open-heart surgery in that a pump withdraws deoxygenated blood from a venous cannula and pumps it through a heat exchanger, a membrane oxygenator, and, finally, a femorally placed arterial cannula back to the aorta. This form of support is also referred to as ECMO. Both femoral and arterial cannulae can be inserted percutaneously. ECMO technology-based devices can completely support...
the circulation and if necessary also oxygenation. As such it is the only percutaneous circulatory assist device capable of oxygenation in addition to circulatory support well beyond 4.5 L/min. Although ECMO can provide large hemodynamic support, it also increases the afterload and preload on the left ventricle (Figure 27.1E), increasing myocardial oxygen demand and potentially impeding myocardial recovery.

These devices are also indicated for use up to 6 hours, after which platelet aggregation, hemolysis, bleeding, and increased capillary permeability with plasma loss may become problematic. However, much longer support times have been reported.

### Insertion Technique and Support

ECMO preparation requires a perfusionist to assemble the circuit and it takes around 10 to 15 minutes to assemble. Whereas the earlier ECMO systems required a surgical approach, today, with current devices, percutaneous cannulation of the femoral artery and vein is quickly achieved, using specific perfusion cannulas. One cannula is advanced to the aorto-iliac junction and the venous cannula is positioned in the right atrium. During true bypass for cardiac surgery full heparinization is required, but for ECMO usually an activated clotting time of 150 to 180 seconds is sufficient to prevent device-related clotting. One important downside of veno-arterial ECMO is that, whereas all other devices unload the ventricle, ECMO in fact can overload the left ventricle and measures may be necessary to actively unload the ventricle (Figure 27.1E). Similar to the systemic hemodynamic changes that occur with TandemHeart, the increase in afterload secondary to perfusion in the arterial system can lead to loss of pulsatile flow across the aortic valve. Despite the withdrawal of unoxygenated blood from the venous circulation, there is still blood return to the left ventricle via the bronchial veins and the pulmonary veins. This blood return can lead to progressive left ventricular distension and to acute increase in pulmonary capillary wedge pressure resulting in the development of pulmonary edema and occasionally pulmonary hemorrhages. Thus, as ECMO tends to overload the left ventricle, it is important to continue medical therapy that increases cardiac contractility in order to prevent left ventricular dilatation. In addition, left ventricular venting with a trans-septal or apical left ventricular vent or with balloon atrial septostomy might be required.²⁴,³⁵

### Management and Complications During Support

The use of ECMO generally requires a multidisciplinary team of perfusionists, nurses, surgeons, and cardiologists and close monitoring of various parameters including arterial blood pressure, pulmonary artery pressures (PAP), pulmonary capillary wedge pressure (PCWP), central venous pressures (CVP), and cardiac output. Complications associated with ECMO use are largely similar to those seen with other devices⁵⁶,⁵⁷ with the marked difference that prolonged support tends to be associated with more systemic inflammatory response in addition to pulmonary hypertension, overloading of the left ventricle, and rarely pulmonary hemorrhages.

### Clinical Results

CPS and ECMO have been used in the settings of postcardiotomy syndrome,⁵⁸ cardiac arrest, cardiogenic shock,⁵⁹ and high-risk PCI. In the latter application, it has been used both prophylactically (i.e., inserted electively prior to PCI) and in a standby mode in which CPS equipment and personnel are available in the cardiac catheterization laboratory should hemodynamic collapse develop. When inserted following development of hemodynamic collapse, the time delay prior to institution of hemodynamic support appears to be associated with a detrimental impact on survival.⁶⁰-⁶⁴ Accordingly, the application of CPS is most effective when used in the catheterization laboratory that is already prepared for insertion and technical support,⁶¹ and use in other settings is rare.

In addition, as interventional catheter techniques have advanced, the necessity for prophylactic support with a device that provides the magnitude of support provided by CPS has diminished. This reduction in use is substantiated by a retrospective comparison of outcomes in patients undergoing high-risk angioplasty who either received prophylactic CPS or were part of a control group for whom CPS was readily available (standby group). This study showed a need for use of CPS in <10% of patients in the standby group with comparable procedural success in both groups, but at higher rate of femoral-access complications and the requirement for transfusion in the prophylactic group.⁶²

An interesting development in this field has been the creation of “shock teams” with tertiary care centers. These teams travel, on demand, to community hospitals and provide means of supporting patients during transport back to the tertiary center. Some reports of using ECMO systems for this purpose have been published.⁶⁵,⁶⁶

Thus, in the current interventional era, the full hemodynamic support provided by CPS is rarely necessary in the cardiac patient, and the continuous technical backup required for operation of the CPS device and availability of increasingly simpler devices are major impediments to widespread use. Nevertheless, the European guidelines⁶⁷ clearly recommend ECMO implantation in patients who fail IAB therapy. This recommendation is not supported by any clinical evidence, and further clinical studies are needed before such recommendations will be followed in the clinical arena.
Percutaneous Ventricular Support as a Bridge to Recovery or as a Bridge to a Bridge

The initial experience with the use of ECMO as a bridge to heart transplant was extremely negative due to the high complication rates associated with prolonged ECMO support in patients with circulatory failure, in contrast to the relatively good outcomes with prolonged support in patients with pure pulmonary failure. The introduction of implantable left ventricular assist devices (LVAD) has changed the paradigm. As of today, percutaneous left ventricular assist devices have been used successfully as a bridge to LVAD in patients with cardiogenic shock, end-stage cardiomyopathy or acute myocarditis associated with multisystem organ failure, and who are not deemed initially to be LVAD candidates. Temporary use of percutaneous support can stabilize the patient, allow some organ recovery (particularly with regard to renal function and liver function), and “bridge” the patient to LVAD. This shift in paradigm is leading to the new concept of “centers for circulatory support,” which can be defined as centers that can tailor support to different types of conditions and bridge patients to recovery, to LVAD as destination therapy, and to LVAD as bridge to transplant.

Concluding Remarks

Mechanical support devices are increasingly used for high-risk PCI and cardiogenic shock–like conditions. The IAB is still the most widely used support device, despite lack of evidence for its utility in any clinical setting. The perceived benefits from other more potent devices need to be supported by sound clinical evidence before widespread adoption. One thing that has been learned, especially in the setting of cardiogenic shock, is that more flow does not necessarily equate with improved survival; clearly, other factors need to be considered. An overview of current US and European recommendations for usage of the discussed devices are summarized in Table 27.6. It is anticipated that these devices will continue to evolve and, perhaps more importantly, that new studies will address the long-standing question of whether and how these devices can be used most effectively to reduce mortality in cardiogenic shock.

Table 27.6 Guideline Recommendations of Mechanical Assist Devices

<table>
<thead>
<tr>
<th>Indication</th>
<th>Assist Device</th>
<th>ESC/EACT Guidelines</th>
<th>ACCF/AHA/SCAI Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiogenic shock</td>
<td>IAB</td>
<td>Class IIb [Level of Evidence B]</td>
<td>The use of intra-aortic balloon pump (IABP) counterpulsation can be useful for patients with cardiogenic shock after STEMI who do not quickly stabilize with pharmacological therapy.</td>
</tr>
<tr>
<td>Other devices</td>
<td>IAB</td>
<td>Class IIb [Level of Evidence C]</td>
<td>Alternative LV assist devices for circulatory support may be considered in patients with refractory cardiogenic shock.</td>
</tr>
<tr>
<td>High-risk PCI</td>
<td>IAB</td>
<td>No recommendation</td>
<td>Class IIb [Level of Evidence C]</td>
</tr>
<tr>
<td>Other devices</td>
<td>No recommendation</td>
<td>No recommendation</td>
<td>Class IIb [Level of Evidence C]</td>
</tr>
</tbody>
</table>

(Continued)
### Table 27.6 Guideline Recommendations of Mechanical Assist Devices (Continued)

<table>
<thead>
<tr>
<th>Indication</th>
<th>Assist Device</th>
<th>ESC/EACT Guidelines (^6^7)</th>
<th>ACCF/AHA/SCAI Guidelines (^5^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unstable Angina/ NSTEMI</td>
<td>IABP</td>
<td>Class I</td>
<td>Class IIa</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[Level of Evidence C]</td>
<td>[Level of Evidence C]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IABP insertion is recommended</td>
<td>Intra-aortic balloon pump</td>
</tr>
<tr>
<td></td>
<td></td>
<td>in patients with haemodynamic instability (particularly those in cardiogenic shock and with mechanical complications).</td>
<td>counterpulsation is reasonable in UA/NSTEMI patients for severe ischemia that is continuing or recurs frequently despite intensive medical therapy, for hemodynamic instability in patients before or after coronary angiography, and for mechanical complications of myocardial infarction.</td>
</tr>
<tr>
<td>Other devices</td>
<td>Class III</td>
<td>Routine use of percutaneous centrifugal pumps is not recommended.</td>
<td>No recommendation</td>
</tr>
<tr>
<td></td>
<td>[Level of Evidence B]</td>
<td></td>
<td>No recommendation</td>
</tr>
<tr>
<td>CABG</td>
<td>IABP</td>
<td>No recommendation</td>
<td>Class Ila</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If repeat PCI fails to abort evolving significant MI, immediate CABG is indicated.</td>
<td>The use of mechanical circulatory support is reasonable in patients with STEMI who are hemodynamically unstable and require urgent CABG.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>When severe instability is present, IABP should be inserted prior to emergency revascularisation.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cardiopulmonary assistance may be considered if the patient does not stabilise prior to emergency CABG.</td>
<td></td>
</tr>
<tr>
<td>Other devices</td>
<td>No recommendation</td>
<td>No recommendation</td>
<td>Class Ila</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No recommendation</td>
<td>[Level of Evidence C]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>In the absence of severe, symptomatic aorto-iliofemoral occlusive disease or peripheral artery disease, the insertion of an intra-aortic balloon is reasonable to reduce mortality rate in CABG patients who are considered to be at high risk (e.g., those who are undergoing reoperation or have LVEF &lt;30% or left main CAD).</td>
</tr>
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</tbody>
</table>

Other devices currently include Impella, TandemHeart and ECMO. Abbreviations: LV = left ventricular, PCI = percutaneous coronary intervention, UA = unstable angina, NSTEMI = non ST-segment elevation myocardial infarction, CABG = coronary artery bypass graft, LVEF = left ventricular ejection fraction, CAD = coronary artery disease, STEMI = ST-segment elevation myocardial infarction, ESC = European Society of Cardiology, EACTS = European Association for Cardio-Thoracic Surgery, ACCF = American College of Cardiology Foundation, AHA = American Heart Association, SCAI = Society for Cardiac Angiography and Interventions.
REFERENCES


Dotter and Judkins\(^1\) were the first to propose the concept of transluminal angioplasty—enlargement of the lumen of a stenotic vessel by a catheter—technique in 1964. Their technique used a spring-coil guidewire over which a series of progressively larger rigid dilators were advanced to dilate the atherosclerotic arterial stenosis. While the Dotter technique proved effective in peripheral arteries, the need to insert large-caliber rigid dilators through the arterial puncture (and the high shear forces applied by the dilators as they crossed the atherosclerotic lesion) ultimately restricted its clinical application. Gruentzig's pioneering work in 1974\(^2\) replaced the rigid dilators with an inflatable nonelastomeric balloon mounted on a comparatively smaller catheter shaft which could be introduced percutaneously, advanced across a vascular stenosis in its smaller (collapsed) state, and then inflated with sufficient force to enlarge the stenotic lumen. Although others had speculated about the possibility, Gruentzig was the first to refine balloon angioplasty into a usable clinical tool, through a series of experiments in animals, cadavers, peripheral arteries, and the coronary arteries of patients undergoing bypass surgery. This culminated in the first percutaneous transluminal coronary angioplasty (PTCA) of a stenotic coronary artery in a conscious human (September 16, 1977)\(^3\).

Balloon angioplasty remained the only catheter-based revascularization technique in widespread use until the mid-1990s, when other modalities including atherectomy and stents (see Chapters 29 and 31) were introduced. Accordingly, the technique is now more commonly referred to as percutaneous coronary intervention (PCI). This chapter will review the basic equipment, techniques, and results of coronary angioplasty as a historical and conceptual foundation for the entire field of catheter-based PCI.

**HISTORY**

Gruentzig's new technique of balloon angioplasty was initially met with a great deal of skepticism by many cardiologists, but a small group around the world recognized its great potential.\(^4\) In 1979, these early adopters met to form a registry of all coronary angioplasty cases worldwide under the sponsorship...
of the National Heart, Lung, and Blood Institute (NHLBI) which had enrolled 3,000 cases by 1981. Over time, progressive improvements in equipment and technique have produced dramatic growth in PTCA and transformed it into the dominant form of coronary revascularization (Figure 28.1). In 2009, approximately 596,000 PCI (in-patient) procedures were performed in the United States; also it is one of the most common procedures used worldwide.

Over the past 15 years or so, the role of balloon dilation has become much less prominent as a stand-alone treatment. In current practice, it serves predominantly as an adjunctive therapy for preparing (i.e., predilating) or optimizing (i.e., postdilating) stent placement. Despite the fact that PCI is being performed in increasingly more complex lesions and patients, the advent of the stents and other new interventional devices, as well as adjunctive antithrombotic pharmacology (see Chapter 5), has improved the procedural success rate of PCI to approximately 95%, the procedural mortality to approximately 1%, and the emergency bypass rate to <0.5% among an unselected cohort.

### Equipment

A coronary angioplasty system consists of three basic components (Figure 28.2): (a) a guiding catheter, which provides stable access to the coronary ostium, a route for contrast administration, and a conduit for the advancement of the equipment; (b) a guidewire that can be passed through the guiding catheter, across the target lesion into the distal coronary vasculature to provide a rail over which therapeutic devices can be advanced; and (c) a balloon dilatation catheter filled with contrast medium.

### Guiding Catheters

The original guiding catheters were thick-walled 10F- or 11F–outer diameter tubular structures that had small lumens, minimal torque control, and traumatic edges. In contrast, current guiding catheter designs more closely emulate the performance of diagnostic coronary angiographic catheters. To allow passage of therapeutic instruments, however, guiding catheters must have a lumen diameter at least twice that of a typical diagnostic catheter (e.g., 0.076 inch [2 mm] versus 0.038 inch [1 mm]). To achieve this lumen in a catheter of outer diameter as small as 6F, the catheter walls must be very thin (<0.12 mm, or 0.005 inch). Yet the catheter must still incorporate a Teflon liner to reduce friction, metal or plastic braid to transmit torque and provide sufficient stiffness to offer backup support during device advancement, and a smooth outer coating to resist thrombus formation. The complexity of this design goal requires use of special materials the properties of which are typically varied along the length of the catheter to optimize the balance between support and flexibility at each point. Most guiding catheters now also include a very soft material in the most distal 2 mm of the catheter to reduce the chance of vessel trauma during engagement of the nontapered tip.

Guiding catheters are available in virtually all of the conventional Judkins and Amplatz curves, as well as in a wide range of custom shapes (extra backup [XB], hockey stick, multipurpose, Voda, etc.) designed to ease engagement or provide better support during balloon advancement. As thin-wall technology has improved and balloon shaft diameters have decreased, the size of the guiding catheters needed to perform PCI has fallen progressively. In the 1980s and 1990s, 9F and 8F/7F guiding catheters predominated, respectively. Although larger guiding catheters are sometimes still needed for rotational atherectomy, or treatment of bifurcation lesions (7F for kissing balloons and 8F for two stents) or chronic total occlusions, most procedures in current practice can be completed through 6F guiding catheters. Also available are 5F guiding catheters, but they offer no major advantage and are not routinely used.

To function adequately, the guiding catheter must be able to selectively engage the ostium. This requires the selection of an appropriate catheter shape and the ability to manipulate the catheter under fluoroscopic guidance (see Chapter 15). Engagement of the desired vessel, however, should not interfere with arterial inflow. This is routinely possible in the left coronary artery, but damping of the guiding catheter pressure when the right coronary artery ostium is engaged was once a common and vexing problem. This has been overcome by the smaller-diameter (e.g., 6F) guiding catheters and by the introduction of guiding catheters equipped with side holes that allow ongoing perfusion despite wedged engagement. Since the guiding catheter is also used to deliver small boluses of contrast medium into the target vessel (as needed to visualize vascular side branches and the target lesion for angioplasty), contrast flow out of such side holes may increase the total contrast volume used during a procedure. Also, use of catheters with side holes may provide a false sense of security by showing a normal pressure tracing in the face of reduced coronary perfusion. For these reasons, their use should be minimized.

A second important function of the guiding catheter is to provide adequate support for advancement of interventional devices across the target stenosis. This support is derived from the intrinsic stiffness of the guiding catheter, the shape that allows it to buttress against the opposite aortic wall, and deep engagement of the guiding catheter into the coronary ostium (Figure 28.3). While deep engagement of the guiding catheter is sometimes required in challenging cases, it is also well-recognized as a potential cause of complications (e.g., ostial or proximal coronary dissection). This complication has become far less frequent with incorporation of an atraumatic tip on most guiding catheters and the performance of deep engagement only by relying on coaxial advancement over the balloon catheter. After a deeply engaged guiding catheter has been used to position a dilatation balloon or other device across the lesion, it is important to then withdraw the guiding...
catheter back to avoid its migration into an even deeper position as the device is withdrawn. In this sense, the ability to actively use the guiding catheter constitutes one of the important skills required for effective management of the overall angioplasty equipment system.

**Guidewires**

The original dilatation balloon designed by Gruentzig had a short fixed segment of guidewire (spring coil) attached to its tip to lead the balloon in the vessel lumen and help avoid subintimal passage as the catheter was advanced across the stenosis (see Figure 28.2). These devices provided the operator no control over whether the catheter followed the desired path or was diverted into one or more side branches proximal to the lesion, because neither the shape nor the orientation of the leading wire could be modified. In the early 1980s, Simpson designed a movable guidewire system in which a 0.018 inch Teflon-coated wire extended and moved freely through a central lumen within a coaxial dilatation catheter. If this guidewire selected the desired vessel, it was advanced until it crossed the target lesion. If the guidewire instead selected a more proximal side branch, the balloon catheter was advanced to a point just before the side branch and the wire was withdrawn and reshaped in an effort to choose the desired path beyond. By a series of such iterative advancements of wire and dilatation catheter, many lesions could be crossed by the guidewire and then by the dilatation catheter. In 1983, this concept was advanced further with the introduction of the first steerable guidewires, the rotational orientation of which could be controlled precisely using a “torquer” (pin vise) attached to the proximal end of the wire.

In contrast to crude early guidewires, modern guidewires are designed to combine tip softness, trackability around curves, radiographic visibility, and precise torque control, which together allow the guidewire to be steered past vascular side branches and through tortuous or stenotic segments. With these refinements, crossing a subtotal lesion with the guidewire has become a task that takes seconds rather than minutes to hours, opening up all portions of the epicardial...
Figure 28.2 Components of the coronary angioplasty system. The original Gruentzig fixed guidewire balloon (A) is compared with the steerable guide wire system (B). Although both are advanced through a guiding catheter positioned in the coronary ostium, neither the wire shape nor its orientation could be changed once the original Gruentzig catheter was introduced, whereas the steerable design allows the guidewire to be advanced, withdrawn, and reshaped, and steered independently of the balloon catheter to select the desired vessel. Once in place in the distal vessel beyond the target lesion, the guidewire serves as a rail over which the angioplasty balloon or other device can be advanced.

coronary circulation to a variety of interventional devices. The basic guidewire consists of a solid core (stainless steel or superelastic nitinol) that is ground to a progressive taper in its distal portion. This taper helps retain torque control when the wire is steered around the series of bends located in the guiding catheter and proximal coronary anatomy and allows the stiffer proximal portions of the wire to follow the soft tip into side branches. This core is generally covered by a spring
Use of deep guiding catheter engagement to facilitate coronary intervention. **Left.** Complex lesion in the right coronary artery including aneurysm (*dark arrow*) and diffuse distal disease (*open curved arrow*). **Center.** Left Amplatz guiding catheter (AL-1) is deeply engaged to provide optimal support for stent placement. **Right.** After stent placement, the vessel is widely patent, but replacement of the Amplatz catheter with a conventional right Judkins catheter (JR4) shows how effective the Amplatz has been in straightening out a severe upward bend (shepherd’s hook) in the proximal right coronary artery. Although progressive improvement in device profile and trackability has made such deep engagement less necessary, the technique is still of great value in selected cases. Deep seating of the guiding catheter needs to be done with great care and by coaxial advancement of the guiding catheter over a balloon catheter to avoid injuring the proximal coronary artery.

coil, and a coating (e.g., Teflon, Silicone) is generally applied to the body of the wire. Radiopaque platinum is often applied to the distal 3 to 25 cm. A family of hydrophilic polymer covered tip guidewires are also available to aid in crossing vessels with extreme tortuosity, calcification, side branches through stent struts, and total occlusion. It must be remembered that hydrophilic wires allow reduced tactile feel and are more likely to cause dissections or perforations.

There is substantial choice of tip stiffness, driven by the way the tapered core wire is attached to the outer coil at the wire tip. In soft wires, the tapered core is generally welded to the coil via a flattened intermediary shaping ribbon that allows the operator to kink or bend the tip of the wire into a shape that is appropriate for navigating the vessel features it must pass while maintaining the required level of atraumatic softness. Even with soft “work horse” wires, it is still important to heed the advice of Dotter and Judkins¹ that “the guidewire is passed across the atheromatous block more by the application of judgment than of force.” Wires with preshaped tips are generally used for the majority of cases in contemporary practice, but the tips may be manually shaped, particularly to meet the challenges of anatomic navigation. Longer primary tips or a secondary bend are used for large-diameter arteries and for entering tortuous segments. Short and less-angled tips are best suited for entering diffusely diseased and chronically occluded arteries.

When larger _probing force_ is required (e.g., for crossing a chronic total occlusion), stiffer tip designs are available. These “core-to-tip” guidewires are often graded by the force that the straight guidewire tip can apply to a strain gauge from a distance of 1 cm. Wires are available with force increments of 3, 4.5, 6, 9, and 12 g in the United States, though wires with even higher tip stiffness are available in other countries. The core-to-tip design also provides better torque control. Use of these stiff-tip guidewires requires a high degree of skill and feel to avoid unintentional vessel injury (dissection or perforation), and in general, less experienced operators are well advised to start with softer guidewires and work up to the stiffer wires progressively.

Independent of the tip stiffness, advancing certain devices around bends may take more _shaft support_ from the guidewire. This is provided by extra-support wires, which have a thicker and firmer inner core. Alternatively, some operators prefer to place a second guidewire across the lesion in parallel (a “buddy” wire) to straighten vessel bends and facilitate device passage. With the wide variety of choices in 0.014 inch guidewires, it is currently rare to use larger-diameter guidewires in coronary work, although wires of 0.016 and 0.018 inch were previously used for this purpose (requiring, of course, the use of matching devices with larger internal lumen diameters). Guidewires with a diameter of <0.014 inch offer little advantage except with certain devices such as the 0.009 inch Rotablator wire (see Chapter 29), but some specialty chronic total occlusion guidewires have a tapered tip (0.014 inch to 0.009–0.012 inch) to help penetrate the plaque and find microchannels.

Standard coronary guidewires are approximately 190 cm long, that is, some 50 cm longer than the average balloon...
catheter shaft. This allows the wire to be advanced across the lesion while the balloon catheter remains in the guiding catheter, but does not generally offer sufficient length for exchange of one “over-the-wire” (OTW) device for another. Most guidewires are therefore also available in a 300 cm exchange length, or are extendable to that length by attachment of an extension. Such wires can be passed through the guiding catheter and across the target lesion and remain in place as a series of OTW devices (balloons, rotational atherectomy burrs, stents) are delivered or removed without the need for recrossing the lesion, OTW devices have largely been replaced by rapid-exchange (Rx) or monorail balloon catheters and stent delivery systems compatible with shorter guidewires.

**Dilatation Catheters**

The dilatation catheters for coronary angioplasty have undergone radical evolution since 1977. As described above, the original Gruentzig catheters were designed with a short segment of guidewire permanently affixed to the catheter tip to decrease the risk of subintimal passage during advancement down the coronary tree. The shaft of these catheters had two lumens—one for inflation and deflation of the balloon and one for distal pressure measurement and/or contrast injection. This reflected the initial reliance on monitoring trans-stenotic (i.e., aortic root to distal coronary) pressure gradient as a way of assessing lesion severity, since it was very difficult to perform adequate contrast injections through small-lumen guiding catheters around the large (4.3F; 1.3 mm) shafts of early balloon catheters. In contrast, contemporary catheters are delivered over independently movable and/or steerable guidewires (see Figure 28.2). The central lumen of such dilatation catheters must have a sufficient caliber to allow free movement of the guidewire, but are no longer used for either pressure measurement or contrast injection. However, it is of interest that the measurement of trans-stenotic pressure gradients to evaluate the significance and completeness of correction of coronary stenoses has evolved into pressure measurement guidewires (see “Fractional Flow Reserve,” Chapter 24).

An important characteristic of the dilatation catheter is the diameter of the smallest opening through which the deflated balloon can be passed (its profile). The original Gruentzig catheters had a 0.060 inch (1.5 mm) profile, but current dilatation catheters have profiles as small as 0.020 inch (0.5 mm). To preserve the best balloon profile, a “negative” or “aspiration” preparation should be performed in which a contrast-filled 20 mL syringe is attached to the balloon inflation hub, the plunger is pulled back to apply a vacuum, and gently released to allow the balloon to draw in a small volume of dilute (1:2 dilution with saline) contrast. The crossing profile increases significantly after a balloon is used, and this may be relevant when one attempts to reuse a previously inflated balloon to cross a second lesion and finds that the secondary (or rewrap) profile is far less satisfactory than the primary (prior to inflation) profile.

Balloon angioplasty catheters are available either as OTW catheters in which the guidewire runs through a central lumen in the shaft throughout its entire length or as monorail Rx catheters in which the wire is contained within the balloon shaft only over its distal 25 cm and then runs outside the balloon shaft more proximally. The latter type of catheters can be exchanged quickly by a single operator over a standard-length (190 cm) guidewire and generally have smaller shaft profiles to allow better contrast injection or simultaneous placement of two balloons for the treatment of bifurcation lesions. Fixed-wire devices, which consisted of a balloon mounted directly on a steerable wire core (deflated profile of 0.020 inch or 0.5 mm), were widely used in the late 1980s, but are no longer in use today.

Although profile is important, the ability of the balloon to bend so as to advance easily through tortuous vascular segments (trackability) and the presence of sufficient shaft stiffness (pushability) to force it through the stenosis are also important. Delivery of the balloon is also aided by the incorporation of a friction-resistant coating to improve surface lubricity. Specialized balloon catheters include perfusion balloon catheters, which have a series of side holes in the shaft proximal and distal to the balloon segment or a spiral channel within the balloon to allow ongoing antegrade blood flow and thereby mitigate myocardial ischemia during prolonged balloon inflations. In an era when stents provide definitive control of elastic recoil and dissection, however, the use of perfusion balloons has become rare except for controlling hemorrhage from a coronary perforation without producing severe distal myocardial ischemia (see Chapter 4). Some special balloons exploit the concept of focused force angioplasty, in which a wire (Angiosculpt balloon, AngioScore, Fremont, CA) or microblades on the balloon surface (cutting balloon, Boston Scientific, Natick, MA) concentrate the delivery of dilating force from the balloon to the lesion to lower stenosis resolution pressure and reduce balloon slippage forward or backward during inflation (the so-called watermelon seeding effect). These technologies have not, however, improved the long-term patency as compared with conventional PTCA, and the cutting balloon carries a small but real risk of perforation when oversized. These devices have been promoted for use in ostial lesions or in-stent restenosis owing to neointimal proliferation, but there is no definitive evidence that they improve procedural outcomes.

Other than these factors, the most important characteristic of the dilatation catheter is its ability to inflate to a precisely defined diameter despite application of pressures that average 10 to 16 atm. This was not possible with early balloons manufactured from polyvinyl chloride (PVC); their compliance led to balloon oversizing and rupture at pressures as low as 6 atm. More suitable performance can be readily achieved today using balloons manufactured from high-density polyethylene, polyethylene terephthalate (PET), or nylon, despite balloon wall thicknesses as low as 0.0003 to 0.0005 inch (7.62 to 12.7 μm). Based on material and wall thickness, each balloon has an individual compliance characteristic reflecting...
the pressure at which the balloon reaches its specified (nominal) diameter and how much that diameter increases as the balloon is inflated to even higher pressures. More compliant balloon materials tend to reach their nominal diameter at 6 atm and then grow by ≤20% above their nominal size (i.e., a 3.0 mm balloon growing to 3.5 mm) at 10 atm. Semicompliant balloon materials such as high-density polyethylene or nylon grow by <10% over this pressure range, whereas truly noncompliant balloon materials such as PET can retain their defined diameter up to 20 atm to allow dilatation of calcific stenoses or full expansion of coronary stents (Figure 28.4).

Balloon compliance characteristics must be kept in mind especially when inflating a compliant or semicompliant balloon to pressures above nominal (usually roughly 6 to 10 atm) to avoid overdistending the adjacent normal vessel. Noncompliant balloons are desirable when high pressure inflation is needed (resistant lesions and postdilation of stents) so that the dilating force is applied to treat the stenosis rather than in enlarging the balloon.

Regardless of which balloon type is used, it is important to stay within the stated range of inflation pressures in order to avoid balloon rupture. This pressure range is specified in terms of the rated burst pressure (i.e., an inflation pressure at which the probability of balloon rupture is <0.1%). Taking any balloon catheter above its rated burst pressure (usually 16 to 20 atm) increases the risk of balloon rupture, with the potential for air embolization (if the balloon was incompletely purged), vessel rupture, local dissection, or difficulty in removing the balloon from an incompletely dilated lesion.11 This risk grows further with pressures above the rated burst pressure to which the balloon is inflated, until it reaches 50% risk of rupture when the maximum burst pressure is reached. Instead of relying solely on high balloon inflation pressures, we recommend the use of rotational atherectomy for treating resistant lesions which are invariably associated with severe calcification. An uncommon exception to this rule is stent postdilation in a calcified or fibrotic lesion that has not been adequately predilated or pretreated with rotational atherectomy before stent placement, and where there is no alternative for achieving full stent expansion.

Various manufacturers currently provide dilatation catheters that meet these design specifications with inflated diameters of 1.25, 1.5, 2.0, 2.5, 3.0, 3.5, and 4.0 mm to match the size of the coronary artery in which the stenosis is located. Larger balloons (i.e., 4.5, 5.0, and 6.0 mm) are occasionally needed for treatment of large right coronary arteries or saphenous vein grafts. Quarter-sized balloons (e.g., 2.25, 2.75, and 3.25 mm) are also available, but that degree of precision probably exceeds the operator’s ability to gauge vessel size, and stocking quarter-sizes tends to unfavorably increase the size of a laboratory’s balloon inventory. The typical lesion requires a predilation balloon that is 12 to 15 mm long, but balloons are also available for shorter (8 mm for dilating or postdilating focal lesions) or longer (20 or 30 mm for dilation of a diffusely diseased segment) diffuse lesions.12 Although most lesions can be dilated effectively with balloon catheters from any of the several manufacturers, subtle differences in performance characteristics can make the difference between success and failure; therefore, each interventional laboratory still needs to stock a variety of balloon types. Although balloon prices were once nearly $700, competition and widespread use have brought current prices down to approximately $150.

Figure 28.4 Successful dilatation of a rigid calcific lesion (arrows). This rigid lesion (top) in the midleft anterior descending coronary artery of a postbypass patient (note surgical clips) resisted dilatation at 300 lb/in² (20 atm), but yielded to an inflation pressure of 330 lb/in² (22 atm; middle two views) with reduction in the stenosis (bottom). Such pressures are obtainable only with high-pressure noncompliant balloons. In current practice, such “nondilatable” lesions would most appropriately be treated by rotational atherectomy (see Chapter 29).
giving little incentive for resterilization and reuse, with the risk of infection, prolonged procedure time, and device failures with resteriled products.

**PROCEDURE**

A coronary angioplasty procedure bears a superficial resemblance to diagnostic cardiac catheterization in that catheters are introduced percutaneously under local anesthesia. However, since angioplasty involves selective cannulation of coronary arteries with guidewires and balloon catheters, temporary occlusion of antegrade coronary arterial flow, as well as manipulation of the culprit lesion by balloon inflation and/or stent deployment, the procedure is significantly more complicated and entails approximately 10-fold higher risk (i.e., 1% versus 0.1%) as compared with a diagnostic catheterization. However, the risks of coronary angioplasty vary widely with the baseline clinical condition of the patient, the characteristics of the lesion to be treated, and the techniques used (see “Complications” below and Chapter 4).

When obtaining informed consent, the estimated individual risks together with the potential benefits, alternatives, and goals should be discussed in detail with the patient and family prior to the procedure. To mitigate the very real risks of major complications, angioplasty should be attempted only by experienced personnel and generally only in a setting where full cardiac surgical and anesthesia support is available. One exception is the performance of primary PCI for the treatment of acute ST-elevation myocardial infarction (STEMI), where the need for rapid revascularization has led to the allowance of such procedures in approved catheterization laboratories staffed by experienced interventional operators, even when onsite cardiac surgical care is not available. An expert consensus document from the Society for Cardiovascular Angiography and Interventions details the requirements for establishing a PCI program without onsite surgical backup. The practice of elective angioplasty without onsite surgery, however, remains outside the recommendations of PCI guidelines at this time, though it is performed in some hospitals in the United States and Europe that have appropriate program development using clinical and angiographic criteria for patient selection.

Historically patients were admitted the night before elective angioplasty, but currently elective patients are admitted on the morning of the procedure. Details of patient evaluation, informed consent, and preprocedure laboratory work will thus generally have been completed in a separate outpatient visit or be compressed into a very brief encounter immediately prior to the procedure. This is particularly true for patients who come to catheter-based intervention at the conclusion of what began as a diagnostic catheterization that progressed to coronary intervention (the so-called ad hoc PCI). Although a major proportion of PCI is now performed in the ad hoc fashion, consideration of staging is important in case of the following situations: (a) high anticipated procedural risk or technical complexity (e.g., chronic total occlusion) making surgical consultation or additional discussions with the patient and family desirable before proceeding with a nonemergency intervention; (b) Nonavailability of PCI at the diagnostic catheterization facility; and (c) the likelihood of the combined procedure leading to a large volume of contrast being used. Similar considerations apply to the decision to stage a complex multivessel procedure into two or more sessions (e.g., patient tolerance, clinical stability, total contrast load, stability of the initial treatment results), but current techniques generally make staging (between diagnostic and interventional procedures, or between treatment of some lesions and others) an uncommon clinical necessity. Finally, patients should be counseled on the need for and risks of dual antiplatelet therapy before placement of intracoronary stents, especially drug eluting stents, and alternative therapies should be pursued if patients are unwilling or unable to comply with the recommended duration of dual antiplatelet therapy.

Oral intake should be restricted after midnight on the evening prior to the procedure, and the patient should be pretreated with aspirin 325 mg/day to diminish platelet deposition on the disrupted endothelium. Patients not on aspirin therapy should be given nonenteric aspirin 325 mg, while those already taking daily aspirin therapy should receive 81 to 325 mg before PCI. In the aspirin-allergic patient requiring an elective PCI, a graded aspirin desensitization protocol may be considered prior to the procedure. An oral platelet ADP-receptor antagonist (such as clopidogrel, prasugrel, ticagrelor) should generally be administered prior to the procedure, supplemented by intravenous platelet glycoprotein IIb/IIIa receptor antagonists in patients with acute coronary syndromes, to reduce the incidence of periprocedural myocardial infarction or repeat emergency revascularization for vessel closure or stent thrombosis. Since aspirin reduces late cardiac mortality in patients with coronary disease, it is generally continued indefinitely after the procedure. Similar data now exist for longer-term clopidogrel treatment, and hence ADP-receptor antagonists may be used as an alternative to aspirin in patients with aspirin allergy. Statins appear to have some benefits when pretreatment is initiated from 7 days to just prior to PCI, especially in statin naive patients. Hence, it is reasonable to administer a high dose of statin before PCI to reduce the risk of periprocedural MI. Patients with a past history of an hypersensitivity reaction to contrast media should receive steroid and antihistamine prophylaxis; this prophylaxis is not beneficial in patients with a prior history of allergic reactions to shellfish or seafood. Finally, patients should be assessed for risk of contrast-induced acute kidney injury (nephropathy). Important risk factors for contrast-induced acute kidney injury include advanced age, chronic kidney injury, diabetes mellitus, congestive heart failure, and the volume of contrast used during the procedure. The risk may be estimated using a scoring system. Adequate hydration and minimizing the volume of contrast administered are
the only interventions demonstrated to reduce the risk of contrast-induced acute kidney injury (see Chapter 4). It is most important to do so in patients with creatinine clearance of <60 mL/minute. There is now good evidence demonstrating that administration of N-acetylcysteine is not beneficial.

The 2011 PCI guidelines advocate that a “time-out” is performed before all PCI to verify that the correct patient is having the intended procedure.16 The aim of this process is to improve patient care by collective discussion of the case immediately prior to the procedure. The timeout may be checklist driven or conversational, depending on each laboratory’s established practice.28

PCI is performed either via the femoral or via the radial approach, based on considerations about potential complications related to vascular access, as well as operator and patient preference. The 2011 PCI guidelines state that it is reasonable to use radial artery access to decrease access site complications. However, femoral access remains the most commonly used approach in the United States. Vascular complications via the femoral approach may be minimized by the use of fluoroscopic landmarks or ultrasound guidance. Low punctures are associated with hematomas and other vascular complications while high punctures increase the risk of retroperitoneal hemorrhage. Most catheter-based interventions are performed safely without right heart catheterization, but occasionally venous access is also required for the initiation of ventricular pacing, although placement of a prophylactic pacemaker is seldom needed except in cases of rotational atherectomy of the right coronary artery or rheolytic thrombectomy (see Chapter 29). In addition, there are some high-risk procedures in which measurement of right heart pressures may aid in fluid management.

After placement of the arterial sheath, intravenous antithrombin therapy is initiated (see Chapter 5). The most common agent is still unfractionated heparin (70 U/kg), which may be reduced to 50 U/kg when there is concomitant administration of a platelet glycoprotein IIb/IIIa receptor antagonist. Alternatives include low-molecular weight heparin (e.g., enoxaparin) in patients who have been on such agents pre-procedure29 or a direct thrombin antagonist (e.g., bivalirudin [Angiomax, the Medicines Company, Parsippany, NJ]).30,31 If unfractionated heparin is used, it should be noted that there is wide patient-to-patient variability in heparin binding and activity. So, ACT (activated clotting time) should be measured and additional heparin administered as needed to prolong the ACT to 275 to 300 seconds (reduced to 250 seconds if a platelet glycoprotein IIb/IIIa receptor blocker is to be given) before any angioplasty devices are introduced. Additional doses or an infusion of the antithrombotic agent may be required to maintain the ACT at this level throughout the case—ACTs <250 seconds are associated with a marked increase in the incidence of occlusive complications unless an adjunctive IIb/IIIa receptor blocker is used, whereas ACTs >300 to 350 seconds tend to increase the risk of bleeding.32 ACTs may also be used to monitor the effect of direct thrombin inhibitors such as bivalirudin, which have found increasing use during PCI based on more predictable dose–response characteristics than that of heparin, greater efficacy against clot-bound thrombin, reduced platelet activation, less bleeding, and lack of cross-reactivity in patients with heparin-induced thrombocytopenia (HIT, Chapter 5). Since low-molecular weight heparin has relatively more activity against factor Xa than against thrombin, it causes less prolongation of the ACT so that specialized anti-Xa assays are required to monitor low-molecular weight heparin effects.

Baseline angiograms are then obtained of one or both coronary arteries using either a standard diagnostic catheter or the angioplasty guiding catheter. Baseline angiography serves to (a) evaluate any potential changes in angiographic appearance (interval development of total occlusion, thrombus formation) since the previous diagnostic catheterization, (b) permit the selection of the angiographic views that allow optimal visualization of the stenoses, and (c) aid in planning of the detailed interventional strategy. Coronary injections should be repeated after the administration of sublingual or intracoronary nitroglycerin to demonstrate that spasm is not a significant component of the target stenosis and to minimize the occurrence of coronary spasm during the subsequent angioplasty. Occasionally, unnecessary intervention is avoided when the intended target of a catheter-based intervention resolves with nitroglycerin (coronary spasm)! This is more frequent with lesions of the ostium of the RCA. In this setting, at the time of diagnostic angiography catheter-induced spasm may occur. If the patient returns at a later time for intervention, this ostial “stenosis” may prove to have been unrecognized catheter spasm.

The best working views that show the target lesions and the adjacent side branches most clearly and with the least foreshortening are recorded and transferred to the roadmap monitor for reference during the procedure. The approximate reference diameter and length of each target lesion is estimated by comparing it to the diagnostic catheter (generally 5F or 1.65 mm) or selected guiding catheter. Decisions are then made regarding the sequence of lesions to be approached (integrating lesion severity, myocardial territory involved, and noninvasive test data) and the specific interventional approach that will be used. For example, a bifurcation lesion that may require kissing balloon inflations and/or a two-stent approach (see Chapter 31) may warrant use of a guiding catheter that is larger than 6F.

The appropriate guiding catheter is connected to the pressure manifold (see Chapter 15) by way of an extension tube and a rotating hemostatic valve (e.g., Tuohy-Borst valve), and positioned in the appropriate coronary ostium. The hemostatic valve contains an adjustable O-ring that allows introduction and free movement of the PCI devices while maintaining a sufficient seal around the shaft to permit pressure measurement and contrast injection while minimizing blood loss. The angioplasty guidewire is first introduced into the guiding catheter, either through a needlelike guide-wire introducer (bare-wire technique for Rx systems) or, less frequently, loaded into an OTW balloon or support catheter,
and then steered across the target lesion. The guidewire is advanced across the lesion with the aid of puffs of contrast material through the guiding catheter as the vessel is imaged fluoroscopically in a projection that shows the desired path free of foreshortening or overlapping side branches. Once the position of the wire tip in the distal vasculature has been confirmed by contrast angiography, the desired angioplasty balloon or other device is selected.

Optimal stand-alone angioplasty results are obtained using a balloon with a diameter that closely approximates the diameter of a presumably nondiseased reference segment adjacent to the site being treated (balloon/artery ratio 0.9:1.1). Slightly larger balloons (approximately 1.1 to 1.2 times the size of the reference lumen) may be used if intravascular ultrasound (see Chapter 25) is used and shows that the outer vessel (external elastic membrane [EEM]) diameter in the reference segment is significantly larger than the reference lumen (diffuse disease without a true normal reference segment). On the other hand, slightly smaller initial balloons are used when it is difficult to estimate the correct reference size of a diffusely diseased or rapidly tapering vessel, when difficulty is anticipated in crossing the lesion, or if the risk of complications must be minimized in a patient who cannot receive a stent. In the era when stenting (especially drug-eluting stenting) has become the definitive treatment, however, it is routine to predilate the target lesion with a balloon that is slightly undersized relative to the reference vessel and roughly the same length as the target lesion (see Chapter 31). Modern low-profile stents can often be delivered without predilation of the target lesion (the so-called direct stenting), but predilation makes delivery and accurate placement of the stent within the lesion easier, facilitates the selection of the correct stent diameter and length (by comparison with the diameter and length of the inflated predilating balloon), and ensures that lesion compliance is sufficient to allow full expansion of the stent without pretreatment by rotational atherectomy (see Chapter 29). Predilation is particularly important if a short stent is used, to avoid “missing” the lesion during stenting if “watermelon seeding” is felt likely.

Once the dilatation catheter has been positioned within the target stenosis, the balloon is inflated progressively using a screw-powered hand-held inflation device equipped with a pressure dial. At low pressures (i.e., 2 to 4 atm), the balloon typically exhibits an hourglass appearance owing to central constriction by the coronary stenosis being treated. In soft lesions, this constriction (or “waist”) may expand gradually as the inflation pressure is increased, allowing the balloon to assume its full cylindrical shape. In more rigid lesions, the constriction may remain prominent until the balloon expands abruptly at a stenosis resolution pressure that may be as high as 20 atm. Some operators prefer to increase pressure rapidly until all balloon deformities resolve, but this increases the risk of dissection when a fibrotic or calcified plaque yields suddenly or when the ends of a somewhat compliant balloon grow to excessive diameter on either side of the resistant lesion. If a calcified plaque resists balloon expansion at 10 to 14 atm, one may thus prefer to consider use of a Rotablator (see Chapter 29) rather than inflating the balloon to the very high pressures (≥20 atm, Figure 28.4) that may be required for full dilatation.

At the other extreme, elastic (usually eccentric) stenoses may allow full balloon expansion at low pressures but then tend to recoil promptly once the balloon is deflated. This type of lesion was once treated by repeated inflations, cautious use of oversized balloons, or directional atherectomy, but stent implantation is now the routine treatment. Focused force dilatation (with a cutting balloon or the Angiosculpt balloon) may also be helpful in dilating the fibrotic or elastic lesion effectively (see below). There is little objective evidence that slower speed of inflation or prolonged (1 minute or more) inflations offer more benefit than offered by the 30-second inflations.

Whatever inflation strategy is adopted, the response of each lesion to balloon dilatation must then be assessed individually so that the dilation protocol can be tailored to achieve the best possible result. The most common way to assess lesion response to balloon dilatation is repeat angiography. Complete normalization of the vessel lumen would be the ideal end result of coronary angioplasty, but a typical result of even a successful angioplasty is a 30% residual diameter stenosis (i.e., a 1.9 mm lumen in a 3 mm vessel) with some degree of intimal disruption (reflected as localized haziness, filling defect, or dissection). Although this once created a dilemma about whether to persist with additional balloon inflations (weighed against the risk of creating a vessel dissection), the need to obtain a perfect result with balloon angioplasty is now moot in the stent era—any lesion that can be stented is generally stented. In the current view, the best position for stand-alone balloon angioplasty is thus in lesions that are poorly suited to stenting owing to vessel size below 2 mm or branch ostial disease where bifurcation stenting is not contemplated.

Given the importance of achieving the best acute angiographic result, and the uncertainty inherent in angiographic assessment of the irregular lumen postangioplasty, a number of other techniques have been used to grade the quality of an angioplasty result. Initially, PTCA operators relied heavily on the trans-stenotic gradient as an index of dilatation adequacy, seeking a postdilation pressure difference of <15 mmHg between the aortic pressure (measured through the guiding catheter) and the distal coronary artery pressure (measured through the tip of the dilatation catheter). In practice, such measurements were complicated by the presence of the dilatation catheter within the stenosis and the small size of the dilatation catheter lumen, which led to abandonment of the gradient measurement by 1988. There has been some recent reawakened interest based on the availability of newer solid state pressure-measuring guidewires that can be used to assess the trans-stenotic gradient at baseline flow and during maximal hyperemia (see Chapter 24). The goal is to achieve a fractional flow reserve (FFR)—defined as the ratio of distal mean coronary pressure to aortic mean pressure during adenosine-induced hyperemia—of >0.95 in a successful
postprocedural management

Postprocedure management after PCI has been progressively streamlined. It was once common to leave the arterial sheath in place overnight with continued heparin infusion, while perfusing the sheath lumen and monitoring for distal limb ischemia. This practice allowed prompt vascular access should delayed abrupt closure occur. With the advent of stenting and glycoprotein IIb/IIIa receptor antagonists, such delayed abrupt closures occur so infrequently that the practice shifted to removal of the sheaths later the same day as soon as the heparin effect wore off (ACT <160 seconds), with no postprocedural heparin infusion. In fact, now with the wide adoption of femoral puncture site closure devices and radial access, it is common to remove the arterial sheath in the catheterization laboratory at the end of the interventional procedure, despite a fully anticoagulated state.

After sheath removal, the patient typically remains at bed rest for 6 hours and then ambulates before discharge. The time to ambulation is reduced significantly, however, if a femoral closure device has been used. If a glycoprotein IIb/IIIa receptor antagonist is used intraprocedurally, it is commonly infused for approximately 18 hours postprocedure, though there is a trend toward shorter infusions in order to reduce the risk of bleeding. Aspirin (81 to 325 mg/day) is continued indefinitely, and patients who have received a stent are given clopidogrel 600 mg (or Prasugrel 60 mg, Ticagrelor 180 mg) as a loading dose (300 mg with 24 hours of fibrinolytics) during or prior to the procedure. If Ticagrelor is used, typically the dose of aspirin is reduced (see Chapter 5). The duration of dual antiplatelet therapy varies depending on type of stent, technical factors (left main or bifurcation stenting), clinical factors (stable versus acute coronary syndrome), and the potential risk of bleeding. 

With a good angiographic result in the treated lesions, marked relief of ischemic symptoms should be expected unless other significant disease has been left untreated. In the patient with significant multivessel disease (see below), it may thus be particularly helpful to measure the FFR across any indeterminate lesion using a pressure wire at the time of the procedure or perform a maximal exercise test in a few weeks after discharge. Earlier (i.e., predischARGE) exercise testing was once performed on a routine basis, but has now been abandoned owing to the potential of groin rebleeding, delay of discharge, or the small risk of precipitating thrombotic closure of the dilatation site. Patients may return to full activity within 72 hours, by which time the groin puncture site should have healed sufficiently to allow even brisk physical activity.

Patients should expect to have no or minimal anginal symptoms early after discharge—ongoing anginal symptoms after discharge suggest persistent untreated disease or a poor result at the treatment site. A good initial result, with recurrent symptoms within the first weeks or 1 to 2 months may suggest subacute stent thrombosis, which usually presents as an acute STEMI requiring emergency recatheterization. On the other hand, initial symptomatic relief followed by recurrence...
of symptoms between 2 and 6 months suggests restenosis of the dilated segment. (Clinically significant restenosis has been reduced markedly from 30% with PTCA to 15% with bare-metal stenting and to <5% with drug-eluting stenting.) When symptoms recur 1 or more years after successful angioplasty, it generally suggests progression of disease at another site.

Along with educating the patient and family regarding these possibilities and their proposed management (including additional catheter intervention or bypass surgery, as needed), the acute angioplasty admission should also be viewed as an opportunity to educate about changes in lifestyle (smoking cessation, exercise, weight loss) or drug therapy (for hypertension and/or hyperlipidemia) to reduce the risk for the progression of atherosclerotic disease. Current lipid guidelines call for achieving a LDL level of <70 mg/dL in patients with proven coronary artery disease, as would be the case for the post-PCI patient. Medically supervised exercise programs (cardiac rehabilitation) should be recommended to patients after PCI, particularly for patients at moderate to high risk. Treadmill exercise testing is reasonable for patients entering a formal cardiac rehabilitation program after PCI, but routine periodic stress testing of asymptomatic patients after PCI without specific clinical indications should not be performed.

### Table 28.1

| Recommended Duration of Dual Antiplatelet Therapy Following Stent Implantation |
|--------------------|-------------------------------|
| **Bare-metal stent:** |
| For stable coronary artery disease patients, a minimum of 1 mo and ideally up to 12 mo of clopidogrel 75 mg (unless the patient is at increased risk of bleeding, in which case it should be given for a minimum of 2 wk). |
| For acute coronary syndrome, at least 12 mo after PCI. Options include clopidogrel 75 mg daily, prasugrel 10 mg daily, and ticagrelor 90 mg twice daily. If the risk of significant bleeding outweighs the anticipated benefit, earlier discontinuation should be considered. |
| **Drug-eluting stents:** |
| For stable coronary artery disease patients, clopidogrel 75 mg daily for 12 mo, if patient not at high risk of bleeding. |
| For acute coronary syndrome, at least 12 months after PCI. Options include clopidogrel 75 mg daily, prasugrel 10 mg daily, and ticagrelor 90 mg twice daily. |

Prasugrel should not be administered to patients with a prior history of stroke or transient ischemic attack.

Use with aspirin 81 mg daily.

Use of proton pump inhibitors is indicated in patients with a prior history of gastrointestinal bleeding, and reasonable for those at increased risk (e.g., advanced age, concomitant use of warfarin, steroids, NSAIDs, *Helicobacter pylori* infection).

Continuation of dual antiplatelet therapy beyond 12 months may be considered in a few patients undergoing DES implantation and in patients with left main and bifurcation (2 stent) stenting.

### MECHANISM OF PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY

According to the original explanation proposed by Dotter and Judkins and by Gruentzig et al., the enlargement of the vessel lumen following angioplasty was ascribed to compression of the atheromatous plaque—akin to footprints in the snow. In fact, true plaque compression accounts for a minority of the observed improvement. Extrusion of liquid components from the plaque does permit some compression of soft plaques but contributes minimally to improvement in more fibrotic lesions, even when balloon inflation is prolonged to 1 minute. In the absence of significant reduction in plaque volume, most of the luminal improvement following PTCA seems to result from plaque redistribution—more like footprints in wet sand. Some of this takes place by longitudinal displacement of plaque upstream and downstream from the lesion, but maximum improvement in the lumen following balloon angioplasty or stenting results from controlled overstretching of the entire vessel segment by the PTCA balloon. This stretching leads to fracture of the intimal plaque and partial disruption of the media and adventitia, with consequent enlargement of both the lumen and the overall outer diameter of the vessel (Figure 28.5).

Although use of a full-sized balloon (balloon/artery ratio of 1:1) should theoretically eliminate all narrowing at the treatment site, the overstretched vessel wall invariably exhibits elastic recoil following balloon deflation and some degree of local vasospasm. These processes typically leave the stretched vessel with a residual stenosis. A typical balloon angioplasty result also shows evidence of localized trauma to more superficial plaque components as an almost universal haziness of the lumen. Higher degrees of disruption are reflected by intimal filling defects (Figure 28.6), contrast caps outside the vessel lumen, or spiral dissections that may interfere with antegrade blood flow (Figure 28.7). Such local disruption has been seen on IVUS, angiography, and histologic examination of postmortem angioplasty specimens, and its extent correlates with the risk of an occlusive complication. In contrast, stenting or directional atherectomy reduces or even eliminates this elastic recoil, dissection, and vascular tone, and thereby provides lower (0% to 10% rather than 30%) postprocedural residual stenosis, and a smooth
Figure 28.5 Proposed mechanism of angioplasty. A. Deflated balloon positioned across stenosis. B. Inflation of the balloon catheter within the stenotic segment causes cracking of the intimal plaque, stretching of the media and adventitia, and expansion of the outer diameter of the vessel. C. Following balloon deflation, there is partial elastic recoil of the vessel wall, leaving a residual stenosis and local plaque disruption that would be evident as haziness of the lumen contours on angiography.

and uniform lumen by angiography or IVUS, with less chance of acute or delayed closure.

Given the amount of vascular injury that takes place during balloon dilation, it is remarkable that dislodgment and clinically evident distal embolization of plaque fragments seem to be infrequent both in experimental studies and in most clinical angioplasty procedures. There is increasing evidence, however, that subclinical distal atheroembolization during balloon angioplasty and stent placement occurs frequently. This is most clearly established in patients undergoing dilatation of a saphenous vein bypass graft or patients with large thrombi adherent to the lesion. Distal embolization of large (>1 mm) plaque elements is usually manifest as an abrupt cutoff of flow in the embolized distal vessel. In contrast, microembolization of plaque debris or adherent thrombus may contribute to postprocedure chest pain, enzyme normal healing of PTCA-related coronary dissection. As compared with the baseline angiogram (A), the immediate post-PTCA angiogram (B) shows enlargement of the left anterior descending (LAD) lumen with two small filling defects typical of an uncomplicated coronary dissection (arrow). Follow-up angiogram 3 months later (C) shows preservation of luminal caliber with complete healing of the localized dissection (arrow). (From Baim DS. Percutaneous transluminal coronary angioplasty. In Braunwald E, ed. Harrison’s Principles of Internal Medicine: Update VI. New York: McGraw-Hill; 1985.)
Coronary dissection leading to abrupt closure. The appearance of a right coronary stenosis prior to (A) and immediately following (B) coronary angioplasty, with an evident localized dissection. Within 15 minutes following removal of the dilatation catheter, the patient experienced chest pain associated with inferior ST-segment elevation and angiographic evidence of progressive dissection with impeded antegrade flow (C). Standard management in 1980 (when this case was done) consisted of emergency bypass surgery, which was accomplished without complication. Current practice is to attempt to recross the lesion and treat the dissection with angioplasty and stents. (From Baim DS. Percutaneous transluminal angioplasty—analysis of unsuccessful procedures as a guide toward improved results. Cardiovasc Intervent Radiol 1982;5:186.)
COMPLICATIONS

As a specialized form of cardiac catheterization, coronary angioplasty is attended by the usual risks related to invasive cardiac procedures (see also Chapter 4). In contrast with diagnostic procedures, the larger-caliber guiding catheter used for angioplasty is more likely to result in damage to the proximal coronary artery and cause local bleeding complications at the catheter introduction site. Selective advancement of guidewires and dilatation catheters into diseased coronary arteries may lead to vessel injury if they are manipulated too aggressively.

Several systems have been devised to predict risk, which may be useful in preprocedural discussions with the patient and family or in monitoring how actual procedural outcomes over time compare with what is predicted (risk adjustment, looking at the observed versus expected complication rate ratio). The risk of procedural or in-hospital mortality is driven mostly by clinical factors such as age, cardiogenic shock, congestive heart failure, renal failure, and urgent or emergency PCI(46-49) (Table 28.2). An example of a contemporary risk model for estimating the probability of cardiovascular complications from PCI using clinical variables alone is shown in Figure 28.8. Procedure success and overall complications, however, tend to be driven by lesion-related features. The original AHA/ACC Type A, B, and C lesion categorization9 (Table 28.3) was modified by Ellis73 to discriminate between B1 and B2 lesions (i.e., those with one or more than one B characteristic), but the continued validity of this classification scheme has come into question in the stent era. The Society for Cardiac Angiography and Intervention has thus proposed a simplification into four risk categories (based on whether or not the lesion has a type C feature and whether it is patent or occluded).72 This offers a somewhat better predictive value for both procedural success and major complications (death, myocardial infarction [CK elevation], emergency surgery, or emergency repeat angioplasty) and shows the potent effect of stenting in reducing those complications across the board (Figure 28.9).

The potential effect of stenting (and potentially of platelet glycoprotein IIb/IIIa antagonists) on reducing the need for emergency surgery is shown clearly in an analysis from the prospective Mayo Clinic registry report of 24,410 consecutive PCIs performed from 1979 through 2004,6 In the stent era, emergency surgery was required in approximately 0.5% of cases. The prevalence decreased from 1.6% of PCI in the early 1990s to 0.4% in 2003–2004 (P < 0.001), in parallel with increased stent use (Figure 28.10). Similarly, in-hospital major adverse cardiovascular events and death decreased from 5.1% to 4.0% and 2.6% to 1.8%, respectively, during the same time periods. In contrast, an increase in Q-wave myocardial infarction and stroke rates was noted: 0.9% to 1.8% and 0.2% to 0.6%, respectively. The reversal in the favorable trend, with an increase in these two endpoints, is a reflection of the fact that PCI is increasingly being performed in patients with greater acuity and more complex lesion anatomy, with the use of more potent adjunctive anticoagulant and antiplatelet therapies in contemporary practice. Nevertheless, the event rates in selected patients with stable coronary artery disease in current practice are exceedingly low with the rates for emergency CABG, in-hospital death, Q-wave myocardial infarction, stroke, and the composite of major adverse events being 0.3%, 0.1%, 0.1%, 0.2%, and 3.6%, respectively.73

Periprocedural Myocardial Infarction

The universal definition of myocardial infarction defines PCI-related injury (type 4a) as an elevation of >5 × URL within 48-hours of the procedure together with either (i) evidence of prolonged (>20 minutes) ischemia as demonstrated by chest pain, or (ii) ischemic ST changes or new pathological Q waves, or (iii) angiographic evidence of a flow limiting complication, such as of loss of patency of a side branch, persistent slow-flow or no-reflow, embolization, or (iv) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality and recommends that cardiac troponin be used as the preferred biomarker which, given the advent of high sensitivity assays, establishes the threshold for
### Table 28.2: Multivariable Predictors of Mortality in Various Published Interventional Models

<table>
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<th>Hannan</th>
<th>Kimmel</th>
<th>Ellis</th>
<th>O’Connor</th>
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For each model, the multivariable correlates of mortality found are indicated by the × symbol.

ACC-NCDR, American College of Cardiology–National Cardiovascular Device Registry; IABP, intracorotical balloon pump; LAD, left anterior descending; LV, left ventricular; MI, myocardial infarction; NNE, Northern New England; PVD, peripheral vascular disease; SCAI, Society for Cardiac Angiography and Intervention.


PMI at very low levels of myonecrosis. Based on this definition, 20% to 30% of patients have evidence of periprocedural myocardial infarction, most of which occurs either due to side branch occlusion or due to distal microembolization. The definition is supported by studies correlating the magnitude of biomarker elevation to the extent of irreversible injury in the myocardium on magnetic resonance imaging and to worse in-hospital and long-term outcomes. However, there is considerable evidence to suggest that in the majority of cases, the periprocedural infarction is a reflection of increased preprocedural risk (atherosclerosis burden and disease acuity) and hence the clinical significance of such periprocedural myocardial infarction and its management remain a matter of considerable controversy and uncertainty. The definition of PCI-related myocardial infarction is likely to be modified in the future.
Until there is further clarity on the issue, our recommendation is that cardiac troponin levels be routinely measured prior to PCI. A normal preprocedural cardiac troponin value identifies those in whom PCI can be performed with very low risk and may be discharged early from hospital. Elevated preprocedure cardiac troponin identifies a higher risk cohort who may benefit from preprocedural initiation of therapies such as glycoprotein IIb/IIIa inhibitors and statins to improve outcomes. Post-PCI levels should be routinely measured in patients with complex procedures, suboptimal angiographic results, or procedural complications (e.g., large side-branch occlusion, flow-limiting dissection, no-reflow phenomenon, or coronary thrombosis), as well as in those who have symptoms, signs, or electrocardiographic evidence of myocardial ischemia, in order to quantify the extent of myocardial injury. The current PCI guidelines do not recommend routine measurement of periprocedural biomarkers in patients with uncomplicated successful PCI. It is unlikely that clinically relevant additional information can be gained in these patients, independent of preprocedural risk. While there are no established cutoffs for cardiac troponin to define a “large” periprocedural myocardial infarction, CK-MB elevation of >5× the upper reference limit and/or new Q-waves identify patients with extensive injury. These patients should be monitored in the hospital for an additional period of time because of an increased risk of arrhythmias, hemodynamic instability, heart failure, and death. For the purpose of preprocedural consent for PCI, it is the frequency of these large periprocedural myocardial infarctions (incidence <5%) that ought to be discussed; also, it must be reported to the patient, should they occur after the intervention.

**Coronary Artery Dissection**

Although plaque disruption and dissection may be caused by the guiding catheter or overly vigorous attempts to pass the guidewire through a tortuous stenotic lumen, most dissections are actually the by-product of the “controlled injury” induced intentionally by inflation of the dilatation catheter. In fact, localized dissections can be found routinely in animal or cadaveric models of angioplasty and are evident angiographically in at least one half of patients immediately after balloon angioplasty. When these dissections are small and nonprogressive and do not interfere with antegrade flow in the distal vessel, they have no clinical consequence. Follow-up angiography as soon as 6 weeks after the angioplasty procedure usually demonstrates complete healing of the dissected segment (see Figure 28.6), although occasional localized formation of aneurysms has been described at the site of dissection. Clinically
<table>
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<tr>
<td>Discrete (&lt;10 mm length)</td>
</tr>
<tr>
<td>Concentric</td>
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<tr>
<td>Readily accessible</td>
</tr>
<tr>
<td>Nonangulated segment &lt;45°</td>
</tr>
<tr>
<td>Smooth contour</td>
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<tr>
<td>Little or no calcification</td>
</tr>
<tr>
<td>Less than totally occlusive</td>
</tr>
<tr>
<td>Not ostial in location</td>
</tr>
<tr>
<td>No major branch involvement</td>
</tr>
<tr>
<td>Absence of thrombus</td>
</tr>
<tr>
<td><strong>Type B1 lesions (moderate success, 60-85%; moderate risk)</strong></td>
</tr>
<tr>
<td>Tubular (10–20 mm length)</td>
</tr>
<tr>
<td>Eccentric</td>
</tr>
<tr>
<td>Moderate tortuosity of proximal segment</td>
</tr>
<tr>
<td>Moderately angulated segment, 45°–90°</td>
</tr>
<tr>
<td>Irregular contour</td>
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<tr>
<td>Moderate to heavy calcification</td>
</tr>
<tr>
<td>Ostial in location</td>
</tr>
<tr>
<td>Bifurcation lesions requiring double guidewires</td>
</tr>
<tr>
<td>Some thrombus present</td>
</tr>
<tr>
<td>Total occlusion &lt;3 months old</td>
</tr>
<tr>
<td><strong>Type B2 lesions (Ellis modification of AHA/AOC system)</strong></td>
</tr>
<tr>
<td>Two or more type B characteristics</td>
</tr>
<tr>
<td><strong>Type C lesions (low success, &lt;60%; high risk)</strong></td>
</tr>
<tr>
<td>Diffuse (&gt;2 cm length)</td>
</tr>
<tr>
<td>Excessive tortuosity of proximal segment</td>
</tr>
<tr>
<td>Extremely angulated segment &gt;90°</td>
</tr>
<tr>
<td>Inability to protect major side branches</td>
</tr>
<tr>
<td>Degenerated vein grafts with friable lesions</td>
</tr>
<tr>
<td>Total occlusion &gt;3 months old</td>
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significant dissections in contemporary stent-based PCI are generally seen at either the proximal or the distal stent edge. These can be managed conservatively if minor, but may require treatment with an overlapping stent if abrupt closure is considered to be a significant possibility. Guide-induced dissections remain an infrequent but serious complication, generally occur in complex interventions, and invariably need to be treated with a stent.

**Abrupt Closure**

Prior to the widespread use of stents, large progressive dissections not uncommonly interfered with antegrade flow and led to total occlusion of the dilated segment (a phenomenon known as abrupt closure; see Figure 28.7). With balloon angioplasty alone (before the advent of new devices), abrupt closure occurred in roughly 5% of patients as the result of compression of the true lumen by the dissection flap, with superimposed thrombus formation, platelet adhesion, or vessel spasm. In one study, postangioplasty dissections were evident angiographically in 40% of dilated lesions, with spiral (type D) dissections in 3.5% of patients. The presence of a type D dissection increased the risk of frank or “threatened” abrupt closure (residual stenosis >50%, with reduced antegrade flow) from a baseline of 6.1% to 28%. This finding supports the earlier findings of Ellis et al. showing a fivefold increase in abrupt closure with postprocedure dissection and stressing the relative importance of the postprocedure result (as opposed to preprocedure clinical or angiographic variables) on the risk of abrupt closure. Most abrupt closures after stand-alone balloon angioplasty developed within minutes of the final balloon inflation, so that it became the routine practice to observe the lesion for 10 minutes after the last balloon inflation, before leaving the catheterization laboratory. But abrupt closure also occurred up to several hours later (in 0.5% to 1% of cases) as the heparin anticoagulation wore off (particularly prior to the use of IIb/IIIa receptor antagonist infusions in patients with marginal angiographic results of stand-alone balloon angioplasty).

Before 1985, most patients who experienced abrupt closure of a major epicardial coronary artery went directly to emergency surgery, in an effort to minimize the amount of consequent myocardial damage. The rate of emergency surgery was thus 5% to 6%, but even with emergency surgery within 90 minutes of the onset of vessel occlusion, up to 50% of patients sustained a Q-wave myocardial infarction. The development of perfusion catheters—infusion catheters or angioplasty balloons with multiple side holes along their distal shaft to allow 40 to 60 mL/minute of blood to enter proximal to the site of occlusion, flow through the central lumen, and re-enter into the lumen distal to the point of occlusion—allowed patients to go to the operating room in a nonischemic state (Figure 28.11), and was shown to reduce the incidence of transmural infarction during emergency surgery to approximately 10%.

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**Figure 28.9** Lesion risk scores. **Top.** The probability of success by AHA type lesion (left) and the new SCAI class (right), treated with (open bars) and without (closed bars) coronary stenting. **Bottom.** The probability of a major complication based on AHA lesion type (left) and the new SCAI class (right), treated with (open bars) and without (closed bars) coronary stenting. The SCAI score, based simply on whether the vessel has one or more type C characteristics and is open or occluded, has a stronger predictive value for success and complications than that of the traditional AHA/ACC score. The beneficial effect of stenting on complications is evident (see also Table 28.3; From Krone RJ, Shaw RE, Klein LW, et al. Evaluation of the American College of Cardiology/American Heart Association and the Society for Coronary Angiography and Interventions lesion classification system in the current “stent era” of coronary interventions). (From the ACC-National Cardiovascular Data Registry. *Am J Cardiol* 2003;92:389–394, with permission.)
The Mayo Clinic experience from 1979 through 2004 shows the progressive trends in procedural success and in-hospital outcomes. Group 1, 1979–1989; group 2, 1990–1996; group 3, 1996 to February 2003; and group 4, March 2003 to 2004. Group 1 consisted of patients who principally underwent PTCA alone. Group 2 consisted of patients in whom stents were used mainly as a bailout strategy, with aggressive periprocedural anticoagulation. Group 3 included patients who regularly received bare-metal stents and frequent adjunctive glycoprotein IIb/IIIa inhibitors, accompanied by dual oral antiplatelet therapy. Group 4 consisted of patients whose PCI reflected contemporary practice and included treatment with DES. (From Singh et al. twenty-five-year trends in in-hospital and long-term outcome after percutaneous coronary intervention. Circulation 2007;115:2835–2841, with permission.)

abrupt closures can be reversed by simply readvancing the balloon dilatation catheter across the lesion to “tack up” the dissection via repeated balloon inflation, the emergency surgery rate fell in half to roughly 3%. Prolonged balloon inflations (up to 20 minutes, using an autoperfusion balloon to limit ongoing development of ischemia) further improved the ability to reverse abrupt closure.83

Since 1993, however, the availability of coronary stents has made the certainty of reversing abrupt closure >90%.84 This success has made it routine to stent any patient with a large postprocedure dissection as a preemptive treatment for threatened abrupt closure even when flow compromise is not apparent. Of course, with elective stenting of >90% of interventional procedures, this problem has been largely eliminated, with emergency surgery rates having fallen to <0.5%.6

Beyond the mechanical issues of residual stenosis and local dissection, it is now clear that platelet-rich clots contribute significantly to the abrupt closure process. The presence of thrombus, reflected as a globular filling defect, increases the risk of abrupt closure from 7.2% to 27.8%.79 The role of thrombus in abrupt closure is further supported by an increased risk of abrupt closure in patients with a subtherapeutic ACT and the reduction of ischemic endpoints seen in patients treated with glycoprotein IIb/IIIa inhibitors (see Chapter 5).83 Although platelets may adhere to a damaged vessel wall through a variety of receptors, activation of the glycoprotein IIb/IIIa receptors represents the final common pathway that allows them to bind avidly to fibrin to cause platelet aggregation and thrombosis (see Chapter 5). Vessels with moderate local dissection but preserved antegrade flow are thus more likely to stay patent in the presence of potent antiplatelet therapy (e.g., glycoprotein IIb/IIIa antagonists or pretreatment with thienopyridines), thereby reducing the incidence of emergency surgery. These agents also significantly reduce the incidence of periprocedural myocardial infarction, and particularly the incidence of biomarker elevations (non-Q-wave myocardial infarctions) that are seen in 20% to 30% of patients undergoing coronary intervention.

Branch Vessel Occlusion

Occlusion of a side branch originating from within the stenotic segment occurs in 14% of vessels at risk during angioplasty of the main vessel. This is generally owing to shifting of plaque which is sometimes referred to as the snowplow effect.85 If the branch vessel is small, this event usually has no significant
Figure 28.11 Use of a perfusion balloon catheter. **Top.** The inflated perfusion balloon (arrow) is shown in the left anterior descending artery and can be recognized by the presence of the non-contrast-filled (white) perfusion lumen running through the center of the balloon. **Bottom.** Injection through the guiding catheter (left curved arrow) shows direct opacification of the circumflex (straight arrow) as well as contrast flow into the distal left anterior descending. This flow enters through proximal side holes, passes through the perfusion lumen within the balloon, and flows out into the distal vessel (right curved arrow). The 40- to 60-mL/minute flow to the distal vessel through the perfusion lumen helps mitigate myocardial ischemia during prolonged balloon inflations. However, this device is no longer used in contemporary PCI practice since routine use of stents has made persistent abrupt closure a rare event.

Coronary Perforation

Guidewire-induced perforation occurs rarely; is typically seen in complex cases, especially during PCI for chronic total occlusions; and does not necessarily have dire consequences, unless a device is passed over the wire or the wire perforation takes place in a patient receiving a platelet IIb/IIIa receptor antagonist. Frank rupture of the coronary artery owing to the use of too large a dilatation balloon or the use of an atherectomy device can also cause vessel perforation that leads to rapid tamponade and hemodynamic collapse.60-61 Perforations may be classified based on angiographic appearance as type I—extra-luminal crater without extravasation; type II—pericardial and myocardial blush without contrast jet extravasation; and type III—extravasation through a frank (1 mm) perforation. In the absence of extravasation (type III), most perforations may be effectively managed without urgent surgical intervention. Even type III perforations can be managed nonoperatively with the combination of pericardiocentesis, reversal of anticoagulation, and either prolonged balloon inflation at the site of perforation or deployment of a covered stent. If these approaches are not successful, perforations usually require surgical repair.

Tamponade also may result from perforation of the right atrium or right ventricle during placement of temporary pacemaker electrode catheters, particularly in angioplasty patients who are receiving antiplatelet therapy in addition to full anticoagulation. This potential complication and the infrequency (<1%) of severe bradycardic complications support the recommendation against prophylactic pacing during clinical sequelae and should not discourage attempted angioplasty. On the other hand, if a large branch vessel originates from within the stenotic segment, simultaneous dilatation of the main vessel and the involved branch with two separate dilatation systems (the kissing-balloon technique) may be required for preservation of both vessels.66 This originally utilized two guidewires that could be inserted through a single guiding catheter (one guidewire placed into the main vessel and the other one into the involved side branch) to allow alternating advancement of a balloon catheter into one and then the other vessel.67 Current large-lumen guiding catheters and low-profile dilatation systems, however, now allow kissing balloon inflations through a single 7F or even 6F guiding catheter. The effective side-by-side balloon diameter in the proximal vessel can be estimated as the square root of the sum of the squares of the individual balloon diameters (two 3.0 balloons have an effective combined diameter of 4.25 mm [square root of 18 = 9 + 9]). Multiple studies have evaluated different bifurcation strategies, and in general have concluded that provisional stenting is the best, with stent placement in the main branch and stenting of the side branch only if needed. The results of PCI for some true bifurcation lesions can be improved, however, by the use of various bifurcation stent strategies (see Chapter 31) or atherectomy of both the parent and branch vessel68 (see Chapter 29).
coronary angioplasty, although such pacing is required for certain atherectomy and thrombectomy procedures (see Chapter 29). Ventricular fibrillation occurs in approximately 1% of angioplasty procedures, usually as the result of prolonged ischemia during balloon advancement or inflation. In addition to causing electrical instability, ischemia during balloon inflation may cause marked electrocardiographic changes, abnormalities in regional left ventricular systolic and diastolic function.

### Bleeding

Periprocedural bleeding is increasingly recognized as a risk factor for mortality, and its risk should be assessed prior to the procedure using one of several published risk scores. The incidence of periprocedural bleeding ranges from 3% to 6% depending on the patient population and the definition used. Several definitions, derived from clinical trials, are summarized in Table 28.4. Recently, the Bleeding Academic Research Consortium (BARC) has published a consensus classification that is likely to be helpful for standardizing definitions in clinical trials, but its value in routine practice is unclear.

The adverse effects of bleeding may be either owing to the direct consequence of the bleed or secondary to the ischemic complications that may occur owing to the discontinuation of the essential antplatelet or anticoagulant therapies. Bleeding may also be a marker of comorbidities associated with worse prognosis (e.g., frailty, gastrointestinal pathology, malignancy). Risk factors for bleeding include patient factors (e.g., advanced age, gender, low body mass index, preprocedural anemia, chronic kidney disease, acuity of presentation), potency of the anticoagulant and antiplatelet regimen used, vascular access site, and sheath size. Strategies to reduce the risks of bleeding include (a) the use of anticoagulation regimen with the optimal risk–benefit profile, (b) weight-based dosing of heparin and other agents, (c) use of activated clotting times to guide unfractionated heparin dosing, (d) avoidance of excess anticoagulation, (e) dosing adjustments in patients with chronic kidney disease, (f) use of radial artery access, and (e) avoidance of inadvertent femoral vein cannulation.

### Device Failures

Although guidewires and balloon catheters are extremely reliable, device failure can infrequently occur when any device is subjected to severe operating stresses (e.g., when a guidewire is rotated repeatedly in a single direction while its tip is held fixed in a total occlusion or when a balloon catheter is inflated past its operating pressure range in an attempt to dilate a resistant stenosis). In a small percentage of cases, this may lead to detachment of a part of the wire or dilatation catheter, with a fragment remaining in the coronary artery. In the stent era, this also includes dislodgment of the stent from its delivery balloon or failure of the stent delivery balloon to inflate or deflate properly. To avoid the need for surgical removal, the angioplasty operator should be familiar with various techniques (baskets, bioptomes, intertwined guidewires) for catheter retrieval. Although hard to remember in the heat of the moment, any failed products should be saved, sealed in a bag, and returned to the manufacturer for structural analysis, which may disclose a root-cause manufacturing flaw. Device failures should also be reported to the Food and Drug Administration’s (FDAs) Manufacturer and User Facility Device

<table>
<thead>
<tr>
<th>Table 28.4</th>
<th>Definitions of Major Bleeding</th>
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<tbody>
<tr>
<td><strong>TIMI (1988)</strong></td>
<td>Intracranial bleed</td>
</tr>
<tr>
<td><strong>GUSTO (1997)</strong></td>
<td>Intracranial bleed</td>
</tr>
<tr>
<td><strong>ACUITY (2006)</strong></td>
<td>Intracranial or intraocular</td>
</tr>
<tr>
<td><strong>REPLACE-2 (2007)</strong></td>
<td>Intracranial, intraocular, or retroperitoneal</td>
</tr>
<tr>
<td><strong>HORIZONS AMI (2009)</strong></td>
<td>Intracranial or intraocular</td>
</tr>
<tr>
<td>↓Hgb &gt;5 g/dL or ↓Hct &gt;15%</td>
<td>↓Hgb ≥ 3 g/dL with overt bleeding  Any ↓Hgb ≥ 4 g/dL</td>
</tr>
<tr>
<td>Any transfusion</td>
<td>Transfusion ≥2 units of PRBCs</td>
</tr>
<tr>
<td>Hemodynamic compromise requiring intervention</td>
<td>Access site bleeding requiring intervention</td>
</tr>
<tr>
<td>Access site bleeding requiring intervention Hematoma ≥5 cm</td>
<td>Reoperation for bleeding</td>
</tr>
<tr>
<td>Access site bleeding requiring intervention Hematoma ≥5 cm</td>
<td>Reoperation for bleeding</td>
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</tbody>
</table>

TIMI and GUSTO trials were in patients receiving fibrinolytic therapy for acute myocardial infarction. ACUITY, REPLACE-2, and HORIZONS trial recruited patients undergoing percutaneous coronary intervention.
Experience (MAUDE) database (online at www.accessdata.fda.gov/scripts/medwatch) to facilitate the recognition and tracking of patterns that may otherwise appear as just a random device failure event to a single operator.

THE HEALING RESPONSE TO CORONARY ANGIOPLASTY—RESTENOSIS

Following successful balloon angioplasty, the body attempts to repair the damage caused by the procedure-related mechanical injury. Within minutes, a layer of platelets and fibrin is deposited. Within hours to days, inflammatory cells infiltrate the site, cytokines are released, and vascular smooth muscle cells migrate from the media toward the lumen. These smooth muscle cells and fibroblasts transform into a synthetic phenotype and remain in this state as they undergo hypertrophy, proliferate, and begin to secrete extensive extracellular matrix (Figure 28.12). The luminal surface is simultaneously colonized by endothelial cells that slowly regain their normal barrier function and secretory functions (e.g., tissue plasminogen activator (t-PA) and nitric oxide synthesis). Along with this proliferative neointimal response, there may also be further elastic recoil and fibrotic contraction of the vessel wall (i.e., negative vessel remodeling) during this period. The extent of proliferation and remodeling appears to vary according to the artery and type of intervention—for example, obstruction within stents is predominantly caused by neointimal hyperplasia, whereas significant amount of late narrowing following stand-alone angioplasty occurs owing to contraction of the vessel wall. Although vessel recoil is eliminated by coronary stenting, incomplete stent expansion at the time of implantation is an important mechanism for recurrent stenosis, especially in calcified and fibrotic lesions. Stent fracture owing to mechanical fatigue caused by repetitive cardiac contraction that causes compression, torsion, bending, and shear stress may also account for some cases of recurrent stenosis (at least 4%).

Hypersensitivity to one or more components (e.g., Nickel) of the implanted stent has been proposed as a potential mechanism, although the evidence for this is limited. There are also significant patient-to-patient variations in the late healing response after coronary intervention, reflected in variable amounts of late loss in lumen diameter between the completion of the intervention and the time when the repair process stabilizes (-6 to 12 months). Follow-up angiography shows continued maintenance of lumen diameter at the treated site beyond this period in the majority of patients.

If the healing response is excessive, however, most or all of the gain in lumen diameter produced by the initial intervention may be lost to the healing process. This causes the return of a severe stenosis and ischemic symptoms—a phenomenon known as restenosis of the dilated segment (Figure 28.13). Throughout the 1980s, restenosis was considered a dichotomous outcome (like death) that either did or did not develop. Although a great deal was learned about restenosis from the study of conventional angioplasty patients (e.g., its time course, histology, and various clinical factors that correlated with an increased incidence of restenosis), data derived from stent and atherectomy procedures led to a new paradigm for evaluating restenosis. In this paradigm, restenosis was considered as a continuous variable,
and cumulative distribution curves were used to show the ranked population distribution of the late result (expressed as either late lumen diameter or late percent diameter stenosis) for the whole treated population (Figure 28.14). On the diameter stenosis curve, the percentage of the population that has a late diameter stenosis of >50% (binary restenosis) serves as a useful benchmark for comparing the angiographic restenosis rates between different populations or treatment groups. Target lesion revascularization owing to recurrent ischemia is an index of restenosis that is clinically significant, and its incidence is approximately 50% of angiographic restenosis.

Every treated lesion undergoes some degree of late loss, but fortunately late loss usually negates only part (roughly half) of the acute gain, so that a long-term net gain in lumen diameter results with alleviation of myocardial ischemia. In fact, there tends to be a roughly linear relationship between the acute gain in lumen diameter caused by the intervention and late loss in lumen diameter (caused by the proliferative and fibrotic reaction of the artery during the healing phase), with a slope (the loss index) of roughly 0.5 for most interventions. This means that larger lumen diameters immediately after intervention translate into larger lumen diameters at 6-month angiographic restudy (the “bigger is better” dictum). Prior to drug-eluting stents (see below), all new mechanical devices that have been able to deliver a lower restenosis rate than that of balloon angioplasty have done so by providing a larger acute lumen diameter (more acute gain), rather than by reducing the loss index (Figure 28.15). Angiographic restenosis following balloon angioplasty alone is common (up to 50%), is less frequent with bare-metal stents (20% to 30%), and is least often seen with drug-eluting stents (5% to 10%).

Figure 28.13  Clinical restenosis. A–D. A totally occluded right coronary artery with filling of the distal vessel by way of left to right collaterals. E The essentially normal appearance of the right coronary artery following successful angioplasty. F The appearance 6 weeks later when angina had recurred. G The appearance following successful re-PTCA. Restenosis developed again 6 weeks following the second PTCA, but the patient was then asymptomatic for more than 6 years after a third PTCA procedure. (From Dervan JP, Baim DS, Cherniles J, Grossman W. Transluminal angioplasty of occluded coronary arteries: use of a movable guide wire system. Circulation 1983;68:776.)
The view of restenosis as a continuous process that takes place to some degree in every treated segment favors displaying the late result (here, percent stenosis at follow-up) for the whole treated population. For patients treated by balloon angioplasty, directional atherectomy, or stenting, the Y axis shows the percent of patients who have a stenosis larger than the stenosis value on the X axis. The ability of stenting and atherectomy to lower restenosis is shown by a shift of their cumulative distribution function curves to the left. If a dichotomous definition of restenosis is applied, the intersection of each curve with a late diameter stenosis of 50% (vertical line) corresponds to a dichotomous restenosis rate of 43% for angioplasty, 31% for atherectomy, and 26% for stenting. (From Kuntz RE, et al. Novel approach to the analysis of restenosis. *J Am Coll Cardiol* 1992;19:1493.)

Except for antiproliferative therapies (e.g., drug-eluting stents and brachytherapy), the strongest determinants of the probability of restenosis (late diameter stenosis of >50%) are a large postprocedure lumen diameter and a low residual percent stenosis. Once these variables are taken into account, it no longer matters which device had been used—it is the result and not the device that matters. Balloon angioplasty (*triangles*) thus has a 2- to 2.3-mm lumen with a 40% restenosis rate, whereas stenting has a 2.9- to 3.2-mm lumen with a 20% restenosis rate (slightly worse results with stenting in the STRESS study are shown, as well). Directional atherectomy (*squares*) has an angioplastylike result in CAVEAT but a more stentlike result in BOAT and OARS (see Chapters 29 and 31). (Modified from Kuntz RE, et al. A generalized model of restenosis following conventional balloon angioplasty, stenting, and directional atherectomy. *J Am Coll Cardiol* 1993;21:15.)
The central importance of the acute postprocedure geometry to the late result, however, does not reduce the importance of factors that modulate the loss index. Clinical factors such as diabetes mellitus have a major effect on increasing loss index and restenosis for any given postprocedure result. The risk of restenosis may be estimated using models entirely dependent on clinical variables. One example is the Mid-America Heart Institute model, which uses the following characteristics: age >55 years, male gender, diabetes mellitus, acute myocardial infarction, severity of angina, previous PCI, and multivessel coronary artery disease. The range for the restenosis scores is 0 to 19. Scores in the ranges of 0 to 4, 5 to 8, and 9 to 19 have an estimated risk of restenosis of 15%, 23%, and 44%, respectively, with bare-metal stents in the year following the procedure.\textsuperscript{108} Although such a model is helpful, it is limited by the fact that it does not include lesion (e.g., length, vessel diameter, type C lesion, calcification, restenotic lesion, chronic total occlusion, and severe tortuosity), and procedural (e.g., minimal lumen diameter post PCI, type of stent) characteristics that strongly influence the likelihood of restenosis. A model for restenosis with drug-eluting stents has also been derived and validated from the EVENT registry using the following variables: age <60 years, prior PCI, unprotected left main PCI, saphenous vein graft PCI, minimum stent diameter ≤2.5 mm, and total stent length ≥40 mm.\textsuperscript{109} Scores of 0, 2, and 5 to 10 were associated with restenosis rates of 2.2%, 4.3%, and 7.5%, respectively.

There has been a relentless search for drugs or procedural variations that could decrease the late loss index. Although manipulating procedure-related variables (such as duration of conventional balloon inflation) has been unrewarding and trials of numerous systemic drug regimens (aspirin, nifedipine, ticlopidine, steroids, prolonged heparin administration, fish oil, mevinolin, ketanserin, etc.) have shown little or no beneficial effect against restenosis, two modalities (brachytherapy and drug-eluting stents) have shown important benefits against late loss and consequently, restenosis.

### Brachytherapy

Coronary brachytherapy was used in clinical practice for a short period of time in the past, but is no longer performed given the superiority of drug-eluting stents in preventing and treating restenosis. The therapy was based on the fact that delivery of 2,000 centigray of either beta\textsuperscript{110} or gamma\textsuperscript{111} radiation to the tissues of the coronary arterial wall greatly retards intimal proliferation and recurrent restenosis within bare-metal coronary stents. Thus, the combination of mechanical dilation plus coronary brachytherapy was shown to be an effective treatment for in-stent restenosis, though much of the benefit, in later studies, was found to be lost by 5-year follow-up. Trials of primary radiation at the time of stenting for de novo lesions were less impressive. As with drug-eluting stents, the inhibition of stent endothelialization by radiation treatment was associated with an increased risk of delayed stent thrombosis which had to be mitigated by long-term dual antiplatelet therapy.

### Drug-Eluting Stents

Contrary to the inability of systemic therapy to inhibit restenosis after angioplasty or stenting, the local release of antiproliferative drugs (e.g., sirolimus, paclitaxel, zotarolimus, everolimus) from a polymer matrix over the first few months after stent implantation can substantially reduce inflammation and smooth muscle cell proliferation within a stent (see Chapter 31). In this context, an effective drug reduces in-stent late loss from the usual 1 mm (500 μm on each side of the stent) to as little as 0.2 mm (100 μm on each side of the stent).\textsuperscript{112} This dramatically reduces the restenosis rate after initial stent implantation or after secondary implantation of a drug-eluting stent within an in-stent restenosis. To provide maximal benefit, the length of such drug-eluting stents should generally be somewhat (approximately 10 mm) longer than that of the lesion being treated to prevent injured but nontreated diseased areas at each end of a shorter stent. Since drug-eluting stents have delayed endothelialization as compared with bare-metal stents, the duration of dual antiplatelet therapy must be extended (minimum 12 months). Thus, it is important to carefully consider the appropriateness of using these stents in each case and review the need for, the duration of, and the ability of the patient to comply with dual antiplatelet therapy prior to the implantation. Drug-eluting stents are appropriate as an alternative to bare-metal stents in cases in which the risk of restenosis is higher (Table 28.5). In contrast, bare-metal stents or PTCA alone should be considered in patients who have a high bleeding risk, inability to comply with prolonged dual antiplatelet therapy, or have the potential need for a planned surgical procedure following the PCI which will require interruption of the dual antiplatelet therapy (Table 28.5).

#### CURRENT INDICATIONS

With the improvements in equipment and technique described above, PCI has become the dominant form of coronary revascularization (596,000 PCI versus 416,000 CABG procedures in the United States in 2009).\textsuperscript{5} However, the previous trend of steady rise in PCI volumes in the United States has reversed; the numbers of diagnostic cardiac catheterization and PCI being performed have gradually decreased since the mid 2000s onward\textsuperscript{5,113} (Figure 28.1). Potential reasons for the decline include (a) reduction in smoking and improved treatment of cardiovascular risk factors, (b) use of drug-eluting stents and the associated reduction in in-stent restenosis, and (c) potential impact of the COURAGE trial demonstrating similar outcomes for both medical therapy and PCI in a select population with stable coronary artery disease.\textsuperscript{114} Key issues that need to be addressed in patient selection for PCI include the following: (a) clinical justification for revascularization, (b) disease complexity which impacts the safety and efficacy of PCI, (c) potential advantages
and disadvantages of PCI as compared to other therapeutic options such as medical therapy or bypass surgery, and (d) what combination of interventional devices would offer the best short- and long-term outcomes. This evaluation process thus involves integration of complex clinical, angiographic, pathophysiologic, and procedural knowledge, and constitutes an important component of operator training (see Chapter 1). The current guidelines recommend that this function be executed in stable patients with unprotected left main and complex disease (e.g., SYNTAX score >22) via a multidisciplinary approach by establishing a “Heart Team” that is composed of an interventional cardiologist, a cardiac surgeon, and (often) the patient’s general cardiologist. Support for this strategy comes from studies showing that patients with complex CAD referred for revascularization in concurrent trial registries have lower mortality rates than those randomly assigned to PCI or CABG in the trials. Moreover the guidelines state that it is reasonable to use the STS and SYNTAX scores to assist making decisions regarding revascularization. The advantage of the SYNTAX score is that it is a unique tool that allows quantification of the angiographic complexity of coronary artery disease. However, it is complex to calculate and that introduces the potential for significant error. It may be calculated using an online calculator available at http://www.syntaxscore.com. The STS score is based on clinical characteristics and as such is easier to use and can also be derived from an online calculator at http://209.220.160.181/STSWebRiskCalc261/de.aspx.

With the rapid growth of PCI, there has been a series of guidelines and position papers published in Europe and the United States. The ACC/AHA first published Angioplasty Guidelines in 1988, updating them in 1993, 2001, 2005, and 2007. A comprehensive revision was published in 2011. These statements are useful compilations that outline some well-accepted indications and contraindications for PCI and are available online at http://www.cardiosource.org/science-and-quality.aspx. It is beyond the scope of this chapter to review these guidelines in detail, and the reader is referred to this excellent source of material and summaries. The discussion below includes some general commentary on specific situations.

**Percutaneous Coronary Intervention to Improve Survival in Stable Disease**

The 2011 guidelines do not give a class I recommendation for patients with left main stenosis. They recommend that PCI for this purpose is reasonable (class IIa), as an alternative to CABG, in selected stable patients with significant (>50% diameter stenosis) unprotected left main disease with (1) anatomic conditions associated with a low risk of PCI procedural complications and a high likelihood of good long-term outcome (e.g., a low SYNTAX score [<22], ostial or trunk left main stenosis); and (2) clinical characteristics that predict a significantly increased risk of adverse surgical outcomes (e.g., STS-predicted risk of operative mortality >5%; Table 28.6). In patients with unstable angina/non-ST-elevation myocardial infarction, PCI is reasonable when an unprotected left main coronary artery is the culprit lesion and the patient is not a candidate for CABG. Finally, in patients with acute STEMI, PCI is reasonable for an unprotected left main coronary artery that hosts the culprit lesion causing decreased blood flow (Thrombolysis In Myocardial Infarction [TIMI] grade <3), and PCI can be performed more rapidly and safely than CABG.

The only recommendation for PCI to improve survival in patients without left main disease is for those who survive sudden cardiac death with presumed ischemia-mediated ventricular tachycardia caused by significant (>70% diameter) stenosis in a major coronary artery Table 28.6. This is a class I recommendation for which either PCI or CABG may be performed, as considered appropriate.
### ACCF/AHA/SCAI Guidelines on Revascularization to Improve Survival as Compared to Medical Therapy

<table>
<thead>
<tr>
<th>Anatomic Setting</th>
<th>COR</th>
<th>LOE</th>
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</thead>
<tbody>
<tr>
<td>UPLM or complex CAD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG and PCI</td>
<td>I—HeartTeam approach recommended</td>
<td>C</td>
</tr>
<tr>
<td>CABG and PCI</td>
<td>IIa—Calculation of STS and SYNTAX scores</td>
<td>B</td>
</tr>
<tr>
<td>UPLM*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>PCI</td>
<td>IIa—For SIHD when both of the following are present</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>- Anatomic conditions associated with a low risk of PCI procedural complications and a high likelihood of good long-term outcome (e.g., a low SYNTAX score of &lt;22, ostial or trunk left main CAD)</td>
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<tr>
<td></td>
<td>- Clinical characteristics that predict a significantly increased risk of adverse surgical outcomes (e.g., STS-predicted risk of operative mortality ≥5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IIa—For UA/NSTEMI if not a CABG candidate</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>IIa—For STEMI when distal coronary flow is TIMI flow grade &lt;3 and PCI can be performed more rapidly and safely than CABG</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>IIb—For SIHD when both of the following are present</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>- Anatomic conditions associated with a low to intermediate risk of PCI procedural complications and an intermediate to high likelihood of good long-term outcome (e.g., low-intermediate SYNTAX score of &lt;33, bifurcation left main CAD)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Clinical characteristics that predict an increased risk of adverse surgical outcomes (e.g., moderate-severe COPD, disability from prior stroke, or prior cardiac surgery; STS-predicted risk of operative mortality &gt;2%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>III: Harm—For SIHD in patients (versus performing CABG) with unfavorable anatomy for PCI and who are good candidates for CABG</td>
<td>B</td>
</tr>
<tr>
<td>3-vessel disease with or without proximal LAD artery disease*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>IIa—It is reasonable to choose CABG over PCI in patients with complex 3-vessel CAD (e.g., SYNTAX score &gt;22) who are good candidates for CABG</td>
<td>B</td>
</tr>
<tr>
<td>PCI</td>
<td>IIb—Of uncertain benefit</td>
<td>B</td>
</tr>
<tr>
<td>2-vessel disease with proximal LAD artery disease*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>PCI</td>
<td>IIb—Of uncertain benefit</td>
<td>B</td>
</tr>
<tr>
<td>2-vessel disease without proximal LAD artery disease*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>PCI</td>
<td>IIb—Of uncertain benefit</td>
<td>B</td>
</tr>
</tbody>
</table>
Percutaneous Coronary Intervention to Improve Symptoms

PCI is more often performed to relieve symptoms than improve survival. For this purpose, the 2011 guidelines state that PCI (or CABG) is beneficial in patients with one or more significant (> 70% diameter) coronary artery stenoses amenable to revascularization and unacceptable angina despite guideline-directed medical therapy Table 28.7.16 A lower level of indication (class IIa) is given by the guidelines for PCI (or CABG) to improve symptoms in patients with one or more significant (> 70% diameter) coronary artery stenoses and unacceptable angina for whom guideline-directed medical therapy cannot be implemented because of medication contraindications, adverse effects, or patient preferences. Similarly, PCI is reasonable in patients with previous CABG,
Table 28.7  
ACCF/AHA/SCAI Guidelines on Use of Revascularization to Improve Symptoms as Compared to Medical Therapy

<table>
<thead>
<tr>
<th>Clinical Setting</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 significant stenoses amenable to revascularization and unacceptable angina despite GDMT</td>
<td>I—CABG</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>I—PCI</td>
<td></td>
</tr>
<tr>
<td>≥1 significant stenoses and unacceptable angina in whom GDMT cannot be implemented because of medication contraindications, adverse effects, or patient preferences</td>
<td>IIa—CABG</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>IIa—PCI</td>
<td></td>
</tr>
<tr>
<td>Previous CABG with ≥1 significant stenoses associated with ischemia and unacceptable angina despite GDMT</td>
<td>IIa—PCI</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>IIb—CABG</td>
<td></td>
</tr>
<tr>
<td>Complex 3-vessel CAD (e.g., SYNTAX score &gt;22) with or without involvement of the proximal LAD artery and a good candidate for CABG</td>
<td>IIa—CABG preferred over PCI</td>
<td>B</td>
</tr>
<tr>
<td>Viable ischemic myocardium that is perfused by coronary arteries that are not amenable to grafting</td>
<td>IIb—TMR as an adjunct to CABG</td>
<td>B</td>
</tr>
<tr>
<td>No anatomic or physiologic criteria for revascularization</td>
<td>III: Harm—CABG</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>III: Harm—PCI</td>
<td></td>
</tr>
</tbody>
</table>

CABG indicates coronary artery bypass graft; CAD, coronary artery disease; COR, class of recommendation; FFR, fractional flow reserve; GDMT, guideline-directed medical therapy; LOE, level of evidence; N/A, not applicable; PCI, percutaneous coronary intervention; SYNTAX, Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery; and TMR, transmyocardial laser revascularization.


one or more significant (>70% diameter) coronary artery stenoses associated with ischemia, and unacceptable angina despite guideline-directed medical therapy.

Percutaneous Coronary Intervention in Acute Coronary Syndromes

A detailed discussion on the application of PCI in patients with non–ST-elevation acute coronary syndrome or STEMI is provided in Chapter 30. The purpose of angiography and revascularization, if needed, in non–ST-elevation acute coronary syndrome is to relieve ischemia and symptoms as well as reducing the risk of death and (recurrent) myocardial infarction. Selection of patients for an early invasive strategy (i.e., diagnostic angiography with intent to perform revascularization) is based on risk stratification. Patients in whom this approach is indicated are individuals without serious comorbidities or contraindications to the procedures, who either have an elevated risk for clinical events or have refractory angina/hemodynamic compromise/electrical instability. The selection of PCI or CABG as the means of revascularization should generally be based on the same considerations as those for patients without ACS. The indications for angiography in STEMI are summarized in Table 28.8.

Hybrid Coronary Revascularization

Hybrid revascularization is defined as the combination of planned minimally invasive CABG with a left internal...
Table 28.8 Indications for Coronary Angiography in STEMI

<table>
<thead>
<tr>
<th>Indications</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate coronary angiography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candidate for primary PCI</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Severe heart failure or cardiogenic shock (if suitable revascularization candidate)</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Moderate to large area of myocardium at risk and evidence of failed fibrinolysis</td>
<td>Ila</td>
<td>B</td>
</tr>
<tr>
<td>Coronary angiography 3–24 h after fibrinolysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemodynamically stable patients with evidence for successful fibrinolysis</td>
<td>Ila</td>
<td>A</td>
</tr>
<tr>
<td>Coronary angiography before hospital discharge</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable patients</td>
<td>Iib</td>
<td>C</td>
</tr>
<tr>
<td>Coronary angiography at any time</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients in whom the risks of revascularization are likely to outweigh the benefits or the patient or designee does not want invasive care</td>
<td>III: No Benefit</td>
<td>C</td>
</tr>
</tbody>
</table>

COR indicates class of recommendation; LOE, level of evidence; N/A, not applicable; PCI, percutaneous coronary intervention; and STEMI, ST-elevation myocardial infarction.


Mammary (LIMA) graft to the left anterior descending (LAD) artery and PCI in one or more non-LAD coronary arteries. The available data on this topic are too limited to allow definitive recommendations, and no randomized trial has compared the hybrid strategy with PCI or CABG alone. Small observational studies have reported low mortality rates (0% to 2%) and acceptable event-free survival rates (83% to 92% at 6 to 12 months), and similar outcomes for conventional CABG at 30 days and 6 months.122 126 The goal of hybrid revascularization is to combine the advantages (durability and survival benefit) of the LIMA graft with the relative simplicity of PCI in patients who have multivessel disease involving the LAD. Hybrid revascularization is reasonable in patients in whom technical or anatomic limitations to performing one form of revascularization alone are present (e.g., lack of suitable graft conduits, heavily calcified ascending aorta, a non-LAD coronary artery unsuitable for bypass but amenable to PCI, nonfeasibility of PCI of the LAD). The procedures may be performed in a hybrid suite in one operative setting or as a staged procedure (typically during the same hospital stay) when CABG is performed before PCI in order to document the patency of the LIMA graft during subsequent angiography and to avoid the risk of perioperative bleeding in patients requiring dual antiplatelet therapy. Angiography of grafts placed during minimally invasive surgery is generally recommended because of the lower graft patency rates as compared with traditional surgery through a midline sternotomy.

Complete Revascularization

CABG more often results in complete or near complete revascularization than does PCI. There are no data from any randomized trial comparing complete and incomplete revascularization. The extent to which initial incomplete revascularization influences outcomes is unclear. In a retrospective analysis from the BARI trial comparing CABG to PCI with bare-metal stents, there was no independent survival advantage from complete as compared to incomplete revascularization. The authors concluded that construction of more than one graft to any system other than the LAD conferred no long-term advantage.127
In a contemporary single-center retrospective study of 1914 consecutive patients with multivessel coronary disease undergoing drug-eluting stent implantation (1,400 patients) or coronary artery bypass graft surgery (514 patients), the frequency of complete revascularization ranged from 40.9% to 56.6% for PCI and 66.9% to 78.2% for CABG depending on the definition of complete revascularization. Anatomically complete revascularization did not improve the long-term clinical outcomes after either PCI or CABG. In patients with extensive coronary artery disease, however, multivessel incomplete revascularization was associated with unfavorable long-term clinical outcomes. In general, as one would expect, the need for subsequent CABG is usually higher in those with initial incomplete revascularization with PCI.

**APPROPRIATENESS CRITERIA FOR USE OF PERCUTANEOUS CORONARY INTERVENTION IN CORONARY REvascularization**

As described in this chapter, PCI is associated with significant benefits which are accompanied by inherent risks and costs. Advances in technique and widespread availability allow PCI to be performed in a wide spectrum of patients. However, medical therapy and CABG are often viable alternatives, and in some cases, superior options. Thus, assessing the appropriateness of PCI in clinical practice, as with any diagnostic or therapeutic modality, may provide a process to facilitate communication between patients and physician, identification of procedural overuse, quality improvement, education, and potential cost savings. Recently, appropriate-use criteria for coronary revascularization have been developed by consensus among six professional organizations with subsequent minor revisions. The criteria are based on the acuity of disease (stable versus acute coronary syndrome), assessment of ischemic burden by a stress test, severity of symptoms, adequacy of medical therapy, and angiographic complexity of the coronary atherosclerosis (Figures 28.16 and 28.17). They are intended to provide guidance rather than be a substitute for good clinical judgment and experience, and acknowledge the difficulty or uncertainty that often exists in clinical decision-making. While the role of these criteria in clinical practice remain to be established, a recent study from a large multicenter national registry reported that 98.6% of all PCI performed in the United States for acute indications (STEMI and high-risk non–ST-elevation acute coronary syndrome) was for appropriate indications. In contrast, among PCI performed for non-acute indications, 50.4% was

![Figure 28.16](image-url) Appropriateness criteria for acute coronary syndromes. A indicates appropriate; CAD, coronary artery disease; HF, heart failure; I, inappropriate; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; U, uncertain; and UA/NSTEMI, unstable angina/non–ST-elevation myocardial infarction. (From Patel M et al. Appropriateness Criteria for Coronary Revascularization: a report by the American College of Cardiology Foundation Appropriateness Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, and the American Society of Nuclear Cardiology Endorsed by the American Society of Echocardiography, the Heart Failure Society of America, and the Society of Cardiovascular Computed Tomography. *Circulation* 2009;119:1330–1352.)
Chapter 28 Percutaneous Balloon Angioplasty and General Coronary Intervention

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Low-Risk Findings on Noninvasive Study</th>
<th>Stress Test</th>
<th>Asymptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Med. Rx</td>
<td></td>
<td>U A A A A</td>
<td>U A A A A</td>
</tr>
<tr>
<td>Class II or IV Max Rx</td>
<td></td>
<td>U U A A A</td>
<td>U U A A A</td>
</tr>
<tr>
<td>Class I or II Max Rx</td>
<td></td>
<td>I I U U U</td>
<td>Int Risk Max Rx</td>
</tr>
<tr>
<td>Asymptomatic Max Rx</td>
<td></td>
<td>I U A A A</td>
<td>Int Risk No/min Rx</td>
</tr>
<tr>
<td>Class II or IV No/min Rx</td>
<td></td>
<td>I U U A A</td>
<td>Int Risk No/min Rx</td>
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<tr>
<td>Class I or II No/min Rx</td>
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<td>I I U U U</td>
<td>Int Risk No/min Rx</td>
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<tr>
<td>Asymptomatic No/min Rx</td>
<td></td>
<td>I I U U U</td>
<td>Int Risk No/min Rx</td>
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<table>
<thead>
<tr>
<th>Coronal Anatomy</th>
<th>CTO of 1 vz; no other disease</th>
<th>1-2 vz; disease; no Prox. LAD</th>
<th>1 vz; disease of Prox. LAD</th>
<th>2 vz; disease with Prox. LAD</th>
<th>3 vz; disease; no Left Main</th>
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<tbody>
<tr>
<td></td>
<td>CTO of 1 vz; no other disease</td>
<td>1-2 vz; disease; no Prox. LAD</td>
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<td>2 vz; disease with Prox. LAD</td>
<td>3 vz; disease; no Left Main</td>
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<table>
<thead>
<tr>
<th>Intermediate-Risk Findings on Noninvasive Study</th>
<th>CCS Class I or II Angina</th>
</tr>
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<tbody>
<tr>
<td>Symptoms</td>
<td>Med. Rx</td>
</tr>
<tr>
<td>Class III or IV Max Rx</td>
<td>U A A A A</td>
</tr>
<tr>
<td>Class I or II Max Rx</td>
<td>U U A A A</td>
</tr>
<tr>
<td>Asymptomatic Max Rx</td>
<td>I U U U U</td>
</tr>
<tr>
<td>Class III or IV No/min Rx</td>
<td>I U U U U</td>
</tr>
<tr>
<td>Class I or II No/min Rx</td>
<td>I U U U U</td>
</tr>
<tr>
<td>Asymptomatic No/min Rx</td>
<td>I I U U U</td>
</tr>
</tbody>
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<tr>
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<tr>
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<td>CTO of 1 vz; no other disease</td>
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<td>2 vz; disease with Prox. LAD</td>
<td>3 vz; disease; no Left Main</td>
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<thead>
<tr>
<th>High-Risk Findings on Noninvasive Study</th>
<th>CCS Class III or IV Angina</th>
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<tbody>
<tr>
<td>Symptoms</td>
<td>Med. Rx</td>
</tr>
<tr>
<td>Class III or IV Max Rx</td>
<td>A A A A A</td>
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<tr>
<td>Class I or II Max Rx</td>
<td>U U A A A</td>
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<tr>
<td>Asymptomatic Max Rx</td>
<td>U U U U U</td>
</tr>
<tr>
<td>Class III or IV No/min Rx</td>
<td>I U U U U</td>
</tr>
<tr>
<td>Class I or II No/min Rx</td>
<td>U U U U U</td>
</tr>
<tr>
<td>Asymptomatic No/min Rx</td>
<td>I U U U U</td>
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</tbody>
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<tr>
<td></td>
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<td>2 vz; disease with Prox. LAD</td>
<td>3 vz; disease; no Left Main</td>
</tr>
</tbody>
</table>

Figure 28.17 Appropriateness criteria for patients with stable coronary artery disease without prior bypass surgery who have low-risk findings on noninvasive imaging (top left panel), are asymptomatic (top right panel), have intermediate-risk findings on noninvasive imaging study (middle left panel), CCS Class I or II angina (middle right panel), high-risk findings on noninvasive imaging (bottom left panel), and CCS Class III or IV angina (bottom right panel). A indicates appropriate; CTO, chronic total occlusion; I, inappropriate; Int., intervention; Med., medical; Prox. LAD, proximal left anterior descending artery; Rx, treatment; U, uncertain; and vz., vessel. (From Patel M, et al. Appropriateness Criteria for Coronary Revascularization: a report by the American College of Cardiology Foundation Appropriateness Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, and the American Society of Nuclear Cardiology Endorsed by the American Society of Echocardiography, the Heart Failure Society of America, and the Society of Cardiovascular Computed Tomography. *Circulation* 2009;119:1330–1352.)
classified as appropriate, 38.0% as uncertain, and 11.6% as inappropriate. The majority of inappropriate PCIs for non-acute indications were performed in patients without angina, with low-risk ischemia on stress testing, or with suboptimal (≤1 medication) antianginal therapy.\textsuperscript{130} The findings suggest that the great majority of procedures in contemporary practice are performed for appropriate indications and that there appears to be substantial variation among hospitals in the rate of “inappropriate” procedures for non-acute indications (median 10.8%; interquartile range 6.0% to 16.7%).

**QUALITY AND REGULATORY CONSIDERATIONS**

The 2011 PCI guidelines recommend that every PCI program operate a quality improvement program that routinely (a) reviews quality and outcomes of the entire program; (b) reviews results of individual operators; (c) includes risk adjustment; (d) provides peer review of difficult or complicated cases; and (e) performs random case reviews. In addition, every PCI program should participate in a regional or national PCI registry for the purpose of benchmarking outcomes against current national norms.\textsuperscript{13} PCI quality and performance considerations are defined by attributes related to structure (e.g., equipment, supplies, staffing, institutional and operator-level volumes, and the availability of electronic medical records, processes, and risk-adjusted outcomes) and processes (protocols for pre- and postprocedural care, appropriate procedural execution and management of complications, participation in databases and registries). Risk-adjusted outcomes are the consequence of these structural and procedural elements of care, and when available are more reliable measures of quality than are the institutional or individual operator volumes. These data can be used for internal quality-improvement efforts and public reporting.

Early in the development of coronary angioplasty, physicians active in diagnostic catheterization learned to perform angioplasty by attending live demonstration courses and watching or assisting on a small number of procedures (e.g., 10 to 20) under the guidance of a knowledgeable operator. Given the ever-increasing complexity of the procedure, however, virtually all new PCI operators since the mid-1980s have received formal training consisting of a third (and often fourth) year of interventional fellowship beyond completion of their training in diagnostic coronary angiography. These fellowships are now approved by the Accreditation Council for Graduate Medical Education (ACGME; see Chapter 1) and require the interventional trainee to perform a minimum of 250 procedures.\textsuperscript{131} It is reasonable for all physicians who perform PCI to participate in the American Board of Internal Medicine interventional cardiology board certification and maintenance of certification programs.

Broadly speaking there is a volume–outcome relationship at both the institutional and operator level.\textsuperscript{132,133} However, this relationship is complex and inconsistent across low-volume institutions or operators. Operator experience may modify the volume–outcome relationship, and hence risk-adjusted outcomes is the preferred metric.\textsuperscript{134,135}

The 2011 PCI guidelines recognize that there is controversy on this topic, and recommend the following operator and individual volumes for maintaining competency.\textsuperscript{16} Elective/urgent PCI should be performed by operators with an annual volume of >75 procedures at high-volume centers (>400 procedures) with on-site cardiac surgery with outcomes that meet national benchmarks. The guidelines allow some flexibility by stating that it is reasonable for operators with >75 PCI/year to perform elective/urgent PCI at low-volume centers (200 to 400 PCI procedures per year) with on-site cardiac surgery. Also, it is reasonable that low-volume operators (<75 PCI per year) perform elective/urgent PCI at high-volume centers (>400 PCI procedures per year) with on-site cardiac surgery. Ideally, operators with an annual procedure volume of <75 should only work at institutions with an activity level of >600 procedures per year, and should develop a defined mentoring relationship with a highly experienced operator who has an annual procedural volume of at least 150 procedures per year. Finally, primary PCI for STEMI should be performed by experienced operators who perform >75 elective PCI procedures per year and, ideally, at least 11 PCI procedures for STEMI per year. Ideally, these procedures should be performed in institutions that perform >400 elective PCI per year and >36 primary PCI procedures for STEMI per year. These recommendations for operator volume may change in the future.\textsuperscript{137}

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47. Sanborn TA, Faxon DP, Haudenschild CC, Gottsman SB, Ryan TJ. The mechanism of transluminal angioplasty: evidence for
82. Paik GY, Kuntz RE, Baim DS. Percusion therapy to resolve myocardial ischemia en route to emergency bypass grafting for failed percutaneous transluminal angioplasty. J Intervent Cardiol 1995;8:319.


Coronary stenting with or without adjunctive balloon angioplasty is currently the definitive strategy for the large majority of coronary interventions. While this approach generally achieves stable acute results and excellent long-term outcomes, in certain cases alternative techniques remain critical for clinical success, either as an adjunct to stenting or as the definitive strategy. Important techniques include plaque removal (atherectomy), thrombus extraction (thrombectomy), and the capture and removal of embolic debris (embolic protection). Appropriate application of these strategies will optimize clinical outcomes in the most cost-effective manner.

ATHERECTION

The role of coronary atherectomy has evolved dramatically since its introduction as a method to improve upon the results of balloon angioplasty. While angioplasty relied upon the fracture and displacement of obstructing coronary atherosclerotic plaque, it was hypothesized that plaque removal would achieve a larger post-procedural luminal diameter and yield reduced long-term restenosis rates. Despite great early enthusiasm for atherectomy as a definitive primary strategy, after two decades of study and clinical experience this technique now generally serves to facilitate coronary stenting in certain complex lesion subsets.

Percutaneous Transluminal Rotational Atherectomy

Mechanism of Percutaneous Transluminal Rotational Atherectomy

Percutaneous transluminal rotational atherectomy (PTRA) operates on the principle of “differential cutting” in which hard, fibrocalcific plaque can be ablated by a rotating burr while softer tissue in the treated coronary segment deflects away from the device and remains relatively unaltered. Plaque is ablated and pulverized into particles generally <10 to 15 μm in diameter that can pass through the coronary microcirculation for uptake by the reticuloendothelial system.1-3

Device Specifics

The Rotalink® burr catheter (Boston Scientific, Boston, MA) consists of an elliptical, nickel-coated brass burr attached to a hollow flexible 4.3F drive shaft, which is encased in a Teflon sheath (Figure 29.1). The sheath protects the artery proximal to the lesion from the rotating drive shaft and allows flush solution to be pumped to lubricate the drive shaft and burr. The burr’s ablative distal surface is embedded with 20 μm diamond chips, with 5 μm protruding from the surface. The proximal nonablative surface of the burr is smooth. The back end of the Rotalink® burr catheter is connected to a Rotalink® advancer, which allows the operator to extend and retract the burr within the vessel (Figures 29.2 and 29.3). A control console delivers air or nitrogen through a pneumatic hose to the turbine housed within the Rotalink® advancer to spin the drive shaft and the burr (Figures 29.4 and 29.5). The console is activated by a foot pedal (Figure 29.6); turbine pressure is adjusted by a control knob; and rotational speed is monitored by a fiberoptic tachometer. The RotaWire™ guidewires combine a 0.009-inch diameter body with a 0.014-inch tip (Figure 29.7), and are supplied with a specific wire clip to facilitate wire manipulation (Figure 29.8). The burr can be advanced over the 0.009-inch section, but its forward movement is delimited by the wider wire tip. During turbine activation, a wire brake is engaged to prevent spinning of the guide wire, which could otherwise traumatize the distal vessel. The wire clip provides a secondary brake. The RotaWire™ guidewires have no lubricious coating, no shaping ribbon, and are easily kinked.
Figure 29.1  Rotablator burr, drive shaft, and sheath. Ablative distal burr surface (thick white arrow); burr proximal nonablative surface (double arrow); drive shaft (solid white arrow); and Teflon sheath (dashed arrow). (Courtesy of Boston Scientific.)

Figure 29.2  Rotalink® advancer. (Courtesy of Boston Scientific.)

Figure 29.3  Rotalink® advancer. (Courtesy of Boston Scientific.)
Technique

The selection of PTRA depends on specific characteristics of the lesion and the patient. Generally, this technique is not applied in acute myocardial infarction, thrombotic lesions, coronary dissections, or saphenous vein grafts (SVG) with poor distal runoff, nor in the setting of severe left ventricular dysfunction. Patients are pretreated with aspirin and possibly a calcium channel blocker to counteract PTRA-induced vasospasm. The role of thienopyridines with PTRA has not been rigorously studied, but glycoprotein (GP) IIb/IIIa receptor antagonists have shown benefit in limiting speed-dependent platelet activation.\textsuperscript{4,5} Appropriate anticoagulation is instituted. Some operators prefer unfractionated heparin over bivalirudin to facilitate reversal of anticoagulation in the event of vessel perforation, although bivalirudin has been used with similar clinical outcomes.\textsuperscript{6} Rotaglide™, a lipid emulsion, can be added to the flush solution to reduce friction, limit heat generation, and facilitate device deliverability.
This should not be used in patients who are allergic to egg products or olive oil. Various combinations of vasodilators are often added as well to counteract vasospasm and microvascular no-reflow. Typical “RotaFlush” solutions mix 4 mg of nitroglycerin and 5 mg of verapamil in 500 mL of saline. A temporary pacing wire is generally utilized in PTRA of the right coronary or dominant circumflex owing to the risk of profound bradycardia, which is believed to result from adenosine release with red cell fragmentation.

A guiding catheter with a gentle curve and an inner diameter at least 0.004 inch longer than the anticipated largest burr diameter is recommended, to minimize resistance to device advancement. Complex lesions are often difficult to cross with rotablator wires owing to their poor torquability. In such cases, a conventional exchange length angioplasty wire is used to cross and then exchanged for the rotablator guidewire using a suitable transport or low-profile balloon catheter. Typically, a RotaWire™ floppy is chosen in order to minimize guidewire bias—a phenomenon observed when a stiff guidewire straightens a curved vessel segment and causes deeper cuts or dissection as the burr is forced against the tautly stretched lesser curvature of the vessel. On the other hand, the floppy guidewire may fail to adequately constrain the burr’s passage around tight bends, leading to uncontrolled cutting on the greater curvature of the vessel. The RotaWire™ extra-support wire is generally utilized for some distal or very heavily calcified lesions. Burrs for coronary use are available in 1.25 to 2.5 mm diameters. The selection of burr size is largely empirical, but the final burr-to-artery ratio should generally not exceed 0.7 (e.g., 2.15-mm burr in a 3.0-mm vessel). In treating long segments of disease, heavily calcified lesions, and subtotal de novo lesions, it is generally advisable to start with a smaller (1.5 or 1.75 mm) burr and step up to the final burr size in 0.5-mm increments.

Once the guidewire is placed across the lesion, the burr should be advanced to within a few centimeters of the rotating hemostatic valve, with the lines for compressed air supply and tachometer readout attached to the drive console and the advancer lever locked in its midway position. The compressed air or nitrogen source to the console is confirmed to have a pressure of at least 500 PSI. A preprocedural “DRAW” checklist, consisting of the following steps, is then applied: (i) “Drip”—Adequate flow of the pressurized heparinized flush through the Teflon sheath is visualized; (ii) “Rotation”—While the operator holds the catheter carefully so that the burr tip is not in contact with the sterile drapes, the system should be tested by depressing the foot pedal and having an assistant adjust the turbine pressure to achieve the desired burr speed; (iii) “Advancer”—Test whether the advancer moves the burr freely; (iv) “Wire”—Ensure that the wire clip is in place on the wire and test whether the brake locks the wire in place during rotation. Once this test has been completed, the static burr can be advanced over the wire into and through the guiding catheter. Any resistance encountered as the burr is passed around the primary curve of the guiding catheter can be overcome by firm traction on the guidewire or gentle traction on the guiding catheter itself to lessen the curve slightly. It may be noted, however, that the guiding catheter must remain well seated in the vessel ostium to prevent kinking or looping of the guidewire in the aortic root while the burr is advanced—such unrecognized loops in the radiolucent wire can lead to its transection when the burr is activated at the ostium.

Once the burr has been advanced to 1 to 2 cm proximal to the target lesion, the advancer lever should be unlocked and pulled gently back to near its proximal limit as the entire catheter is withdrawn gently by 1 or 2 mm. This relieves any

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**Figure 29.7**  Rotablator wires. (Courtesy of Boston Scientific.)

**Figure 29.8**  Rotablator wire clip. (Courtesy of Boston Scientific.)
compression in the drive shaft that might otherwise cause the burr to lurch forward into the lesion on activation. Under fluoroscopy, the burr is then activated by the foot pedal and adjusted to the desired “platform” speed (generally 160,000 to 180,000 rpm for burrs ≤ 2.0 mm, 140,000 to 160,000 rpm for burrs > 2.0 mm) before engaging the lesion. Advancement of the lever then brings the spinning burr slowly into contact with the lesion. It is important to be aware of the sound of the turbine, the rotational speed display, and tactile feedback during rotablation. When the burr face encounters excessive resistance to rotation, the speed will fall, but it is essential to avoid speed drops of >5,000 rpm during advancement.8 Larger speed drops caused by excessive pressure on the burr against the lesion may result in the liberation of larger particles, frictional heating of the plaque, or torsional dissection. We prefer advancing with a “pecking” motion in which brief (1 to 3 seconds) periods of plaque contact are alternated with longer (3 to 5 seconds) periods of reperfusion provided by pulling the burr back from the plaque face. This reduces speed drops and aids in the clearance of particulate debris through the distal circulation. Some operators favor intermittent injections of dilute contrast through the guide during the burr run to monitor for vessel complications and to enhance clearance of particulate debris.

After a brief run (usually <30 seconds of operation), the device should be withdrawn into the proximal vessel and rotation suspended for a similar time before reactivating and advancing the burr again. During each pause, a small test injection should be performed to ensure antegrade flow and absence of vascular trauma or perforation. This sequence should be repeated until the device can be advanced through the full length of the lesion without any fluoroscopic or tactile resistance to burr advancement and with no audible change in the pitch of the turbine or reduction in burr speed. The foot pedal is then used to activate the lower speed “dynaglide” mode, and the burr is removed while depressing the brake-release button. It is important to note that in the dynaglide mode the burr is not subject to pressure control (spinning at 90,000 rpm in all circumstances) and should never be advanced in this mode.

Clinical Results
Rotablator as a Definitive Strategy
Despite the intuitive appeal of plaque ablation, three randomized trials have failed to demonstrate superiority of PTRA as a stand-alone procedure when compared to PTCA for the treatment of native coronary lesions (Table 29.1).9 In the Excimer Laser, Rotational Atherectomy, and Balloon Angioplasty (ERBAC) study 685 patients with a symptomatic, complex native coronary lesion (>70% AHA/ACC type B2 or C) were randomized to PTCA, excimer laser coronary Angioplasty (ELCA), or PTRA.10 While PTRA achieved superior procedural success as compared to PTCA, target lesion revascularization at 6 months was higher with PTRA (42.4% versus 31.9%, P = 0.01). In the randomized Comparison of Balloon-Angioplasty versus Rotational Atherectomy (COBRA) study of 502 patients with complex native coronary lesionsPTRA had higher acute procedural success, but no improvement in a composite clinical outcome at 6 months.11 Rotational atherectomy was compared to PTCA for small coronary artery (2 to 3 mm) lesions in 446 patients in the randomized Dilatation versus Ablation Revascularization Trial Targeting Restenosis (DART) trial.12 Procedural success was similar for the two strategies, with no difference in binary restenosis at 8 months (50.5% for both) or in target vessel failure at 1 year (30.5% versus 31.2%).

Attempts to enhance PTRA results with more aggressive debulking have not shown further benefit. In the Study to Determine Rotablator and Transluminal Angioplasty Strategy (STRATAS), a technique using a burr-to-artery ratio of <0.7 plus standard balloon Angioplasty was compared to more aggressive debulking with a burr-to-artery ratio of 0.7 to 0.9 alone or with minimal balloon inflation (1 atm).8 The aggressive debulking technique was associated with similar procedural success, similar dichotomous restenosis rates at 6 months (58% versus 52%), but more periprocedural infarctions (11% versus 7%). Burr decelerations of >5,000 rpm lasting >5 seconds were associated with increased periprocedural MI and restenosis. In the Coronary Angioplasty and Rotablator Atherectomy Trial (CARAT) evaluating a burr-to-artery ratio of >0.7 versus <0.7, the more aggressive strategy did not reduce target vessel revascularization, but was associated with higher rates of acute complications (12.7% versus 5.1%, P < 0.05).7 Recognizing that even aggressive debulking is not superior to PTCA, current ACC-AHA-SCAI guidelines do not support use of PTRA for routine coronary lesions (Class III recommendation).13

Rotational Atherectomy for In-Stent Restenosis
Randomized trials have reported conflicting data regarding PTRA of in-stent restenosis.14-18 The single-center Randomized trial of Rotational Atherectomy versus Balloon Angioplasty for Diffuse In-Stent Restenosis (ROSTER) used IVUS to exclude patients with poorly dilated stents and demonstrated benefit for debulking with PTRA as compared to PTCA alone.16 In contrast, the multicenter Angioplasty versus Rotational Atherectomy for Treatment of diffuse In-Stent Restenosis Trial (ARTIST), which used only a single small burr and only low pressure postdilation, failed to show any benefit as compared with high-pressure balloon dilation of in-stent restenosis.15 With randomized trials now showing drug-eluting stenting to be superior to brachytherapy for in-stent restenosis, PTRA is generally no longer used for this indication. The 2011 guidelines for percutaneous coronary intervention (PCI) provide a Class III recommendation for PTRA of in-stent restenosis.13

Rotational Atherectomy for Calcified Lesions
Procedural success was achieved in 94% of 1,078 calcified single lesions in the Multicenter Rotablator Registry.19 In several series, adjuvant PTRA improved stent expansion even in...
### Table 29.1

**Randomized Clinical Trials of Percutaneous Transluminal Rotational Atherectomy**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>Relevant Endpoint*</th>
<th>Findings</th>
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<td><strong>Restenosis Trials</strong></td>
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<tr>
<td>ERBAC(^{10})</td>
<td>PTRA versus PTCA in native vessels</td>
<td>TVR 6 mo</td>
<td>PTRA 42.4%</td>
<td>Unfavorable effect of PTRA on TVR</td>
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<td></td>
<td></td>
<td></td>
<td>PTCA 31.9%</td>
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<td>(p = 0.01)</td>
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<tr>
<td>COBRA(^{11})</td>
<td>PTRA versus PTCA in native vessels</td>
<td>Binary restenosis 6 mo</td>
<td>PTRA 49%</td>
<td>No reduction of restenosis with PTRA</td>
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<td></td>
<td></td>
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<td>PTCA 51%</td>
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<td>(p = 0.33)</td>
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<tr>
<td>DART(^{12})</td>
<td>PTRA versus PTCA in small native vessels (2–3 mm)</td>
<td>TVF at 12 mo</td>
<td>PTRA 30.5%</td>
<td>No reduction in TVF with PTRA</td>
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<td>PTCA 31.2%</td>
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<td>(p = 0.98)</td>
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<td>Binary restenosis 8 mo</td>
<td>PTRA 50.5%</td>
<td>No reduction in restenosis with PTRA</td>
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<td>PTCA 50.5%</td>
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<td>(p = 1.0)</td>
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<td><strong>Aggressive Debunking</strong></td>
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<tr>
<td>STRATAS(^{8})</td>
<td>PTRA (B/A &lt;0.7) + standard PTCA versus PTRA (B/A 0.7–0.9) + minimal PTCA</td>
<td>Binary restenosis 6 mo</td>
<td>Standard 58% Aggressive 52%</td>
<td>No reduction in restenosis with aggressive debukling PTRA</td>
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<td>(p = \text{NS})</td>
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<td>CARAT(^{7})</td>
<td>PTRA (B/A = 0.7) versus PTRA (B/A &gt; 0.7)</td>
<td>MACE 6 mo</td>
<td>Standard 32.7% Aggressive 36.3%</td>
<td>No reduction in MACE with aggressive debukling PTRA</td>
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<td>(p = \text{NS})</td>
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<td><strong>In-Stent Restenosis</strong></td>
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<tr>
<td>ROSTER(^{16})</td>
<td>PTRA (B/A &gt;0.7) versus PTCA for diffuse ISR. IVUS guided for all pts</td>
<td>TLR 9 mo</td>
<td>PTRA 32%</td>
<td>Less repeat TLR with PTRA versus PTCA for diffuse ISR</td>
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<td>PTCA 45%</td>
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<td>(p = 0.04)</td>
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<tr>
<td>ARTIST(^{17})</td>
<td>PTRA (B/A &gt;0.7) versus PTCA for diffuse ISR. IVUS guided in a subset.</td>
<td>MACE 6 mo</td>
<td>PTRA 80%</td>
<td>PTCA superior to PTRA for diffuse ISR</td>
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<td>PTCA 91%</td>
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<td>(p = 0.0052)</td>
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*Not necessarily the primary endpoint of the trial.

B/A, balloon-to-artery ratio; ISR, in-stent restenosis; IVUS, intravascular ultrasound; MACE, major adverse cardiac events; PTCA, percutaneous transluminal coronary angioplasty; PTRA, percutaneous transluminal rotational atherectomy; TLR, target lesion revascularization; TVF, target vessel failure.

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calcified lesions\(^{20-22}\) In a single-center series, PTRA followed by drug-eluting stenting (DES) for calcified lesions was associated with reduced target lesion revascularization rates as compared to PTRA plus bare-metal stenting (BMS) (10.6% versus 25%, \(p < 0.001\)).\(^{23}\) Another single-center series has suggested that when PTRA is utilized to deliver and expand DES in heavily calcified lesions, clinical outcomes are similar to those of DES alone.\(^{24}\) However, no study has demonstrated superiority of PTRA plus DES over DES alone, even in calcified lesions. Current PCI guidelines provide a Class IIA recommendation for PTRA in heavily calcified or fibrotic lesions that may not dilate with conventional techniques prior to stenting.\(^{13}\)

### Rotational Atherectomy for Bifurcation Lesions

PTRA prior to stenting of bifurcation lesions has been proposed as a strategy to help preserve side branches by minimizing plaque shift (“snow plowing”).\(^{25-28}\) Small nonrandomized studies in the pre-DES era have yielded variable results.

### Lesion Selection for Rotational Atherectomy

Based on the failure of atheroablation to improve clinical outcomes, current PCI guidelines do not recommend routine use of PTRA. With the superiority of DES firmly established over other percutaneous revascularization techniques, the primary role of PTRA is to facilitate delivery and expansion...
of DES. Heavily calcified lesions are the most common indication for PTRA. An illustrative example of the utility of PTRA is presented in Figures 29.9 to 29.18. Rotablator should be avoided if there is angiographic evidence of dissection, thrombus, slow flow or no-reflow (Figure 29.17), excessive vessel tortuosity, or severe left ventricular dysfunction. When aggressive balloon angioplasty has failed to dilate a lesion, PTRA at the same setting should only be considered with caution (Figures 29.9 to 29.11). If balloon-generated dissection is present, PTRA could compound the dissection or induce perforation. Rotational atherectomy has been used to pass through a stent cell to revascularize an ostial lesion in a jailed side branch. However, it is recommended that this approach be used only if the stent cell has been previously dilated; and a small burr is recommended, given that serious complications have been encountered when the burr could not be retracted through the stent.

**Limitations and Complications of Rotational Atherectomy**

Limitations of PTRA include high cost and lack of confirmed impact on restenosis. Procedural success is highly dependent on the operator’s technique and experience. Particularly in longer lesions, there is still a significant incidence of non-Q-wave myocardial infarction and no-reflow related to
Engagement of the right coronary artery with an 8F internal mammary guide from a femoral approach. Severe damping occurs with any engagement. A temporary pacing wire is placed in the right ventricle.

Rotablator burr (2.0 mm; white arrow) being advanced over a RotaWire™ floppy wire (white double arrow). Prior to this, the lesion has been treated with 1.25- and 1.5-mm burrs. Temporary pacing wire in the right ventricle.

Result after 2.0-mm burr. Significant residual stenosis.

Balloon inflation with a noncompliant 3.0-mm balloon after 2.0-mm rotablation still demonstrates persistent waisting (white arrow) of the balloon consistent with an undilatable lesion.
particle embolization, spasm, or microactivation caused by burr surface velocity. In addition, adenosine released secondary to microactivation and red cell hemolysis may lead to bradycardia and atrioventricular block. Therefore, it is recommended that temporary venous pacing be used or have femoral access available during PTRA.

**Directional Coronary Atherectomy**

Directional coronary atherectomy (DCA) is now of historical interest as it is no longer available commercially. In this technique plaque is excised and removed. Inflation of the low-pressure balloon on this bulky device apposes the cutting window to a quadrant of the coronary plaque, prolapsing some portion of the plaque into the window. A battery-operated motor-drive unit then rotates a cutting cup, which the operator advances manually to excise the plaque and capture it in the device nose cone for collection and removal. This process could be repeated in multiple sectors in order to “debulk” the lesion. Plaque removal actually accounts for less than half of the observed gain in volume seen at the lesion site and substantial plaque volume remains even after successful DCA.

As compared to balloon angioplasty (BA), DCA improved acute postprocedural minimal luminal diameter in native coronaries in the Coronary Angioplasty versus Excisional Atherectomy Trial (CAVEAT I) and Canadian Coronary Atherectomy Trial (CCAT), and in SVG lesions in CAVEAT II. Clinical outcomes and restenosis rates were not improved
at 6 months, however. A strategy of more extensive plaque removal and routine postdilation to achieve a residual diameter stenosis of <20% was tested in the Balloon Angioplasty versus Optimal Atherectomy Trial (BOAT).36 Six months’ angiographic restenosis was reduced with optimal DCA as compared to BA (31.4% versus 39.8%; P = 0.016), but revascularization rates and mortality at 1 year were not reduced. In the Atherectomy before Multi-link Improves Lumen Gain and Clinical Outcomes (AMIGO) study, optimal DCA plus bare-metal stenting did not improve restenosis rates or clinical outcomes as compared to bare-metal stenting alone.37 Based on these results and the emergence of DES, DCA is no longer marketed.

Cutting Balloon Angioplasty

The cutting balloon consists of a noncompliant balloon on which several longitudinal microtomes are mounted to create controlled longitudinal incisions (“atherotomy”) into coronary plaque during lesion dilation.

Mechanism of Cutting Balloon Angioplasty

While angioplasty enlarges the coronary lumen by stretching the vessel and fracturing plaque, there is significant elastic recoil, uncontrolled dissections can result, and barotrauma from balloon inflation induces neointimal proliferation. Cutting balloon angioplasty (CBA) was designed to improve lumen enlargement at lower-pressure balloon inflation. In the randomized REDUCE trial comparing CBA to angioplasty in 800 patients, 224 patients underwent IVUS studies to examine the mechanism of lumen improvement.38 As mechanisms of the lumen gain, vessel stretch was expressed as change in external elastic membrane cross-sectional area (EEM CSA) and plaque reduction was expressed as change in plaque plus media CSA (P + M CSA). As compared to angioplasty, CBA used significantly lower maximal expansion pressure but achieved significantly more plaque reduction, with a trend toward improved luminal CSA and similar vessel expansion. In noncalcified lesions CBA achieved larger plaque reduction, similar luminal dimensions, and a trend toward less vessel expansion as compared to angioplasty. In calcified lesions, CBA yielded similar plaque reduction, improved luminal gain, and similar vessel expansion as compared to angioplasty. Thus, the promise of CBA as compared to angioplasty was improved acute results with less barotrauma at the time of intervention, which would translate into long-term clinical benefit.

Device Specifics

The Flextome® Cutting Balloon® dilation device is available in 6, 10, and 15 mm lengths, in both monorail and over-the-wire configurations. Based on the balloon diameter, three or four atherotomes are affixed longitudinally to the noncompliant nylon balloon. The 10- and 15-mm length devices integrate flex points into the atherotomes at 5-mm intervals to enhance deliverability (Figures 29.19 and 29.20).

Technique

The technique of CBA is similar to that of balloon angioplasty. Slow inflation and deflation of the balloon and adherence to the maximal balloon inflation pressure are recommended in order to avoid disruption of the atherotomes.

Clinical Results

De Novo Lesions

Small single-center studies have suggested a significant reduction in restenosis with CBA as compared to angioplasty, but large randomized trials have failed to reproduce these findings (Table 29.2). In the Cutting Balloon Global Randomized Trial (GRT), 1,238 patients were randomized to CBA versus angioplasty.39 There was no difference in the primary endpoint of angiographic restenosis at 6 months (31.4% versus 30.4%), with similar MACE rates at 270 days (13.6% versus 15.1%). Similarly, there was no reduction in restenosis with CBA as compared to angioplasty in the randomized Restenosis Reduction by Cutting Balloon Evaluation (REDUCE) trial of 802 patients.40

In-Stent Restenosis

CBA has also not shown superiority over balloon angioplasty for the treatment of in-stent restenosis (ISR). The Restenosis Cutting Balloon Evaluation Trial (RESCUT) randomized 428 ISR patients to CBA versus angioplasty; there was no difference in angiographic restenosis at 7 months (CBA 29.8%, PTCA 31.4%; P = 0.82).40 The unpublished REDUCE 2 trial from Japan also found no reduction in restenosis with CBA as compared to balloon angioplasty for ISR.41,42 In a randomized trial of 96 patients with focal ISR in DES, repeat restenosis was higher with CBA than with repeat DES (20.7% versus 3.1%, P = 0.06).43

Prestenting

The unpublished REDUCE 3 trial randomized 521 patients to CBA versus angioplasty prior to BMS. In 453 patients with angiographic follow-up, restenosis at 6 months was reduced with CBA (11.8% versus 19.1%, P = 0.032).44

Lesion Selection for Cutting Balloon Angioplasty

Based on these findings, current guidelines do not recommend routine use of CBA for standard coronary lesions.13 The rigidity of CBA renders it less deliverable in tortuous or calcified vessels. Small vessels, bifurcations, and ostial lesions have all been proposed as appropriate targets, but superiority of CBA over other techniques in these situations has not been proven. Reduced balloon slippage with CBA for ISR40 has led to a Class IIb recommendation for CBA for this purpose.13 If
Figure 29.19 Cutting balloon. *White arrows* indicate flexion points on the atherotomes. (Courtesy of Boston Scientific.)

Figure 29.20 Atherotomes and flexion points on cutting balloon. (Courtesy of Boston Scientific.)
**Table 29.2  Cutting Balloon Angioplasty Trials**

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<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>Relevant Endpoint</th>
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<td>Restenosis Trials</td>
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<tr>
<td>GRT&lt;sup&gt;39&lt;/sup&gt;</td>
<td>CBA versus PTCA in native vessels</td>
<td>Binary restenosis at 6 mo</td>
<td>CBA 31.4% PTCA 30.4% (P = 0.75)</td>
<td>No reduction of restenosis with CBA</td>
</tr>
<tr>
<td>REDUCE&lt;sup&gt;3&lt;/sup&gt;</td>
<td>CBA versus PTCA in native vessels</td>
<td>Binary restenosis at 6 mo</td>
<td>CBA 32.7% PTCA 25.5% (P = 0.75)</td>
<td>No reduction of restenosis with CBA</td>
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<td>In-Stent Restenosis</td>
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<td>RESCUT&lt;sup&gt;60&lt;/sup&gt;</td>
<td>CBA versus PTCA for ISR</td>
<td>Binary restenosis at 7 mo</td>
<td>CBA 29.8% PTCA 31.4% (P = 0.82)</td>
<td>No reduction of repeat restenosis with CBA for ISR</td>
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<tr>
<td>REDUCE 2&lt;sup&gt;6,41,42&lt;/sup&gt;</td>
<td>CBA versus PTCA for ISR</td>
<td>Binary restenosis</td>
<td>CBA 24% PTCA 20%</td>
<td>No reduction of repeat restenosis with CBA for ISR</td>
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<tr>
<td>Korean Trial&lt;sup&gt;43&lt;/sup&gt;</td>
<td>CBA versus DES for focal ISR in DES</td>
<td>Binary restenosis at 9 mo</td>
<td>CBA 20.7% DES 3.1% (P = 0.06)</td>
<td>DES is superior to CBA for focal ISR in DES</td>
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</table>

<sup>*Not necessarily the primary endpoint of the trial.</sup>

<sup>*Unpublished.*

CBA, cutting balloon angioplasty; DES, drug-eluting stent; ISR, in-stent restenosis; PTCA, percutaneous transluminal coronary angioplasty.

**Scoring Balloon Angioplasty**

The AngioSculpt Scoring Balloon Catheter (AngioScore, Inc. Alameda, California) utilizes a nitinol scoring element with three spiral struts that wrap around a semicompliant balloon (Figure 29.21). In one small, nonrandomized trial, predilation with AngioSculpt resulted in greater stent expansion by ultrasound criteria as compared to direct stenting or predilation with a standard semicompliant balloon.\(^{45}\) No randomized studies for coronary intervention have been performed with this device.

**Mechanism of Laser Angioplasty**

Laser is the process of creating a coherent beam of monochromatic light with high energy. Lasers for coronary intervention channel this standing wave of intense, monochromatic, coherent light through an optical coupler and down the optical fiber within the multilayer laser catheter the other end of which is positioned within the coronary artery lumen to illuminate the obstructing plaque with a burst of laser light.

Laser can be divided into UV laser (XeCl excimer lasers, 300 nm wavelength) and near-infrared/infrared laser (holmium or neodymium YAG; 2,000 nm wavelength). They can also be categorized as continuous-wave or pulsed systems. Pulsed systems have the theoretical benefit of predilation of ISR is required prior to repeat stenting of the lesion, reduced balloon slippage with CBA may minimize the trauma beyond the target lesion.

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energy-free interpulse intervals to reduce heating of surrounding tissue. Despite this theoretical advantage, all pulsed lasers produce some thermal effect, which is detectable with histologic examination.\(^48\)\(^49\) Normally, tissue ablation takes place by one of three mechanisms: vaporization of tissue (photothermal effect), ejection of debris (photoacoustic effect), or direct breakdown of molecules (photochemical dissociation). Initially, photodissociation was thought to be the predominant mechanism of excimer laser ablation of atherosclerotic plaque in vivo. However, studies under saline or blood disclosed less efficient plaque ablation and more intense photoacoustic effects.\(^30\)\(^31\) Systematic IVUS evaluation in human clinical studies of excimer laser coronary angioplasty (ELCA) has corroborated these findings.\(^32\) Photoacoustic injury can cause significant dissection of adjacent tissue, and vessel perforation occurred in 1% to 2% of patients treated in early studies.\(^33\) Risk factors for this complication include the use of an oversized laser catheter, bifurcation lesions, and diabetes mellitus.\(^35\) Intracoronary saline infusion during ELCA displaces blood and radiographic contrast from the treatment site, reducing laser-induced vapor bubble generation and mitigating the risk of vessel dissection from photoacoustic injury (Figures 29.22 to 29.24).\(^31\)

**Clinical Results**

Randomized trials have not demonstrated an advantage of laser-assisted angioplasty as compared to balloon angioplasty (Table 29.3). In the Excimer Laser–Rotational Atherectomy–Balloon Angioplasty Comparison (ERBAC) trial, 685 patients with a complex lesion were randomly assigned to balloon angioplasty \((n = 222)\), ELCA \((n = 232)\), or PTRA \((n = 231)\).\(^10\) Despite slightly higher procedural success with PTRA, target lesion revascularization at 6 months proved higher with both PTRA (42.4%) and ELCA (46.0%) than with angioplasty (31.9%; \(P = 0.013\)). The Laser Angioplasty Versus Angioplasty (LAVA) trial randomized 215 patients with stable or unstable angina to holmium:YAG laser versus stand-alone angioplasty.\(^54\) Major in-hospital complications increased with laser (10.3% versus 4.1%; \(P = 0.08\)), with similar MACE-free survival rates at 6 months (71.1% versus 76.5%; \(P = 0.55\)). Finally, 308 patients with stable angina and lesions >10 mm long were randomized to ELCA versus balloon angioplasty in the Amsterdam–Rotterdam (AMRO) trial, which found no reduction in MACE (33.3% versus 29.9%) or angiographic restenosis (51.6% versus 41.3%) at 6 months.\(^55\)

**Total Occlusions**

ELCA did not reduce restenosis as compared to angioplasty in a subset analysis of 130 patients with total or subtotal occlusion in the AMRO trial.\(^56\) In several studies, ELCA with a laser guidewire achieved successful recanalization in >60% of total occlusions deemed uncrossable with conventional guidewires.\(^57\)\(^59\)

**Calcified/Undilatable Lesions**

The somewhat higher procedural failure rate of ELCA in the ERBAC trial was attributed to a significant proportion of
heavily calcified lesions. In a prospective registry of undilatable lesions, procedural success with ELCA was significantly reduced in heavily calcified lesions as compared to other lesions (79% versus 96%; \( P < 0.05 \)). Nevertheless, ELCA has a success rate similar to that of rotational atherectomy for the treatment of undilatable lesions. Despite its efficacy in undilatable lesions, laser angioplasty should not be attempted in cases where prior balloon dilation attempts have resulted in local vessel dissection. Use of excimer laser angioplasty in such substrates is invariably associated with worsened dissection or perforation.

**In-Stent Restenosis**

Observational studies have shown no benefit of ELCA as compared to balloon angioplasty or PTRA for ISR.

**Acute Myocardial Infarction and Acute Coronary Syndromes**

ELCA has been shown to be safe for PCI for acute myocardial infarction and acute coronary syndromes. In one small randomized trial of acute MI patients, postprocedural corrected TIMI frame count improved with ELCA plus stent...
### Table 29.3 Laser Angioplasty Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>Relevant Endpoint*</th>
<th>Findings</th>
<th>Implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERBAC⁹⁰</td>
<td>ELCA versus PTCA in native vessels</td>
<td>TVR at 6 mo</td>
<td>ELCA 46.0% PTCA 31.9% ( P = 0.01 )</td>
<td>Unfavorable effect of ELCA on TVR</td>
</tr>
<tr>
<td>LAVA⁹⁴</td>
<td>ILCA versus PTCA in native vessels or SVG</td>
<td>MACE at 6 mo</td>
<td>ILCA 28.9% PTCA 23.5% ( P = 0.55 )</td>
<td>No reduction of MACE with ILCA</td>
</tr>
<tr>
<td>AMRO⁵⁵</td>
<td>ELCA versus PTCA in native vessels</td>
<td>MACE at 6 mo</td>
<td>ELCA 33.3% PTCA 29.9% ( P = 0.55 )</td>
<td>No reduction of MACE with ELCA</td>
</tr>
<tr>
<td></td>
<td>Binary restenosis 6 mo</td>
<td></td>
<td>ELCA 51.6% PTCA 41.3% ( P = 0.13 )</td>
<td>No reduction of restenosis with ELCA</td>
</tr>
</tbody>
</table>

*Not necessarily the primary endpoint of the trial.

ELCA, excimer laser coronary angioplasty; ILCA, infrared laser coronary angioplasty; MACE, major adverse cardiac events; PTCA, percutaneous transluminal coronary angioplasty; SVG, saphenous vein graft; TVR, target lesion revascularization.

As compared to angioplasty plus stent,⁹⁴ No large randomized trials to assess clinical outcomes have been performed, however.

### Lesion Selection for Excimer Laser Coronary Angioplasty

Laser-assisted angioplasty is rarely used at present. Current guidelines provide a IIb recommendation for ELCA in fibrotic or moderately calcified lesions that cannot be crossed or dilated with other techniques.⁹³

### Mechanical Thrombectomy

Acute myocardial ischemia is often precipitated by intracoronary thrombus formation. PCI of these larger thrombi can lead to distal emboli, no-reflow, and abrupt closure. Mechanical devices that either disintegrate or aspirate and remove thrombus are therefore valuable adjuncts in PCI for acute coronary syndromes.

### Cut and Aspirate Devices

These devices are not currently available for coronary intervention. The transluminal extraction catheter (TEC) excised and aspirated plaque and thrombus from vein grafts with a rotating conical cutter connected to a vacuum. In the TEC Best trial,⁶⁷ TEC showed no benefit over conventional approaches in vein graft intervention, and multicenter experience demonstrated substantial distal embolization and vessel injury felt to be owing to the catheter’s large size and stiffness.⁶⁸ The X-Sizer (eV3, White Bear Lake, Minnesota) double-lumen catheter macerated thrombus by means of a rotating (2,100 rpm) helical auger at the tip of its inner lumen, which was then aspirated by a vacuum applied to its outer lumen. In the X-TRACT trial, as compared to stenting alone, the X-Sizer followed by stenting of SVGs significantly reduced both periprocedural “large MI” (new Q waves or CK-MB >8 times the upper limit of normal) and 30-day mortality among the subgroup of patients with visible thrombus.⁶⁹ Clinical outcomes at 1 year did not improve, however. The X-sizer also failed to improve clinical outcomes in acute MI PCI in both the X-AMINE trial⁷⁰ (as compared to primary PCI alone) and the TREAT-MI study⁷¹ (as compared to aspiration plus primary PCI). As a result, the X-Sizer was approved by the FDA in 2004 for use in dialysis grafts, but not for coronary use. With the subsequent development of embolic protection devices for vein graft intervention, enthusiasm for the concept of “cut and aspirate” has further waned.

### Venturi/Bernoulli Suction

Use of a high-speed water jet to create suction via a Bernoulli/Venturi effect is the operating principle of the AngioJet® (MEDRAD, Inc.) system. The AngioJet console houses a drive unit capable of delivering pulses of saline at high pressures of about 10,000 PSI. Activated by a foot pedal, the drive pump injects saline at high pressure through the AngioJet catheter’s hypotube into the stainless steel tip, where the saline stream is deflected and exits retrograde as a set of high-speed jets directed back across a small opening in the catheter tip before re-entering the main catheter lumen for evacuation.
By the Venturi/Bernoulli principle, this creates a low-pressure region at the tip pulling surrounding fluid (blood, thrombus, and saline) into the tip opening. There, the jets break the thrombus into subcellular-sized particles and propel them proximally through the catheter lumen and out of the body. AngioJet rheolytic thrombectomy has been shown to be most effective in removing thrombus <48 hours old. Once cross-linking of fibrin and cellular organization take place, it becomes difficult to remove the thrombus using AngioJet.

Transient bradycardia is the most frequent complication during AngioJet rheolytic thrombectomy, particularly when utilized in the right coronary artery or a dominant circumflex system. This is probably owing to local adenosine release mediated by hemolysis. Temporary venous pacemaker placement is therefore recommended prior to AngioJet in these circumstances.

Clinical Results

The second Vein Graft AngioJet Study (VeGAS-2) randomized 349 patients with native coronary or SVG lesions containing visible thrombus to AngioJet versus intracoronary urokinase (6 to 30 hours) prior to definitive revascularization. Bradycardia occurred more frequently with AngioJet (24% versus 2%), but was successfully managed with atropine and temporary pacing. There was no difference in the primary endpoint (AngioJet, 29%; urokinase, 30%), which consisted of the composite of MACE at 30 days, postprocedural diameter stenosis ≥50%, TIMI flow <3, and <20% improvement in diameter stenosis. However, the AngioJet strategy achieved higher procedural success (86% versus 72%, P = 0.002) with lower major adverse cardiac events (MACE) at 30 days (16% versus 33%, P < 0.001) and fewer hemorrhagic and vascular complications. As a result of this study, AngioJet was approved for treatment in thrombus-containing native coronary arteries and SVGs.

AngioJet was then naturally applied in the setting of acute myocardial infarction intervention where significant thrombus is prevalent (Table 29.4). The AngioJet Rheolytic Thrombectomy in Patients Undergoing Primary Angioplasty for Acute Myocardial Infarction (AIMI) trial randomized 240 patients with ST-elevation MI presenting within 12 hours to adjunctive AngioJet during primary PCI versus standard PCI. Despite effective thrombus removal, AngioJet treatment was associated with larger infarct size, reduced TIMI flow grade, and higher 30-day MACE (6.7% versus 1.7%, P = 0.01), driven by an unexpectedly low mortality rate (0.8%) among control patients.

Several concerns have been raised about the AIMI trial. The enrollment criteria did not require the presence of visible thrombus, and only 21% actually had moderate or large thrombus, possibly diluting any potential benefit of AngioJet. A retrograde technique was adopted in which AngioJet was passed beyond the lesion and then activated during withdrawal. This approach might contribute to excess clot embolization during initial passage of the device. Patients were only randomized after diagnostic angiography, and those with large thrombus may have been treated outside the trial due to investigator bias. Finally, there was potential for more temporary pacemaker–related complications in the AngioJet patients as these were placed in 58% of AngioJet patients as compared to 15% of controls.

Several of these concerns were addressed in the AngioJet Rheolytic Thrombectomy Before Direct Infarct Artery Stenting in Patients Undergoing Primary PCI for Acute Myocardial Infarction (JETSTENT). Only patients with visible thrombus were enrolled, and these patients were randomized to AngioJet plus stent versus direct stenting. An antegrade technique was utilized in which AngioJet was activated starting 1 cm proximal to the lesion, and only 0.7% of AngioJet patients underwent prophylactic temporary pacemaker placement. All patients were pretreated with aspirin, loaded with 600 mg of Plavix, and treated with abciximab. AngioJet...
### Table 29.4

Selected Major Prospective Randomized Trials of Embolic Protection Devices and Thrombus Removal Devices in Primary Percutaneous Coronary Intervention for Acute Myocardial Infarction

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Trial Design</th>
<th>Device</th>
<th>Control</th>
<th>Primary Endpoint</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Distal Protection</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMERALD 2007°2</td>
<td>Prospective randomized multicenter (n = 501)</td>
<td>GuardWire</td>
<td>No distal protection</td>
<td>STR and infarct size at 99mTc Sestamibi Scan</td>
<td>No difference in STR at 30 min (63% versus 62%), MI size (12% versus 9.5%), or MACE at 6 mo (10% versus 11%)</td>
</tr>
<tr>
<td>PROMISE 2005°0</td>
<td>Prospective randomized (n = 200)</td>
<td>FilterWire (EZ)</td>
<td>No distal protection</td>
<td>Infarct related artery max flow velocity and infarct size at MRI</td>
<td>No difference in max flow velocity (34 versus 36 cm/s) or MI size (11.8% versus 10.4%)</td>
</tr>
<tr>
<td>DEDICATION 2008°0</td>
<td>Prospective randomized multicenter (n = 626)</td>
<td>FilterWire (EZ)</td>
<td>No distal protection</td>
<td>STR ≥70%</td>
<td>No difference in STR ≥70% (76% versus 72%)</td>
</tr>
<tr>
<td>PREMIAR 2007</td>
<td>Prospective randomized multicenter (n = 140)</td>
<td>Spider RX</td>
<td>No distal protection</td>
<td>STR ≥70%</td>
<td>No difference in STR ≥70% at 60 min (61% versus 60%)</td>
</tr>
<tr>
<td>PREPARE 2009</td>
<td>Prospective randomized multicenter (n = 284)</td>
<td>Proxis</td>
<td>No distal protection</td>
<td>STR ≥70%</td>
<td>No difference in STR ≥70% at 60 min (80% versus 72%). No difference in infarct size at 6 mo (6.1 versus 6.3 g/cm²)</td>
</tr>
<tr>
<td><strong>Extraction/Aspiration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIMI 2006°3</td>
<td>Prospective randomized multicenter (n = 480)</td>
<td>AngioJet</td>
<td>No AngioJet</td>
<td>Infarct size by Tc Sestamibi perfusion scan</td>
<td>Final Infarct size higher in AngioJet group (12.5% versus 9.8%, ( P = 0.03 ))</td>
</tr>
<tr>
<td>X AMINE ST 2005°0</td>
<td>Prospective randomized multicenter (n = 201)</td>
<td>X-Sizer</td>
<td>No X-Sizer</td>
<td>STR</td>
<td>X-Sizer leads to better STR (7.5 versus 4.9 mm, ( P &lt; 0.04 ))</td>
</tr>
<tr>
<td>JETSTENT 2010°2</td>
<td>Prospective randomized multicenter (n = 201)</td>
<td>AngioJet</td>
<td>No AngioJet</td>
<td>Co-primary: STR and 99mTc-Sestamibi infarct size</td>
<td>AngioJet achieved better STR (85.8% versus 78.8%, ( P = 0.043 )) with no improvement in infarct size (11.8% versus 12.7%, ( P = 0.4 )). One-year estimated freedom from MACE reduced with thrombectomy (85% versus 75%, ( P = 0.009 ))</td>
</tr>
</tbody>
</table>

(Continued)
Table 29.4

Selected Major Prospective Randomized Trials of Embolic Protection Devices and Thrombus Removal Devices in Primary PCI for Acute Myocardial Infarction (Continued)

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Trial Design</th>
<th>Device</th>
<th>Control</th>
<th>Primary Endpoint</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAPAS 2008°75</td>
<td>Prospective randomized multicenter (n = 1071)</td>
<td>EXPORT</td>
<td>No aspiration</td>
<td>MBG ≤1</td>
<td>EXPORT reduced MBG ≤1 from 26.3% to 17.1%, P &lt; 0.001. One-year cardiac mortality reduced from 6.7% to 3.6% (P = 0.02)</td>
</tr>
<tr>
<td>EXPIRA 2010°77</td>
<td>Prospective randomized (n = 175)</td>
<td>EXPORT</td>
<td>No aspiration</td>
<td>MBG ≥2 and STR ≥70%</td>
<td>All patients received abciximab. EXPORT associated with improved MBG ≥2 (74% versus 60%, P &lt; 0.001), reduced MACE at 24 mo (4.5% versus 13.7%, P = 0.038), and reduced cardiac death (0% versus 6.8%, P = 0.012)</td>
</tr>
</tbody>
</table>

MACE, major adverse cardiac events; MBG, myocardial blush grade; MI, myocardial infarction; STR, ST segment resolution.

achieved disparate results with respect to the co-primary endpoints of ST segment resolution at 30 minutes and scintigraphic infarct size, improving the former with no reduction in the latter. Owing to multiple comparisons, the reduction in the co-primary endpoint with AngioJet did not reach statistical significance. However, by Kaplan–Meier analysis, the 1-year estimated freedom from MACE was 85.2 ± 2.3% for the thrombectomy arm and 75.0 ± 3.1% for the direct stent alone arm (P = 0.009). The salutary effect was primarily driven by a reduction in death and TVR. Only bare-metal stents were used, and it has been postulated that the shorter overall stent length in the AngioJet arm—perhaps related to less residual thrombus to cover—might have contributed to the lower TVR rate. This possible benefit may be diluted in the DES era as stent length has less influence on outcomes after DES.

While the JETSTENT findings are intriguing, a larger, appropriately powered trial is needed to assess rigorously whether AngioJet could improve clinical outcomes in primary PCI of thrombotic lesions in the era of DES. In addition, encouraging data from simpler aspiration thrombectomy techniques (see below) may restrict use of rheolytic thrombectomy to patients with excessive thrombus burden. The 2011 PCI guidelines conclude that rheolytic thrombectomy has demonstrated no clinical benefit in primary PCI.

Suction Thrombectomy

These devices generally have a double-lumen construction, allowing them to track over a guide wire passed through one lumen (generally a short monorail), while reserving the other full catheter length lumen for thrombus aspiration. With most devices, suction is applied manually using a large syringe attached to the aspiration port; several others employ a vacuum pump.

Clinical Results

Acute Myocardial Infarction

These aspiration systems have primarily been studied in primary PCI (Table 29.4). In the single-center TAPAS study, 1,071 patients with ST-elevation MI were randomized to primary PCI with or without adjunctive manual aspiration using the Export (Medtronic, Inc., Minneapolis, Minnesota) catheter.°73 There was no requirement for angiographic thrombus for enrollment. Aspiration reduced the primary endpoint of myocardial blush grade 0 or 1 (no or minimal reperfusion) from 26.3% to 17.1% (P < 0.001). This was associated with a reduction in 1-year cardiac mortality from 6.7% to 3.6% (P = 0.02).°76

In the smaller single-center EXPIRA study, 175 ST-elevation MI patients with angiographic thrombus at the target lesion were randomized to primary PCI with or without adjunctive manual aspiration using the Export catheter.°77 All patients were pretreated with aspirin and abciximab. The primary endpoints of both myocardial blush grade and ST segment resolution improved significantly with aspiration, again yielding improved long-term clinical outcomes. At 24 months, MACE rate was 4.5% versus 13.7% (P = 0.038) and cardiac death was 0% versus 6.8% (P = 0.012).

Multiple meta-analyses have now been published with a consistent finding of improved outcomes in primary PCI with adjunctive manual aspiration.°83 Bavry’s analysis of 30 studies with 6,415 patients found that mortality was 2.7%
for aspiration thrombectomy versus 4.4% for PCI alone ($P = 0.018$), 5.3% for mechanical thrombectomy versus 2.8% for PCI alone ($P = 0.05$), and 3.1% for embolic protection versus 3.4% for PCI alone ($P = 0.69$). The 2011 PCI guidelines assign a Class Ila recommendation to adjunctive aspiration thrombectomy during primary PCI, but mechanical thrombectomy and embolic protection are not recommended.

**High-Risk Lesions**

The role of routine aspiration thrombectomy has also been assessed in high-risk lesions. In the recent INFUSE AMI study 452 patients with high-risk lesions in the proximal or mid LAD were treated with aspirin, clopidogrel, and bivalirudin, and randomized in a $2 \times 2$ factorial design to aspiration thrombectomy versus intracoronary abciximab. The primary endpoint of infarct size as assessed by cardiac MRI but not with aspiration (17% versus 17.3%, $P = 0.51$) but not with aspiration (17% versus 17.3%, $P = 0.51$). Larger clinical-outcomes studies will be required to assess these mechanistic results.

**Ultrasonic Thrombectomy**

Ultrasonic thrombectomy is based on the idea that ultrasound vibrations can fragment thrombus into smaller particles. However, in a randomized trial of SVG intervention, ultrasonic thrombectomy using the Acolysis system (Vascular Solutions, Inc., Minneapolis, MN) was found to have lower success rate (63% versus 82%; $P = 0.008$) and higher 30-day MACE (25% versus 12%; $P = 0.036$) when compared to pharmacologic thrombectomy.

**EMBOLIC PROTECTION DEVICES**

Coronary interventions tend to dislodge fragments of friable plaque or thrombus into the distal circulation, which can precipitate the local release of intense vasoconstrictors. Particularly during SVG interventions or PCI of thrombotic lesions, distal microembolization and microvascular spasm are major sources of the dreaded coronary “no-reflow” phenomenon and periprocedural myocardial injury manifested by elevated cardiac enzymes. Coronary aspirates after PCI complicated by no-reflow exhibit a greater burden of atheromatous plaque, and more platelet–fibrin complexes, macrophages, and cholesterol crystals than do aspirates from procedures with normal flow. It has been shown that obstruction of more than 50% of the microcirculatory bed is required to decrease myocardial blood flow irreversibly. The role of vasoconstriction is implicated by the known potential of the multiple cellular elements involved to release vasoactive substances, as well as by the observed responsiveness of no-reflow to vasodilators.

Embolic protection devices were designed to minimize ischemic injury and no-reflow by trapping fragmented plaque and thrombus liberated during PCI. These devices can be divided into three types: (i) distal conduit occlusion, (ii) proximal conduit occlusion, and (iii) distal filtration (Figure 29.26). Table 29.5 summarizes the technical aspects of many of the devices available currently or until recently.

**Distal Occlusion Systems**

These devices incorporate a balloon inflated distal to the target lesion during PCI to interrupt antegrade flow, trapping liberated atherothrombotic debris and soluble vasoactive substances in the epicardial vessel. These components are then aspirated from the stagnant column prior to deflation of the occlusive balloon, thus avoiding embolization to the distal microvasculature when antegrade flow is restored. The advantage of distal occlusion is that debris of all sizes is captured and aspirated, with minimal risk of debris passing around the device. In theory this approach also allows for the removal of soluble vasoactive or prothrombotic substances which would pass through alternative distal filtering devices. Distal occlusion has several important limitations, however. Ischemia during interruption of antegrade flow may not be tolerated in tenuous patients. With cessation of antegrade flow, angiography to guide the intervention is limited for the target lesion and impossible for the distal vasculature. The crossing profile of these devices is larger than those of low-profile coronary balloons and the wires are less steerable than standard coronary guide wires. These factors lead to a risk of distal embolization before distal occlusion is established. PCI of a very proximal or ostial lesion without antegrade flow also risks debris embolization retrograde into the aorta with the potential for stroke. Balloon inflation can also traumatize the distal vessel, and balloon deflation failure can rarely occur.

**PercuSurge GuardWire**

The PercuSurge GuardWire (Medtronic, Minneapolis, MN) system consists of a novel coronary guidewire constructed as a 0.014-inch nitinol hypotube with a radiopaque, flexible tip; a 5.5-m-long elastomeric balloon (mounted 3.5 cm from the tip of the wire) that can be inflated at low pressure (<2 atm to a diameter of 3.5 to 5.0 mm); a side-hole monorail aspiration catheter (Export) with a 0.041-inch aspiration lumen; an EZ Adaptor allowing access to the hypotube lumen; and an EZ Flator for inflating the balloon through the EZ Adaptor (Figure 29.27). Preparation of the device involves several steps: (1) the GuardWire hypotube is placed in a precise position in the jaws of the EZ Adaptor, carefully avoiding any kinking of the wire; (2) the EZ Flator® is connected, and contrast (diluted 1:3 to promote quick balloon deflation) is used to fill the well of the EZ Adaptor; (3) the EZ Adaptor roof is closed to create an airless bath of dilute contrast surrounding the wire; (4) the EZ Adaptor dial is turned to inflate the balloon; (5) the device is deflated and the wire removed from the EZ Adaptor. Owing to this complex series of steps for
Figure 29.26 Embolic protection devices. **Top panel.** Distal occlusion system such as GuardWire occludes antegrade flow during PCI. Liberated debris is then aspirated out from the stagnant column of blood above the balloon, followed by deflation of the balloon to restore antegrade coronary flow. **Middle panel.** Distal filter system is positioned beyond the target lesion in such a way that liberated debris during PCI is captured in the filter rather than embolizing to the distal vasculature. **Bottom panel.** Proximal occlusion system such as Praxis. Occlusion balloons on the device are inflated in the coronary segment above the target lesion and within the guide (black arrows), arresting antegrade flow. Once PCI is completed, aspiration of the stagnant column of blood is performed to remove liberated debris, followed by deflation of the occlusion balloons. (From Mauri L. Circulation 2006;113:2651-2656.)

preparation and removal it is recommended that all equipment for PCI be ready for immediate use prior to delivering the GuardWire.

The GuardWire system is much less steerable than conventional coronary guidewires. The system must be advanced across the target lesion and positioned at least 20 mm distally. The stent/angioplasty balloon is loaded over the wire and positioned proximal to the lesion, and the GuardWire balloon is inflated. A small contrast injection allows visualization up to the occlusive balloon and confirms interruption of antegrade flow. All embolic material is trapped in the stagnant column of blood proximal to the balloon and aspirated with the Export catheter before the GuardWire balloon is deflated and antegrade flow is restored. It may be noted that if over-the-wire systems are used, the GuardWire must be removed from the EZ Adaptor for catheter exchanges and then repositioned in the EZ Adaptor following PCI to deflate the balloon. Extreme attention must be paid to avoiding kinking of the hypotube resulting in failure of the balloon to deflate. Should this happen if ever, the hypotube should be cut distal to its gold marker to allow deflation.

The benefit of embolic protection for vein graft PCI was established in the SAFER (SVG Angioplasty Free of Emboli Randomized) trial, which assigned 801 patients to either a standard guidewire or the GuardWire distal occlusion system. Distal protection yielded a 42% relative risk reduction in MACE at 30 days (9.6% versus 16.5%; \( P = 0.004 \)), driven by prevention of myocardial infarction (8.6% versus 14.7%; \( P = 0.008 \)) and less coronary no-reflow (3% versus 9%; \( P = 0.02 \)). These benefits were maintained even in the 61% of patients receiving glycoprotein IIb-IIIa inhibitors (10.7% versus 19.4%; \( P = 0.008 \)). Angiographic predictors of MACE in the SAFER trial included the degree of graft degeneration and estimated plaque volume in the lesion, but GuardWire demonstrated a significant benefit for all patients, not just high-risk patients.
<table>
<thead>
<tr>
<th>Device Type</th>
<th>FDA-Approved Devices</th>
<th>Manufacturer</th>
<th>Guide Compatibility</th>
<th>Guidewire Compatibility</th>
<th>Distal Landing Zone</th>
<th>Advantages</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distal filtration</td>
<td>SpiderFX</td>
<td>Coviden/Ev3 Plymouth, MN</td>
<td>6F</td>
<td>0.014”</td>
<td>20 mm</td>
<td>*Maintain antegrade flow *Allow angiography with device deployed *Rapid deployment and retrieval in most cases using techniques familiar to interventionists</td>
<td>*Debris may embolize if smaller than filter pore size *Soluble factors not trapped *Filter crossing the lesion may cause distal embolization *Possibly difficult to place in presence of tortuosity</td>
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<tr>
<td></td>
<td>AngioGuard</td>
<td>Cordis Endovascular A Bridgewater, NJ</td>
<td>7F</td>
<td>Integrated Wire</td>
<td>18 mm</td>
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<tr>
<td></td>
<td>(no longer marketed for coronary use, only for carotid use)</td>
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<td></td>
<td>FilterWire</td>
<td>Boston Scientific Natick, MA</td>
<td>6F</td>
<td>0.014”</td>
<td>25 mm</td>
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<tr>
<td>Distal occlusion</td>
<td>GuardWire</td>
<td>Medtronic, Santa Rosa, CA</td>
<td>8F</td>
<td>0.014”/0.018”</td>
<td>20 mm</td>
<td>*Lower profile than filter EPD *More easily delivered in tortuous anatomy</td>
<td>*Temporary flow obstruction may not be tolerated *Crossing lesion more challenging with device wire than with standard wire *Not applicable for very proximal lesions: risk of debris embolization into the aorta *Crossing lesion may cause embolization *Risk of balloon-induced dissection or injury *Limited lesion visualization with the device deployed *Complex procedural steps less familiar to interventionalists *Potential for deflation failure</td>
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<td></td>
<td>TriActiv system</td>
<td>Kensey Nash, Exton, PA</td>
<td>7F</td>
<td>0.014”</td>
<td>≥20 mm</td>
<td></td>
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<td>(no longer marketed)</td>
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(Continued)
Table 29.5  Coronary Embolic Protection Device Specifications (Continued)

<table>
<thead>
<tr>
<th>Device Type</th>
<th>FDA-Approved Devices</th>
<th>Manufacturer</th>
<th>Guide Compatibility</th>
<th>Guidewire Compatibility</th>
<th>Distal Landing Zone</th>
<th>Advantages</th>
</tr>
</thead>
</table>
| Proximal occlusion| Proxis system (no longer marketed) | St. Jude Medical, St. Paul, MN | 6F/7F               | 0.014"                  | 12 mm (proximal)     | *Device does not have to cross lesion  
* Protection of branch vessels  
* Protection in presence of tortuosity  
* Can be used for PCI on multiple separate lesions |

*Distal landing zone = disease-free segment distal to the lesion required to adequately deploy the device.

EPD, emboli protection device; PCI, percutaneous coronary intervention.

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Figure 29.27  PercuSurge GuardWire (Medtronic) system. A. GuardWire is advanced across the lesion to the distal vessel. B. Stent is delivered, positioned, and deployed over the GuardWire and with distal balloon inflated to prevent embolization. C. Aspiration catheter is advanced into the vessel, and debris is aspirated with distal balloon inflated to prevent embolization. D. Distal balloon is deflated to restore antegrade flow. (From Circulation 2002;105:1285–1290.)
GuardWire's salutary effects in vein graft intervention have not been duplicated in the setting of primary PCI for acute myocardial infarction. The EMERALD (Enhanced Myocardial Efficacy and Recovery by Aspiration of Liberated Debris) trial randomly assigned 501 patients with STEMI to primary PCI with or without GuardWire. As compared to conventional PCI, the GuardWire conferred no reduction in in-farct size, no improvement in ST segment resolution, and no reduction in MACE at 30 days (10.0% and 11.0%, respectively; \( P = 0.66 \)).

**TriActiv System**

The Kensey Nash TriActiv system consists of a guidewire with a rapidly inflating and deflating \( \text{CO}_2 \)-filled distal balloon and a selective-infusion catheter that attaches side-to-side to the wire and moves suspended debris toward the tip of the guiding catheter which is placed under suction. In the PRIDE (PProtection during SVG Intervention to prevent Distal Embolization) trial, TriActiv was not inferior to GuardWire for vein graft PCI, with MACE of 11.2% and 10.1%, respectively, at 30 days. However, this device is no longer marketed.

**Distal Filters**

Filtration devices utilize a nonocclusive basket deployed distal to the target lesion to capture embolic material larger than the interstices of the device mesh.

Advantages: Preserved antegrade coronary flow is a distinct advantage of the filter approach, minimizing ischemia and allowing angiographic visualization of the target lesion and distal vasculature during the period of embolic protection. The delivery and retrieval steps are intuitive to most interventionalists, often employing standard coronary guidewires to cross the lesion rather than a less responsive, bulkier occlusion balloon–wire apparatus.

Limitations: Distal filters do have several limitations. The requisite need to traverse the target lesion incurs some risk of device-induced distal embolization before protection is established. The completeness of distal protection may also be compromised when the filter is positioned in tortuous segments where apposition of the basket against the vessel wall is suboptimal. The pore size of the filter also determines the completeness of capture. Available devices have a pore size ranging from 80 to 150 \( \mu \text{m} \) to allow passage of red blood cells and leucocytes through the filter. Smaller particulate matter and soluble factors still traverse the filter and enter the microcirculation. A large burden of embolic material can occlude the filter and mimic no-reflow. This requires either prompt use of an aspiration catheter to clear the filter or urgent filter retrieval to restore antegrade flow. In addition, filters require a distal landing zone of approximately 18 to 30 mm from a graft anastomosis in order to accommodate the length of the device, thereby limiting use of distal filtration in the setting of very distal lesions. However, in practice these devices are sometimes deployed in the native circulation beyond the distal graft anastomosis in the case of very distal lesions if the subtended coronary is of adequate diameter for proper device expansion. Filters also have the potential to traumatize the distal vessel, and advancement of filter retrieval sheaths through freshly deployed stents is sometimes difficult.

**FilterWire**

FilterWire EX\textsuperscript{TM} (Boston Scientific, Natick, MA) was the first filter approved by the FDA in 2003. It consists of a conventional guidewire to which an elliptical, radiopaque, nitinol loop is attached. A polyurethane filter bag with 110-micron pores is suspended from the nitinol loop. Intended for use in vessels 3.5 to 5.5 mm in diameter, FilterWire is delivered in its collapsed state within a 3.2F (6F guide-compatible) delivery sheath, which is withdrawn to allow the filter to expand and the procedure to be performed over the guidewire shaft. At the end of the intervention, a retrieval sheath is advanced over the wire to recollapse and withdraw the filter. The second generation FilterWire EZ was designed to enhance filter centering even in curved segments and utilizes a lower-profile peel-away delivery sheath.

In the FilterWire EX Randomized Evaluation (FIRE) trial, the relative efficacy and safety of FilterWire was directly compared with those of distal occlusion using the GuardWire in patients undergoing vein graft stenting (Table 29.6).

A high 30-day MACE rate of 21.3% was observed with FilterWire in the early roll-in phase of FIRE, which was successfully reduced to 11.3% in the next phase by improvements in procedural technique including (i) ensuring \( >2.5 \) cm distance between lesion and distal anastomosis; (ii) placement of the FilterWire in a straight landing zone segment (\( >2 \) cm); (iii) use of orthogonal angiographic views to document circumferential filter apposition to the vessel wall prior to stenting; and (iv) retracting only the proximal end of the debris-containing filter into the retrieval sheath. This favorable performance was continued in the randomized phase of the FIRE trial, which showed similar 30-day MACE rates with the FilterWire and the GuardWire (9.9% versus 11.6%, \( P = 0.0008 \) for noninferiority).

**SpiderFX**

The SpiderFX (ev3 Endovascular, Inc., Plymouth, MN) distal embolic protection system includes a capture wire and the SpiderFX catheter (Figure 29.28A–C). The capture wire has a nitinol mesh filter with proximal and distal indicators and a distal floppy tip, mounted on a 190-cm or convertible 320/190-cm PTFE-coated 0.014-inch stainless-steel wire. The filter has a heparin coating designed to maintain patency. The wire is designed to rotate and move longitudinally independent of the filter for enhanced stability during the procedure. The SpiderFX catheter has a 3.2F green delivery end and a 4.2F blue recovery end. The capture wire is provided preloaded into the SpiderFX catheter with the filter.
In the SPIDER trial 747 patients undergoing vein graft PCI were randomized to SpiderFX versus GuardWire with similar rates of MACE at 30 days (9.2% versus 8.7%, \( P = 0.012 \) for noninferiority).\(^96\) SpiderFX has subsequently been approved for both carotid and lower extremity intervention.

### Other Filters

The AngioGuard filter device has been tested in coronary intervention but is currently FDA approved only for carotid intervention. MedNova Cardiosheild is a distal protection filter which has the ability to rotate freely on the guidewire to limit vascular injury and enhance apposition. It was compared with the GuardWire in the CAPTIVE randomized trial. However, it failed to demonstrate superiority to no embolic protection and noninferiority to GuardWire.\(^97\) The Interceptor by Medtronic consisted of a nitinol basket affixed to a guidewire. The safety and efficacy of the first generation of

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**Table 29.6** Selected Major Trials of Embolic Protection Devices for SVG Intervention

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Trial Design</th>
<th>Device</th>
<th>Control</th>
<th>Primary Endpoint</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAFER 2002(^29)</td>
<td>Prospective randomized SVG intervention (( n = 801 ))</td>
<td>GuardWire (Occlusion Balloon)</td>
<td>No GuardWire</td>
<td>30-d MACE</td>
<td>MACE reduced with GuardWire (9.6% versus 16.5%, ( P = 0.004 ))</td>
</tr>
<tr>
<td>FIRE 2003(^34,35)</td>
<td>Prospective randomized SVG intervention (( n = 651 ))</td>
<td>FilterWire EX</td>
<td>GuardWire (Occlusion Balloon)</td>
<td>30-d MACE</td>
<td>MACE similar for FilterWire and GuardWire (9.9% versus 11.6%; ( P = 0.0008 ) for noninferiority)</td>
</tr>
<tr>
<td>PRIDE 2005(^33)</td>
<td>Prospective randomized SVG intervention (( n = 631 ))</td>
<td>TriActiv</td>
<td>GuardWire (Occlusion Balloon) or FilterWire EX</td>
<td>30-d MACE</td>
<td>MACE similar for TriActiv and control devices (11.2% versus 10.1%; ( P = 0.02 ) for noninferiority)</td>
</tr>
<tr>
<td>SPIDER 2006(^98)</td>
<td>Prospective randomized SVG intervention (( n = 732 ))</td>
<td>SpiderFX</td>
<td>GuardWire (Occlusion Balloon) or FilterWire EX</td>
<td>30-d MACE</td>
<td>MACE similar for SpiderFX and control devices (9.2% versus 8.7%; ( P = 0.012 ) for noninferiority)</td>
</tr>
<tr>
<td>AMETHYST 2007</td>
<td>Prospective randomized SVG intervention (( n = 797 ))</td>
<td>Interceptor PLUS</td>
<td>GuardWire or FilterWire</td>
<td>30-d MACE</td>
<td>MACE similar for Interceptor PLUS and control devices (8% versus 7.3%; ( P = 0.025 ) for noninferiority)</td>
</tr>
<tr>
<td>PROXIMAL 2007(^99)</td>
<td>Prospective randomized SVG intervention (( n = 594 ))</td>
<td>Proxis</td>
<td>GuardWire or FilterWire</td>
<td>30-d MACE</td>
<td>MACE similar for Proxis and control devices (9.2% versus 10%; ( P = 0.0061 ) for noninferiority)</td>
</tr>
</tbody>
</table>

MACE, major adverse cardiac events; SVG, saphenous vein graft.

protruding from its distal tip. Submerged in saline to avoid air trapping, the wire is pulled into the tip of the catheter and back to a clear space in the catheter proximal to the coronary guidewire monorail exit. Any 0.014F/0.018F coronary wire is used to cross the target lesion. The SpiderFX catheter is advanced in a monorail fashion over the coronary guidewire and positioned in such a way that the proximal end of the filter can be deployed 2 cm beyond the target lesion (Figures 29.29 to 29.34). The coronary wire is then removed and the capture wire advanced out through the distal end of the SpiderFX catheter, allowing the nitinol filter to expand to provide distal protection. The catheter is removed, and PCI is performed over the capture wire. The capture wire has a score at the interface between its gold distal and black proximal ends. This can be used to break the wire if only a short wire is required for monorail systems. Once the PCI is completed, the recovery end of the SpiderFX catheter is advanced over the capture wire to retrieve the filter. At this point, wire positioning across the lesion is obligatorily sacrificed.
Atherectomy, Thrombectomy, and Distal Protection Devices

Chapter 29

**Figure 29.28** SpiderFX distal embolic protection system. **A.** Capture wire is seen extruded from the SpiderFX catheter. **B.** Capture wire is seen partially captured within the SpiderFX catheter. **C.** The filter is delivered through the green (“go”) end of the SpiderFX catheter (single blue arrow). The filter is retrieved with the slightly larger blue (“back”) end of the SpiderFX catheter (double blue arrows).

This device in SVG stenting was studied in the SECURE trial.\(^9\) Subsequent generations of this device have an enhanced delivery system and were studied in AMETHYST trial in 2007. The Rubicon filter was a low-profile filter incorporated directly into a wire, which obviated the need for delivery sheath.

**Proximal Occlusion Systems**

**Proximal Occlusion Devices**

Proximal occlusion systems arrest antegrade flow while the intervention is performed, followed by aspiration of the conduit to remove liberated debris, with subsequent deflation of the occlusion balloon and restoration of flow. This strategy has several advantages. It can be utilized even when there is an inadequate distal landing zone to accommodate a distal protection balloon or filter. Since the lesion is not crossed with the device, the risk of distal embolization during an unprotected period is minimized. In addition, multiple downstream lesions can be addressed without the need for repeated catheter exchanges or repositioning of the device. Limitations of proximal protection include the need for a proximal landing zone, precluding its use in ostial or very proximal lesions. Ischemia during flow interruption
and trauma to the proximal landing zone by the device can also occur.

The Proxix Embolic Protection System (St. Jude Medical, Maple Grove, MN) consists of a hydrophilic balloon-tipped sheath. A coronary guidewire is placed proximal to the target lesion to prevent any liberation of embolic material, the sheath is advanced through a conventional guide catheter (at least 7F or 8F) over the coronary guidewire into the proximal target vessel, and the balloon tip is inflated to stop flow. A more proximal balloon on the Proxix sheath is also inflated.
inside the guiding catheter. Once PCI is completed, manual suction from the guide catheter aspirates any liberated embolic material through the sheath tip prior to balloon deflation and restoration of antegrade flow. A proximal landing zone of 12 mm is required. In the prospective, randomized, PROXIMAL (Proximal Protection during SVG Intervention) trial, Proxis was found to be noninferior to distal protection in 594 patients undergoing SVG stenting. Death, myocardial infarction, or target vessel revascularization at 30 days by intention-to-treat analysis occurred in 10.0% of distal
After successful stent deployment, blue retrieval end of the SpiderFX catheter is gradually advanced over the capture wire (black arrows show tip of the retrieval catheter as it is advanced). The capture wire and the SpiderFX catheter are then removed as a unit leaving no wire in the graft.

Figure 29.34  No-reflow occurs (left panel). After intragraft nitroprusside, there is return of brisk TIMI 3 flow (right panel).
and 9.2% of proximal protection patients ($P = 0.0061$ for noninferiority).  

### Embolic Protection During Acute Myocardial Infarction and Native Coronary Percutaneous Coronary Intervention

Randomized trials have failed to demonstrate significant benefit of routine embolic protection in primary PCI for STEMI (Table 29.4). In the EMERALD trial GuardWire distal occlusion did not improve infarct size or ST segment resolution as compared to a standard guidewire. Similarly, distal protection with the FilterWire in primary PCI did not improve maximal adenosine-induced flow velocity, infarct size, or 30-day mortality in the PROMISE trial, or complete ($\geq 70\%$) ST segment resolution detected by continuous ST-segment monitoring in the DEDICATION trial. Finally, proximal protection with PROXIS in the PREPARE trial did achieve noninferiority.  

### Embolic Protection Recommendations

The current ACC/AHA/SCAI and ESC guidelines provide a class I recommendation for EPD use in SVG intervention based on the results of the SAFER and FIRE trials. Despite this, only 22% of SVG PCIs is currently supported with EPD according to an ACC National Cardiovascular Database Registry analysis. Clearly there is significant opportunity for improved protection against distal embolization and no-reflow in this high-risk population. Use of EPD in STEMI has been disappointing with no significant benefit demonstrated. For this reason, no recommendations regarding EPD use in PCI for native coronary artery acute infarction have been offered.

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Chapter 29 Atherectomy, Thrombectomy, and Distal Protection Devices


Coronary artery disease in general and acute myocardial infarction (AMI) in particular remain the leading cause of death in Western societies. AMI is also becoming increasingly problematic in South and Central America, India, and China. As a result, it will continue to have enormous worldwide health implications. The understanding of the pathophysiology and development of reperfusion therapy of AMI will rank alongside the discovery of penicillin, isoniazid, and the polio vaccine as one of the major triumphs in medicine of the 20th century. In the early 1970s, when patients were admitted to coronary care units a 19% mortality was expected. Currently major angioplasty trials of ST-elevation AMI (STEMI) demonstrate a 1-year mortality of 3.5%. This dramatic reduction in mortality has contributed to a 5-year increase in life expectancy in the United States from 1970 to 1990. This chapter will summarize the current thinking on organization and execution of an optimal angioplasty strategy for STEMI.

**HISTORICAL OVERVIEW**

Catheterization-based strategies for management of STEMI date back to a largely overlooked work performed at Jackson Memorial Hospital by Robert Boucek et al. from the University of Miami. The work was initiated in 1959. Boucek was aware of the work of Fletcher and Sherry with a nonspecific fibrinolytic agent. The Miami investigators performed brachial artery cutdowns, placed nonselective catheters, and infused fibrinolysis in the aortic root of patients with ECG evidence of AMI. They published their work and demonstrated ECG evidence of reperfusion (Figure 30.1). Unfortunately, they were not able to perform selective coronary angiography to actually prove that reperfusion had occurred. Ignatios Voudoukis, a clinical fellow and co-author, explained later that this work was so heavily criticized by the leaders of cardiology in America that Boucek abandoned the work. Had Boucek known of the work Sones was conducting in Cleveland with selective coronary arteriography, the entire field might have advanced 20 years earlier.

In 1960 when Boucek was pioneering reperfusion, controversy existed over the role of thrombotic occlusion. Pathologic studies found occluding coronary thrombosis in only 50% of autopsy cases. Cardiac enzyme markers of acute MI did not exist, and clinicopathologic differentiation of ST versus non-ST MI had not occurred yet. A major breakthrough came in 1979 when DeWood et al. demonstrated that thrombotic occlusion was extremely prevalent in STEMI, especially if catheterization occurred within 6 hours of symptom onset. Furthermore, total occlusion was much less prevalent among patients catheterized after 6 hours. This suggested that the body’s own fibrinolytic system was reversing some occlusions. With this information, Rentrop soon thereafter was able to demonstrate that intracoronary occlusions could be successfully opened with intracoronary streptokinase therapy. Khaja next proved that streptokinase was superior to placebo in opening occluded arteries. This was the first randomized trial in the field of reperfusion. Kennedy et al. finally demonstrated that intracoronary streptokinase improved 1-year survival as compared to placebo. This group also for the first time linked vessel patency, which they termed “complete” perfusion versus “incomplete perfusion” or no perfusion, to 1-year survival. These studies in the early 1980s ushered in the modern era of reperfusion therapy.
Figure 30.1  
A. Schematic diagram of the infusion catheter system employed. A nonselective catheter was placed in the aortic root, and an infusion was performed during diastole using an electronic cardiac programmer triggered by the electrocardiogram R wave.  
At the same time that pharmacologic reperfusion was being introduced, a second parallel cardiovascular intervention also was born: coronary angioplasty therapy. Gruentzig et al. first reported in 1977 that elective angioplasty could be performed in the cath lab on conscious, sedated patients. The University of Michigan group was active in the investigation of intracoronary streptokinase, having collaborated with F. Khaja on the original randomized intracoronary streptokinase trial. Based on their experience with streptokinase, they tested it versus coronary angioplasty in the first randomized trial of thrombolytic therapy versus angioplasty (Figure 30.2). This study ushered in the next phase of investigations into reperfusion therapy: mechanical reperfusion.

Even though intracoronary streptokinase was effective and saved lives, some major drawbacks existed. One of those was the risk of major bleeding, not only at the vascular puncture site, but in remote areas as well. Catastrophic intracranial bleeds occurred in 1% to 2% of cases. These cases were demoralizing especially when this happened in young patients. In addition, angiographic studies revealed severe residual lesions in over 70% of patients in whom successful reperfusion occurred, while in 20% to 30% of cases the therapy was unsuccessful. Coronary angioplasty was an attractive alternative: bleeding risk was lower; intracranial bleeds were unlikely; residual lesions were eliminated; and “complete reperfusion,” now labeled TIMI III (Thrombolysis In Myocardial Infarction) flow, occurred in over 90% of cases. However, these theoretical advantages had to be proven in the context of randomized trials.

Unfortunately, the field of mechanical reperfusion lost momentum between 1985 and 1995. During this time

Figure 30.2 Angiograms of the first patient with STEMI treated with primary angioplasty at the University of Michigan. The procedure was performed on December 23, 1983. A. Total proximal LAD occlusion. B. Guidewire opening of LAD. C. Complete patency of the distal LAD after balloon angioplasty.
investigation focused on the combination of intravenous thrombolytic therapy with coronary angioplasty. The combination was tested in three trials and proven to be dangerous. Bleeding risk was higher, stroke risk was higher, and mortality was increased as compared to intravenous thrombolytic therapy alone.

Fortunately during this same time balloon angioplasty became further refined, more operators became trained, and large numbers of catheterization laboratories became proficient in elective angioplasty.

This set the stage for comparative trials of coronary angioplasty versus thrombolytic therapy. Groups in Royal Oak, Michigan; Rochester, Minnesota; and Zwolle, Netherlands conducted clinical trials which in aggregate demonstrated survival advantage and large reductions in risk of death or reinfarction when angioplasty was used without antecedent thrombolytic therapy. Importantly a 10-fold decrease in the risk of intracranial hemorrhage occurred for angioplasty therapy. The decade between 1995 and 2005 saw 20 further randomized trials conducted, which were summarized by Keeley et al. in a meta-analysis published in 2006. In aggregate these trials demonstrated a reduction in mortality (7.4% versus 5.5%, P = 0.0003), reduction in risk of stroke (2% versus 1%, P = 0.0004), reduction in reinfarction (6.8% versus 2.5%, P < 0.0001), and reduction in death or reinfarction (14% versus 8.2%, P < 0.0001) for angioplasty therapy. This summary ushered in the current era of investigation. Mechanical reperfusion had been proven to be safer and superior to thrombolytic therapy. Now the results needed to be optimized. Over the last decade research attention has turned from finding a role for intravenous thrombolytic therapy to optimizing the efficacy, safety, and durability of mechanical reperfusion. The last vestige of hope for a role for intravenous thrombolytic therapy was quashed when Ellis et al. published the Finesse trial and ASSENT investigators published the ASSENT IV trial (Assessment of the Safety and Efficacy of a New Treatment Strategy for Acute Myocardial Infarction). Ellis found that neither facilitation of PCI with retpalase plus abciximab nor facilitation with abciximab alone improved outcomes as compared to PCI alone. The ASSENT IV investigators found that a strategy of full-dose tenecteplase preceding PCI was associated with an increased number of adverse events than was PCI alone. Keeley et al. recently analyzed 17 randomized trials of PCI alone versus PCI facilitated with thrombolytic therapy (Figure 30.3). This meta-analysis demonstrated that mortality, reinfarction, intracranial bleeds, and total stroke are significantly increased when intravenous thrombolytic therapy is combined with PCI. This combination is harmful and should not be routinely applied.

**SYSTEMS OF CARE**

Angioplasty-mediated reperfusion therapy has enormous efficacy and safety advantages over intravenous thrombolytic therapy. Its major disadvantage, however, is that specialized catheterization facilities and highly trained operators are required to maximize its efficacy. Each hospital has its own obstacles that will take a reperfusion champion to overcome. Bradley has found that the major difference between successful and marginal reperfusion programs is that in successful programs a reperfusion champion is able to get emergency departments, ambulance services, cath labs, and the cardiologist to buy into a collaboration for timely administration of therapy. Rapid and accurate identification of STEMI patients is a prerequisite for an effective program. Key performance indicators include a 90-minute door-to-balloon time for >90% of cases, final TIMI III flow in >90% of cases, non-shock mortality in <4% of cases, and a shock mortality in <50% of cardiogenic shock cases.

**Angioplasty with No Surgery Onsite**

In the United States there are over 5,000 acute care hospitals. Of these, only around 1,000 have coronary bypass surgery and coronary angioplasty programs. For this reason patients with STEMI often present to institutions without angioplasty or bypass available onsite. Wharton pioneered and championed the concept of initiating emergency angioplasty in hospitals without onsite surgery. The Primary Angioplasty in MI (PAMI)–No Surgery On site (SOS) registry suggested that angioplasty performed by experienced operators could accomplish similar outcomes to those achieved by established reperfusion centers. The Atlantic Cardiovascular
Patient Outcomes Research Team (C-POR T) randomized patients presenting to hospitals in Maryland and Massachusett s to angioplasty therapy onsite versus intravenous accelerated tissue plasminogen activator therapy.\(^{26}\) The C-POR T investigators found that the incidence of death, MI, or stroke was significantly reduced with angioplasty therapy (12.4% versus 19.9%, \(P = 0.03\)). These studies demonstrate that institutions with the will to organize programs and obtain cardiology staffing including experienced interventionalists can provide superb reperfusion therapy with angioplasty. It is expected that many states in the United States will allow this approach to expand.

Regional Transfer Centers

In remote, sparsely populated regions angioplasty onsite is not logistically feasible. For such regions, transfer protocols with helicopter or ambulance will still allow for effective mechanical reperfusion therapy. Topol et al.\(^{27}\) first demonstrated the feasibility of helicopter transfer for emergency angioplasty. More recently Henry\(^{28}\) and Ting\(^{29}\) showed that patients presenting as far as 120 miles from a regional center can have outcomes comparable to those of local patients when an organized triage and transfer protocol exists. The viability of this approach was confirmed by the nationwide DANish trial in Acute Myocardial Infarction (DANAMI).\(^{30}\) In this trial patients were randomized to intravenous thrombolytic therapy versus primary angioplasty. Importantly, this was a nationwide trial with 80% of centers not able to perform angioplasty. In those centers patients were identified and transferred for PCI if randomized to that arm. The study was prematurely stopped owing to a mortality advantage for PCI. Thus even with a 120-minute delay for transfer patients, outcomes were improved for the PCI arm. It is crucial to understand that the DANAMI group had an extremely well-organized transfer protocol whereby patients were identified and transferred quickly (door-in-door out time of 30 minutes) and referral centers were immediately activated so that door-to-balloon times were minimized at the accepting center. As a follow-up of this study, Denmark has now established primary angioplasty as a nationwide protocol.

Metropolitan Systems

Densely populated urban areas have a different set of issues concerning reperfusion strategy. Traditionally, heavily populated areas have multiple acute care hospitals, all functioning independently with haphazard referral patterns largely based on physician preferences. In the United States half of patients arrive at the hospital by self transport and the other half by ambulance. Traditionally emergency rooms triaged trauma over chest pain. Most hospitals had myriad options for reperfusion. Even in hospitals with onsite PCI programs, reperfusion method could differ depending on time of arrival, physician on call, or weekday versus weekend arrival.

Fortunately, now that PCI has become the dominant reperfusion strategy in the United States, all this has changed. A nationwide imperative to identify, triage, and treat STEMI patients has forced all US acute care hospitals to develop organized STEMI protocols. Public reporting of acute MI core measures now include time for thrombolytic therapy administration and percentage of patients with a door-to-balloon time of <90 minutes.\(^{31}\) Furthermore, the ACC and AHA have fully endorsed organized STEMI protocols as a Class I recommendation.

The National Registry for Myocardial Infarction (NRMI) has documented very encouraging nationwide trends with more patients receiving reperfusion therapy, more hospitals achieving 90-minute door-to-balloon times, and shorter transport times for patients transferred for emergency catheterization.\(^{32}\)

Two other strategies will be beneficial for improving outcomes in metropolitan areas: First, citywide reperfusion centers like those in Ottawa\(^{33}\) will reduce reperfusion delays and triage patients to STEMI facilities. In the United States, Los Angeles County and Miami Dade County have well-developed programs whereby ambulance rigs are equipped with systems to transmit ECGs from the field. Furthermore, when a STEMI is identified, patients are taken to the closest STEMI facility. This has resulted in dramatic reductions in door-to-balloon time. Currently it is the goal of Miami Dade County to routinely achieve door-to-balloon times of <60 minutes. Recent data suggest that when door-to-balloon times drop below 60 minutes, a dramatic reduction in mortality occurs.\(^{34}\)

As these organized approaches demonstrate value, a second major societal change will occur. Currently there is a delay of over 1 hour for reperfusion when patients arrive by self-transport.\(^{35}\) Since half of US STEMI patients arrive by self-transport, marketing campaigns to persuade people to call for ambulance when a heart attack is suspected will be beneficial for reducing treatment delays. Nonshock mortality rates of under 1% can be achieved by adopting these approaches.

FUNDAMENTAL CONCEPTS OF REPERFUSION

To optimize treatment outcomes, a multipronged approach to the pathophysiology of the clotting system, the coronary lesion, and the ischemic myocardium is required. It is now understood that coronary artery inflammation with macrophage infiltration and destabilization of thin-capped fibroatheroma is the inciting event in vulnerable plaque rupture or erosion.\(^{36}\) This leads to a cascade of platelet activation and aggregation as well as tissue factor–mediated thrombin activation. A platelet-rich, fibrin-laced thrombus quickly develops and totally occludes the affected coronary artery. The local environment of the total occlusion is hostile to
intervention. Clot burden of varying extent occurs, platelet activation is intense, and plaque rupture can cause spontaneous dissections. In some patients even a minor erosion of severe underlying occlusion can totally occlude the vessel. For these reasons, there exists a ceiling of reperfusion for pharmacologic approaches, whereby initial patency rates of <70% occur. Reocclusion rates of 10% to 15% result in a substantial incidence of reinfarction. Thus mechanical opening with pharmacological milieu passivation results in larger numbers of patients with initial successful reperfusion and less reocclusion. Clinical trials have in fact corroborated this superiority. Angioplasty-treated patients are less likely to die or develop shock and less likely to develop reinfarction than those treated with thrombolytic therapy.

DeWood et al. demonstrated that total occlusion with inadequate collateral protection causes the electrical epicardial injury resulting in ST segment elevation. He further demonstrated that patients with non-ST segment elevation MI have either subtotal occlusions with maintained antegrade flow or total occlusions with well-developed collaterals. This understanding of the difference in coronary anatomy between ST segment elevation and non-ST segment elevation has prompted the evolution of entirely different approaches to the management of these conditions. Patients with ST elevation have a central ischemic zone of sufficient severity to cause myonecrosis. To resolve this, timely restoration of coronary blood flow is mandatory. Conversely, those patients with coronary events not resulting in ST elevation have sufficient antegrade flow or collateral flow to prevent extensive central ischemic zone necrosis. In these patients plaque passivation with antiplatelet agents is the first priority. Mechanical intervention is beneficial primarily in limiting reinfarction.

Plaque rupture occurs with equal frequency in the proximal areas of the left anterior descending (LAD), right, and circumflex vessels. Angiographic studies and clinical trials tend to over-represent the LAD territory and under-represent the circumflex. This occurs because circumflex occlusions tend to cause posterior infarctions that can be electrically silent on the 12-lead ECG, or can present with ST segment depression in V1-V3, often dismissed as unstable angina. Occasionally, branch occlusions (right ventricular, acute marginal, or posterior descending) of the right and left anterior descending (diagonals) or circumflex (obtuse marginal or posterior descending) can occur. The 12-lead ECG can provide some initial guidance on localization of the culprit coronary occlusion. Left mainstem occlusions are uncommon but can be suggested when extensive ECG ST elevation in the anterior leads occur with ST elevation in aVR. This lesion is incredibly dangerous and if suspected warrants consideration of emergency surgery. Proximal LAD occlusion presents with ST elevation in the anterior and lateral (I, aVL) leads. Rarely, isolated occlusions of right ventricular branches can present with ST elevation of V1 and V2. If the LAD is a dominant vessel and wraps around the apex, elevation of ST in II, III, and aVF can occur along with anterior lead involvement. Right coronary occlusions can be divided into those that occur proximal or distal to the major right ventricular branches. Occlusions distal to the RV branches present with ST elevation in II, III, and aVF. If the right coronary is a hyper-dominant vessel, reciprocal ST depression of V1-V3 along with inferior lead ST elevation suggests a large amount of myocardium at jeopardy which results in large infarcts if reperfusion does not occur. When coronary occlusion is proximal to the RV branches, ECG signs of RV infarction are present. ST elevation in the right precordial leads also occurs. It is important to recognize this MI pattern because RV infarct patients are extremely sensitive to nitrates. It is strongly advisable to avoid nitrates in patients with inferior STEMI for this reason. The quick drop in preload following nitroglycerin therapy can cause dangerous drops in systemic pressure. Generally occlusions of the left circumflex artery present with ST elevation of the inferior leads or ST depression of V1-V4. If the circumflex is a dominant artery, extensive inferoposterior infarction can occur, often out of proportion to the extent of ST elevation on the ECG. In addition, small obtuse marginal infarctions can lead to severe ischemic mitral regurgitation. This can progress to papillary muscle rupture with flail mitral leaflets and life threatening acute mitral regurgitation.

During the initial period of development of mechanical reperfusion therapy, contrast ventriculography was considered essential prior to coronary angiography. However, as door-to-balloon time has taken increased emphasis, many operators now skip ventriculography. It must be emphasized that measurement of left ventricular end-diastolic pressure and analysis of the ventriculogram provide enormously useful information concerning hemodynamic status and short-term prognosis. In addition, determination of the extent and location of regional wall motion abnormalities allows an early recognition of the myocardium at risk and corroborates location of the culprit vessel. Therefore if ventriculography is not performed prior to PCI or if culprit vessel status is questionable, ventriculography should be performed thereafter. On occasion small side branches with flush occlusion are difficult to detect and can be found once regional wall motion abnormalities are found. Finally, episodes of contained myocardial rupture, small ventricular septal defects, or ischemic mitral regurgitation can be quickly diagnosed with ventriculography.

**Time to Therapy**

Reimer and Jennings initially elucidated time dependency of evolution of a total coronary occlusion infarction in a canine model. In this model a wave front of necrosis occurs whereby subendocardial-to-transmural necrosis begins within 40 minutes of occlusion and is largely complete within 3 hours. Further, small epicardial areas can continue to necrose for up to 96 hours (Figure 30.4). Twenty-five
years after publication of these canine studies, Gersh and Stone have correlated clinical trials and demonstrated that the maximum value for reperfusion occurs within 60 to 180 minutes of onset of occlusion and only modest benefit is derived thereafter.

Time to reperfusion is the dominant but not the sole determinant of final infarction size. Extent of collateral flow is critical as well. It has been well recognized that right coronary occlusions have more collaterals than do LAD or circumflex occlusions. This occurs because the right coronary bed has collateral sources through the LAD septal arcade as well as through the distal circumflex. The LAD generally gets collaterals only from the right, and the circumflex as well gets collaterals usually only from the right. These differences in the extent of collaterals result in larger infarctions occurring in the LAD distribution. Not only are infarcts larger with LAD occlusions, but infarct size reduction is far more time dependent for LAD occlusions. Brodie as well as our group showed that the maximum infarct size reduction for LAD occlusions occurs if treated within 3 hours of symptom onset whereas right occlusions tend to result in smaller infarcts and there is minimal time dependency for infarct size reduction (Figure 30.5). Based on this understanding, shortening the time to reperfusion is crucial for patients with anterior MI who present within 3 hours of symptom onset. Patients with inferior MI, irrespective of the time of presentation, derive less benefit from reduction of time to reperfusion.

Apart from minimizing time to therapy, efforts to reduce myocardial oxygen demand such as decreasing blood pressure in hypertensive patients, using nitrates and diuretics in patients with congestive heart failure also are prudent measures. In addition, supplemental oxygen can be useful as well. Use of intravenous beta blockers offers no benefit but increases the risk for development of cardiogenic shock and should be generally avoided.

**Clinical Risk Assessment**

In addition to symptom duration, assessment of risk drives decision making, especially for patients presenting at non-PCI facilities. The PAMI investigators first used TIMI risk classification to determine outcomes for angioplasty therapy in nonshock patients (Figure 30.6). Risk is defined by three easy-to-ascertain factors: (i) age < 70 years, (ii) admission heart rate of < 100 bpm, and (iii) non-anterior MI location. For these low-risk patients, mortality was low irrespective of whether angioplasty or thrombolytic therapy was used. Conversely, mortality was significantly higher for patients of age > 70, with admission heart rate > 100, or with anterior MI location. Recently, Cantor et al. demonstrated that segregation by a similar risk-scoring system allows identification of high-risk patients who may benefit from transfer even when they are initially treated successfully with thrombolytics. Based on risk assessment, a simple transfer protocol can be organized (Figure 30.7). Low-risk patients who present early and are not at increased risk for intracranial bleeding can be treated with IV thrombolytics and transferred electively. All other patients should be transferred immediately. Time to transfer must be minimized by an organized transfer protocol.

**Optimal Preprocedure Therapy**

Because of the increased risk of stroke and lack of efficacy, preprocedure intravenous thrombolytic therapy agents are largely avoided. Antiplatelet therapy with aspirin, ideally chewable aspirin, is the mainstay. Recently, Sabatine et al. demonstrated that a 300-mg loading dose of clopidogrel followed by a 75-mg daily maintenance dose reduced the risk of death/MI or stroke from 6.2% to 3.6% (P = 0.008) in the TIMI 28 (clarity trial) with patients undergoing PCI for STEMI who had also received thrombolytic therapy. Dangas demonstrated that a 600-mg pretreatment dose is more effective than a 300-mg dose.
More recently, Motalescot et al.\textsuperscript{47} randomized 3,534 patients with STEMI to 300 mg of clopidogrel load with a 75-mg maintenance dose versus 60 mg of prasugrel with a 10-mg maintenance dose. They found that death, MI, or stroke was reduced from 9.5\% to 6.5\% ($P = 0.0017$) at 30 days and was maintained for 15 months, in the prasugrel group. Given these clinical findings and pharmacokinetic studies that reveal early platelet inhibition with oral prasugrel, this agent should be preferred except in elderly patients or those of small body weight for whom excessive stroke risk is of concern.

Because of the crucial implications of platelet activation and aggregation that occurs with STEMI, intravenous glycoprotein receptor IIb/IIIa antagonists have undergone extensive evaluation. When oral antiplatelet therapy is problematic owing to nausea or vomiting, intravenous agents—either abciximab or small-molecule GP IIb/IIIa antagonists—are essential. In most settings, however, anticoagulation with bivalirudin and clopidogrel or prasugrel provides adequate therapy. It must be remembered that the combination of weight-adjusted heparin and abciximab has one major advantage: this therapy is immediately reversible with protamine sulfate and platelets. This may be required when emergency surgery is necessary or when coronary perforation occurs. Fortunately, these complications are rare, so as a routine, oral therapy with aspirin and thienopyridines followed by intravenous bivalirudin has become the mainstay therapy.

**Milieu for Reperfusion**

Given the time dependency of myocardial salvage, especially with anterior MI, most research interest has focused on minimizing time delays. Over the last 10 years a variety of methods to limit infarct size after successful PCI have been tested. Supersaturated oxygen may have a role in patients with anterior MI who are reperfused within 6 hours of symptom onset.\textsuperscript{48} Systemic hypothermia has been tested\textsuperscript{49}; unfortunately few patients can be cooled to temperatures $<35^\circ$C prior to reperfusion, with older technology. Newer methods that permit to more quickly cool the patients hold promise to limit MI size and need further testing. Intracoronary administration of adenosine\textsuperscript{50} at doses of up to 70 $\mu$g/kg may limit MI size in anterior infarction. This agent cannot be used in the setting of right coronary occlusion owing to a high incidence of heart block that occurs with intracoronary infusion in the RCA.
Extensive testing has been carried out with removal or pulverization of occlusive thrombi. The best data exist for extraction thrombectomy. Svilass et al. showed that 1-year mortality improved for PCI after extraction thrombectomy in 1,071 patients randomized to PCI alone versus PCI after extraction thrombectomy. Myocardial blush was enhanced and ST resolution was more complete with aspiration thrombectomy. These findings suggest that aspiration thrombectomy should be routinely attempted, especially in large vessels or those with an obvious thrombus burden.

Recently, prophylactic intra-aortic balloon (IABP) counterpulsation was tested in the CRISP-AMI trial. Patel et al. reported that infarct size measured by cardiac magnetic resonance imaging was no different for the 337 patients with anterior MI who were treated with standard PCI versus those treated with IABP before PCI. Nevertheless, interest persists in this topic, and three studies are testing the role of prophylactic support with the Impella, axial flow percutaneous left ventricular support device.

Finally, efforts to prevent reperfusion injury have been on for 25 years. However, no agent has been found of value. A small pilot study of intravenous cyclosporine has shown promising results but needs more extensive testing in multicenter outcome trials.

### Pre- and Postischemic Conditioning

An exciting new development that may dramatically enhance myocardial salvage relates to ischemic preconditioning and postconditioning. The concept that brief repetitive episodes of ischemia followed by reperfusion can enhance myocardial salvage was initially demonstrated in an animal model. Thibault et al. subsequently found a 36% enzymatic infarct size reduction in patients who underwent postconditioning with four episodes of 1-minute balloon inflation followed by 1-minute deflation after stent placement. The same investigators randomized 38 patients to usual stent therapy versus repetitive ischemia–reperfusion and found PET infarct size reduced from 19.5 ± 13% to 11.8 ± 10% (P = 0.04) in the latter group. At 1 year, echo-derived ejection fraction was larger and regional wall motion was enhanced in the ischemic postconditioning group. These are extremely promising findings and need definitive evaluation in the context of large outcomes trials. Since very little extra time and expense and risk are associated with this therapy, proof of concept may quickly make it a mainstay.

Perhaps even more revolutionary is the concept that ischemia of remote organs can limit myocardial infarct size after reperfusion. Biter et al. randomly assigned 333 patients being transported for PCI therapy for STEMI to usual care (n = 167) versus four cycles of 5-minute arm ischemia followed by 5-minute release. Ischemia was accomplished by inflation of a blood pressure cuff and subsequent release. Myocardial salvage was assessed by injection of technetium sestamibi prior to intervention with imaging performed after therapy. This assessed the area at risk. Final infarct size was determined by SPECT imaging performed at 1 week. Myocardial salvage index was determined as a ratio of final infarct size to the area at risk (Figure 30.8). Salvage index was higher for patients presenting with patent coronary arteries and was higher in LAD infarcts. Preconditioning did independently increase myocardial salvage, especially in anterior MI. Again, large outcome trials will be required but the simplicity of use of this therapy warrants more broad-based recommendation.

### Stent Therapy

Grines et al. first randomly assigned patients selected for PCI therapy of STEMI to balloon angioplasty alone versus implantation of a Johnson and Johnson heparin-coated stent. The STENT-PAMI investigators found that routine stent implantation reduced reocclusion and target vessel revascularization but that it was also associated with a disturbing trend toward fewer patients with TIMI III flow. Subsequently Stone et al. tested newer bare-metal stents in the CADILLAC TRIAL. They found that routine stent therapy did enhance clinical outcomes, primarily by decreasing target vessel revascularization, and was not associated with reductions in TIMI III flow outcome. The excellent angiographic outcomes caused stent therapy to become routine. With the advent of drug-eluting stents (DESs), several randomized trials were conducted, which were summarized by Stone et al. He demonstrated that drug-eluting stents decreased target vessel revascularization as compared to bare-metal stents. Importantly, a trend toward more subacute recurrences occurred in DES treated patients. Today stent therapy has become the default treatment. Decisions about use of DES largely relate to social issues since lack of compliance with long-term thienopyridine therapy increases to a great extent the risk of subacute thrombosis.

### PROCEDURAL ASPECTS

In the end, infarct angioplasty is an invasive procedure, and ultimately the operator is held accountable for outcomes. With this in mind, operators must exercise exquisite judgment in deciding on suitability of the patient for catheterization and intervention. The current process of care poses an enormous challenge to the operator. The near mania that can occur for rapid door-to-balloon times can cause basic steps to be missed prior to intervention. At a minimum the operator should personally evaluate the ECG to ensure that patients with early repolarization, pericarditis, hyperkalemia, or chronic bundle branch block are not undergoing unnecessary procedures.

In addition, a brief physical examination must be carried out to document vascular status, presence of congestive heart failure, pulmonary status, and presence of cardiac murmurs.
These steps are critical to exclude, at least on the basis of clinical examination, the presence of mechanical complications of myocardial infarction such as papillary muscle rupture or a new ventricular septal defect, which would warrant a surgical approach. It is the operator's ultimate responsibility to ensure that the procedure is necessary and indicated. The initial decision that must be made relates to the patient's overall stability. For patients who are highly unstable (e.g., requiring repetitive electrical cardioversion or vasopressor support) or who have airway compromise for any reason, intubation, and sedation and paralysis make the subsequent procedure far safer and more successful. Conversely, if the patient is stable and can lie quietly on the cath table, rapid arterial access can be obtained.

Radial Artery Access

Elective angioplasty and infarct angioplasty have evolved in parallel since the days of Gruentzig and Hartzler. Advances in technique were initially studied in the elective setting and quickly adopted to the emergency setting. This occurred for over-the-wire balloon catheters, first-generation stents, distal protection devices, and drug-eluting stents. Similarly, angioplasty technique has been refined and these refinements have been adapted to acute infarct angioplasty. Major breakthroughs in stent design and guide catheter design have allowed 6F guide catheters to be routinely used. Once 6F guides could be used, radial access became routinely feasible. Recently a randomized trial of femoral versus radial intervention demonstrated that the radial approach resulted in fewer bleeding complications and a trend toward improved survival after PCI therapy of STEMI. This approach holds great promise, and as PCI operators have become increasingly proficient in the approach, it is expected that many more STEMI patients will be treated via the radial artery access. For patients who are hemodynamically unstable, it is still advisable to use the femoral approach because it permits quick access for temporary pacemaker implantation or ventricular assist devices to be used.

Angiography and Hemodynamic Assessment

Angiography of the noninfarct artery is mandatory prior to infarct artery intervention. This allows assessment of nonculprit vessel status and assessment of degree of collateral flow. There have been occasions when operators have skipped this step, presumably to save time. In some patients this may lead to catastrophic consequences. As an example, infarct vessel stenting of a right coronary occlusion, can take place with

Figure 30.8: Infarct risk reduction of patients treated with remote ischemia versus control. (From Betker HE, Kharbanda R, Schmidt MR, et al. Remote ischaemic conditioning before hospital admission, as a complement to angioplasty, and effect on myocardial salvage in patients with acute myocardial infarction: a randomized trial. Lancet 2010;35.)
survival as well as 1-year survival. Vessel involvement after inferior infarction. Correction so that an appropriate stent size can be determined; an allows blood flow to perfuse the vessel. Administration of hypovolemic owing to nausea or vomiting or they have right ventricular involvement after inferior infarction. Correction of volume status may allow cessation of vasopressor therapy. Similarly, patients presenting late after inferior MI may develop complete heart block after reperfusion. In these patients, atropine and volume therapy usually resolve hemodynamics; on occasion, however, a transvenous pacemaker is required. Hence femoral vascular access may be quickly required.

Culprit Vessel Percutaneous Coronary Intervention

Once complete angiography is performed, culprit vessel identification and sizing is necessary. If the culprit vessel is large or an angiographic dye stain is apparent, reperfusion with a guidewire and aspiration thrombectomy should be performed. This allows blood flow to perfuse the vessel. Administration of intracoronary nitroglycerin or adenosine further enhances blood flow and further perfuses and dilates the vessel so that an appropriate stent size can be determined; an appropriate sized stent of sufficient length to cover the culprit lesion is required. Repetitive balloon inflations can be done after stent placement to attempt postischemic conditioning. Finally, angiography should be performed to assess vessel size and TIMI flow. If any question about stent to vessel size mismatch arises, intravascular ultrasound should be performed. Undersizing of the stent is the most common mistake and may lead to stent malposition and subacute stent thrombosis. If TIMI III flow does not occur, repeated doses of nitroglycerin, adenosine, or nicardipine should be administered. Lack of achievement of TIMI III flow is associated with impaired hospital survival as well as 1-year survival.

Stent therapy should be kept simple. Crush or bifurcation stenting should be avoided since these techniques are known to increase risk of subacute thrombosis in the elective setting. Immediate stent therapy of a nonculprit vessel has been associated with poor outcomes and according to the most recent PCI guidelines it is a Class III indication. It is safer to allow the patients to recuperate and have them return to the cath lab prior to hospital discharge for complete revascularization when indicated.

On occasion when multiple culprit lesions are present, it is difficult to identify the culprit vessel. In this setting, judicious stenting of vessels that could affect the myocardial territory at jeopardy (i.e., anterior versus inferior versus posterior) can be performed.

CONCLUSION

Over the last quarter century, conquest of STEMI has been a major achievement in cardiovascular medicine. Unlike many other acute illnesses, this condition cannot be treated by one physician alone. The system of care and team approach of an organized, well-run reperfusion program is a paradigm for the 21st-century medicine. Each member of the team, from the paramedics in the field to the transfer office personnel, to the air ambulance pilots, to the ER staff, to the cath lab staff, and finally to the interventional cardiologist, must be committed to rapidly, efficiently, completely doing his/her specific job in this process. Delays or missteps anywhere along this “chain of survival” can be life threatening. The victories achieved must be shared with the team. Metrics must be reviewed with the team. Any operator who has treated these patients understands the near miraculous power of timely reperfusion. The challenge for all involved now is to provide this care to every patient, anytime, everytime.

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Coronary Stenting

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Stents are metallic scaffolds that are deployed within diseased segments of coronary arteries to establish and maintain wide luminal patency. Currently, stent-assisted coronary intervention is the most common revascularization modality in patients with coronary artery disease. The acute and late results of stent implantation, however, vary greatly depending on the clinical risk profile of the patient, the complexity of the coronary lesion and interventional procedure, and the specific stent device that is used. A broad range of evidence is available from clinical trials conducted over the past two decades to guide appropriate stent usage in most situations.

The present chapter traces the evolution and development of the coronary stent from its initial applications to treat balloon angioplasty failures to its widespread global adoption for the treatment of patients with ischemic coronary heart disease.

BARE-METAL STENT OVERVIEW

Limitations of Balloon Angioplasty

While the performance of the first successful balloon angioplasty on September 16, 1977, in Zurich, Switzerland, set the stage for the millions of percutaneous coronary intervention (PCI) procedures that have since taken place, stand-alone balloon angioplasty as performed by Andreas Gruentzig and other early pioneers was a highly unpredictable experience. The mechanism of balloon angioplasty involves plaque fracture (dissection) into the deep media, with expansion of the external elastic lamina, as well as partial axial plaque redistribution along the length of the treated vessel. The majority of vessels undergoing balloon angioplasty tolerate balloon dilatation and heal sufficiently to result in an adequate lumen; however, balloon-mediated injury to the vessel wall can at times be uncontrolled and excessive, resulting in balloon angioplasty’s two major limitations: abrupt closure (occurring acutely, or within the first several days after angioplasty) and restenosis (occurring later, within months after the procedure due to a combination of acute recoil and chronic constrictive remodeling). The coronary stent was thus devised as an endoluminal scaffold to create a larger initial lumen, to seal dissections, and to resist recoil and late vascular remodeling, thereby improving upon the early and late results of balloon angioplasty.

Development of the Coronary Stent

The term “stent” derives from a dental prosthesis developed by the London dentist Charles Stent (1807–1885) and is now used to indicate any device used for “extending, stretching, or fixing in an expanded state”.

The first stents were implanted in human coronary arteries in 1986 by Ulrich Sigwart, Jacques Puel, and colleagues, who placed the Wallstent sheathed self-expanding metallic mesh scaffold (Medinvent, Lausanne, Switzerland) in the peripheral and coronary arteries of eight patients. Further experience with this device demonstrated high rates of thrombotic occlusion and late mortality, although patients without thrombosis had a 6-month angiographic restenosis rate of only 14%, suggesting for the first time that stenting could improve late patency in addition to stabilizing the acute results obtained after conventional balloon angioplasty. Another early stent platform developed contemporaneously by Cesare Gianturco and Gary Roubin was a balloon-expandable coil stent consisting of a wrapped stainless steel wire resembling a clamshell (Figure 31.1, left). A phase II study evaluating the Gianturco-Roubin stent to reverse postangioplasty acute or threatened vessel closure was started in 1988, ultimately leading to United States Food and Drug Administration (FDA) approval for this indication in June 1993.

While these stents were being developed and tested, Julio Palmaz designed a balloon-expandable slotted tube stainless steel stent in which rectangular slots were cut into thin-walled stainless steel tubing and deformed into diamond-shaped windows during expansion by an underlying delivery device.
Figure 31.1  **Left.** The Gianturco-Roubin Stent. Stainless steel sutures were wound around a cylindrical rod using pegs to shape the wire, resulting in a clamshell design. **Right.** The Palmaz-Schatz Stent. Note the articulation between the two slotted tubes.

In 1989, while a design modification was made by Richard Schatz, consisting of the placement of a 1 mm central articulating bridge connecting the two rigid 7 mm slotted segments, creating the 15 mm Palmaz-Schatz stent (Johnson and Johnson Interventional Systems, Warren, NJ) (Figure 31.1, right). The first coronary Palmaz-Schatz stent was placed in a patient by Eduardo Sousa in São Paulo, Brazil in 1987 with a US pilot study started in 1988.

In 1989, enrollment commenced in two randomized multicenter studies (STRESS and BENESTENT) comparing balloon angioplasty alone to elective Palmaz-Schatz stenting. In these studies, the use of the Palmaz-Schatz stent was associated with a 20% to 30% reduction in clinical and angiographic restenosis compared with conventional balloon angioplasty (Figure 31.2). The Palmaz-Schatz stent also resulted in markedly improved initial angiographic results, with a larger postprocedural minimal luminal diameter and fewer residual dissections, which translated into a lower rate of subacute vessel closure. These results led to approval...

![Graph](https://via.placeholder.com/150)

**Figure 31.2** Results of STRESS and BENESTENT-1 landmark trials of the Palmaz-Schatz stent, which provided the evidence base for FDA approval of the Palmaz-Schatz stent for the prevention of restenosis in de novo lesions. BA, balloon angioplasty; TLR, target lesion revascularization; MACE, major adverse cardiac events.
of the Palmaz-Schatz stent by the FDA in 1994. Long-term follow-up up to 15 years has subsequently demonstrated few late clinical or angiographic recurrences from years 1 to 5 after coronary stent implantation, with slight and progressive decrements in luminal size thereafter extending beyond 10 years. The mechanisms of this late progression of disease are not entirely known, but have been hypothesized to be related to the development of new atherosclerosis within the originally stented segment rather than clot formation, as overall stent thrombosis rates have remained low (1.5% at 15 years).

Despite the impressive acute and long-term results with the Palmaz-Schatz stent which became the dominant stent design for coronary use, widespread adoption of stent technology was initially hindered by the perceived need for an intense anticoagulation regimen (consisting of aspirin, dipyridamole, heparin, dextran, and warfarin) to inhibit stent thrombosis (which nonetheless occurred in approximately 3% of patients). This profound degree of anticoagulation, however, resulted in a marked increase in hemorrhagic and vascular complications. It was not until further refinements in stent deployment technique and the utilization of dual antiplatelet therapy demonstrated reductions in these complications that stent usage became more widespread. Pioneers such as Antonio Colombo demonstrated reduced rates of stent thrombosis with more aggressive intravascular ultrasound (IVUS)-guided deployment techniques including routine high-pressure adjunctive dilatation (>14 atmospheres), along with the use of aspirin and a second antiplatelet agent (thienopyridine, ticlopidine) rather than prolonged warfarin therapy. These modifications significantly reduced the incidence of stent thrombosis to ~1% to 2%, and concomitantly reduced bleeding and femoral arterial complications.

The confirmation of Colombo’s initial findings in several randomized clinical trials (Figure 31.3) definitively established the superiority of dual antiplatelet therapy (with aspirin and ticlopidine) over an anticoagulation-based approach for prevention of stent thrombosis, and facilitated widespread adoption for coronary stenting by the late 1990s.

Stent Design: Impact on Performance and Clinical Outcomes

Classification

Coronary stents may be classified based on their composition (e.g., metallic or polymeric), configuration (e.g., slotted tube versus coiled wire), bioabsorption (either inert (biostable or durable) or degradable (bioabsorbable)), coatings (either none, passive such as heparin or polytetrafluoroethylene, PTFE), or bioactive (such as those eluting rapamycin or paclitaxel), and mode of implantation (e.g., self-expanding or balloon-expandable). The ideal stent would be made of a nonthrombogenic material and have sufficient flexibility in its unexpanded state to permit ready passage through guiding catheters and tortuous vessels, and yet have an expanded configuration providing uniform scaffolding of the vessel wall with low recoil and maximal radial strength while conforming to vessel bends. In addition, the ideal stent would be sufficiently radiopaque to allow fluoroscopic visualization to guide accurate placement and management of in-stent restenosis, but not so opaque as to obscure important angiographic vessel.

Figure 31.3 Benefits of dual antiplatelet therapy in reducing clinical events post stenting. Shown are the results from four landmark trials demonstrating the efficacy of antiplatelet (over antithrombotic) therapy.
details. In recent years, the importance of the stent delivery system to device profile, flexibility, and trackability around tortuous and calcific coronary vessels has received increasing appreciation. For balloon-expandable stents, the stent must be tightly crimped to the delivery balloon to avoid dislodgment, and the overhang of the balloon beyond the ends of the stent should be minimized (<1 mm) to avoid vessel trauma outside the stent margins. Stent delivery balloons must be able to withstand high pressures (>18 atm) without rupture, and should take into account a balance between deliverability versus a desire for low compliance to facilitate predictable sizing and avoid excessive growth outside the stent edges.

Stent Composition
Until recently, the most widely used stent material was 316L stainless steel. Cobalt chromium and platinum chromium alloys have been employed in more recent stent designs in order to allow lower-profile thin strut struts (~75 μm, versus 100 to 150 μm in most stainless steel stents) that still maintain radial strength and visibility. Most self-expanding stents utilize nitinol, a nickel/titanium alloy that has super-elastic and thermal shape memory properties that allow it to be set into a particular expanded shape by baking at high temperature. Nitinol stents can then be squeezed down and constrained on the delivery system, able to return to that set shape when released in the coronary artery.

Other than gold (which has been shown to increase restenosis), there is little evidence that thrombosis or restenosis rates vary with the specific stent metal, though the final stages of surface finishing, smoothing, and purification or passivation may affect early thrombotic and late restenotic processes. There is a burgeoning interest in biodegradable stents, which theoretically offer the advantages of increased longitudinal flexibility (though at the expense of radial force), compatibility with noninvasive imaging, and complete bioabsorption over a period of months to a year or longer, thereby restoring underlying vascular reactivity. Bioabsorbable stents (or bioabsorbable scaffolds) are typically either polymeric in nature (e.g., using proprietary biodegradable polymers or poly-L-lactic acid (PLLA), which is degraded via the Krebs cycle to carbon dioxide and water) or nonpolymeric (e.g., magnesium-based).

Stent Configuration and Design
Stents can be assigned to one of three subgroups, based on construction: wire coils, slotted tubes/multicellular, and modular designs. After early experiences with wire coil stents (e.g., the Gianturco-Roubin stent), these types of stent designs rapidly fell out of favor because they in general lacked axial and radial strength, and due to lesser strut coverage predisposed to plaque prolapse. Thus, the vast majority of stents in current use are either slotted tube/multicellular or modular in design. In an effort to preserve the radial strength and wall coverage of the original tubular designs (e.g. the Palmaz stent) but improve flexibility in their collapsed states, several generations of slotted tube and multicellular stents have been introduced by various manufacturers. Each is laser cut from a metallic tube into a unique pattern that increases the overall flexibility of the stent by distributing bending throughout the stent length without compromising radial strength or elastic recoil in the expanded state. The newer stents are manufactured in a broad range of stent lengths (8 to 48 mm) and diameters (2.25 to 6.0 mm and above for peripheral applications) to facilitate stenting of long lesions, small vessels, saphenous vein grafts (SVGs), and distal lesions. To eliminate the need for a protective sheath, various mechanical, balloon-wrapping, and heat-curing processes have been developed to tightly crimp the stent onto the balloon until it is deployed. This bare mounting onto the delivery balloon has greatly reduced stent delivery profiles, comparable with the best angioplasty balloons of the late 1990s, and has kept stent embolization rates below approximately 1 to 3 per 1,000 procedures.

Despite their enhanced flexibility, even the latest-generation slotted tube stents are sometimes difficult to deliver through tortuous and noncompliant vessels. In an effort to enhance flexibility and deliverability without sacrificing the excellent scaffolding of the slotted tube stents, modular or hybrid stents have been created by flexibly joining multiple short repeating modules to each other. The initial modular stent was the Arterial Vascular Engineering MicroStent (subsequently purchased by Medtronic Corp., Santa Rosa, CA), which had a series of 4-mm-long, rounded stainless steel corrugated ring subunits welded to each other. Subsequent designs have incorporated an elliptorectangular (rounded) strut profile and progressively reduced the length of the individual modules, with progressive reductions in crossing profile and increased surface area coverage. Additionally, variation in the location and frequency of the weld-points has been used to engineer flexibility without attempting to sacrifice radial and axial strength.

Depending on the cellular configuration, multicellular stents can be broadly subclassified as either open cell or closed cell. Open cell designs tend to have varying cell sizes and shapes along the stent, and provide increased flexibility, deliverability, and side branch access by staggering the cross-linking elements to provide radial strength. Open cell designs thus tend to conform better on bends, though the cell area may open excessively on the outer curve of an angulated segment. Closed cell designs typically incorporate a repeating unicellular element that provides more uniform wall coverage with less tendency for plaque prolapse, at the expense of reduced flexibility and side branch access. Closed cell designs also tend to straighten vessel bends more than open cell designs.

Stent design may significantly impact acute and late vascular responses. Stents that possess better conformability, less rigidity, and greater circularity experimentally produce less vascular injury, thrombosis, and neointimal hyperplasia. Ex vivo and clinical studies have suggested that thin stent
struts may be associated with reduced neointimal hyperplasia and lower rates of restenosis,\(^\text{20}\) in addition to inherently less thrombogenicity.\(^\text{21}\)

Due to the recent emphasis upon thin-strutted and more flexible stent designs in order to facilitate deliverability as well as other adverse vascular responses to stent implantation, there have been some concerns regarding the integrity of modern stent platforms. While thin-strutted stents have obvious advantages, some of these stent platforms have been associated with a greater tendency for recoil (radial) or orthogonally, for axial (or “longitudinal”) deformation and/or compression.\(^\text{22,23}\) In the instance of axially oriented deformation, this phenomenon has been described to occur specifically when implanted stents are subjected to repeated stresses, such as multiple balloon exchanges and guide-stent interactions.\(^\text{24}\) Engineering modifications can be employed to maintain flexibility and deliverability without sacrificing axial and radial strength. As such, further investigations of stent-specific differences based upon these characteristics are required.

### Stent Coatings

A variety of coatings have been used to attempt to reduce the thrombogenicity and/or propensity for restenosis of metallic stents (Table 31.1). Experimental studies have demonstrated that coating stents with inert polymers may reduce surface reactivity and thrombosis,\(^\text{19,21}\) though until recently, most polymers used were found to provoke intense inflammatory reactions.\(^\text{25}\) With the advent of the drug-eluting stents (DES) came a renewed interest in the study of stent coatings, primarily to act as drug-carrier vehicles. However, concerns

<table>
<thead>
<tr>
<th>Table 31.1</th>
<th>Stent Coatings Designed to Reduce Thrombogenicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heparin</strong></td>
<td>- Multiple formulations incorporating heparin bonding through covalent bonding, ionic bonds, or heparin complexes [Carmeda BioActive Surface (CBAS) covalently heparin-bonded Palmaz-Schatz and Bx Velocity stents, Jomed Corline Heparin Surface (CHS) heparin-coated Jostent]</td>
</tr>
<tr>
<td><strong>Carbon</strong></td>
<td>- Turbostratic (Sorin Carbostent)</td>
</tr>
<tr>
<td></td>
<td>- Silicon carbide (Biotronik Tenax)</td>
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<td></td>
<td>- Diamond-like films (Phytis Diamond and Plasmachem Biodiamond)</td>
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<tr>
<td><strong>Phosphorylcholine</strong></td>
<td>- Biocompatibles Biodivysio stent</td>
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<tr>
<td></td>
<td>- Medtronic Endeavor drug-eluting stent</td>
</tr>
<tr>
<td><strong>Fluorinated copolymer</strong></td>
<td>- Xience V and Promus Element drug-eluting stents</td>
</tr>
<tr>
<td><strong>Ionic Oxygen penetration into stent</strong></td>
<td>- Iberhospitex Bionert</td>
</tr>
<tr>
<td><strong>CD34 Antibody to capture endothelial progenitor cells</strong></td>
<td>- Orbus-Neich Genous</td>
</tr>
<tr>
<td><strong>Trifluoroethanol</strong></td>
<td>- Polyzene-F coated stent</td>
</tr>
<tr>
<td><strong>Nanolayer protein coating</strong></td>
<td>- SurModics Finale coating on Protex stent</td>
</tr>
<tr>
<td><strong>Nitric oxide scavengers including titanium-nitric oxide</strong></td>
<td>- Hexacath Titan stent</td>
</tr>
<tr>
<td><strong>Single Knitted PET Fiber Mesh</strong></td>
<td>- (MGuard)</td>
</tr>
<tr>
<td><strong>Biolinx Polymer</strong></td>
<td>- Medtronic Resolute drug-eluting stent</td>
</tr>
<tr>
<td><strong>Abciximab and other glycoprotein IIb/IIIa inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Activated protein C</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Hirudin and bivalirudin</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Prostacyclin</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Gold</strong></td>
<td></td>
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<tr>
<td><strong>Turmeric</strong></td>
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</tbody>
</table>
regarding the long-term safety of DES and the requirement for extended duration dual antiplatelet therapy have led to a renewed interest in biocompatible stent coatings. A number of novel stent coatings are currently under investigation. Additionally, covered stents (metallic stents covered by a distensible microporous PTFE membrane) are of unquestioned clinical utility in treating life-threatening perforations (see Chapter 4). They are also used for excluding giant aneurysms, pseudoaneurysms, or clinically significant fistulae.

**Balloon-Expandable Versus Self-Expanding Stents**

Balloon-expandable stents are mounted onto a delivery balloon and delivered into the coronary artery in their collapsed state. Once the stent is in the desired location, inflation of the delivery balloon expands the stent and embeds it into the arterial wall, following which the stent delivery system is removed. Balloon-expandable stents are typically chosen to be 1 to 1.1 times the reference arterial diameter, with a length several millimeters longer than the lesion. Almost all stents implanted in human coronary arteries are balloon expandable.

Self-expanding stents incorporate either specific geometric designs or nitinol shape-retaining metal to achieve a preset diameter. The stent is mounted onto the delivery system in its collapsed state and constrained by a restraining membrane or sheath. Retraction of the membrane allows the stent to resume its unconstrained (expanded) geometry. Self-expanding stents are typically selected to have an unconstrained diameter 0.5 to 1.0 mm greater than the adjacent reference segment to ensure contact with the vessel wall and adequate expansile force to resist vessel recoil. Still, final optimization of stent expansion usually requires additional dilatation within the stent using a high-pressure, noncompliant angioplasty balloon. While self-expanding stents are flexible and often easier to deliver compared to their balloon-expandable counterparts, restenosis has remained a concern, limiting their use in coronary arteries. Moreover, difficulties relating to accurate sizing and precise placement of self-expanding stents necessitate a longer operator learning curve and render these devices unsuitable for treating ostial lesions or stenoses adjacent to side branches. Recently, a renewed interest in self-expanding stents with reduced outward expansion force for treatment of patients with acute coronary syndromes or vulnerable plaque has surfaced.

**Comparisons Between Bare-Metal Stents**

Following early demonstrations of superiority of the originally introduced bare-metal stents (BMS) over balloon angioplasty, a series of stent versus stent trials ensued, either initiated by the industry for regulatory purposes or by independent investigators to assess stent performance in more complex patients and lesions. The present applicability of these early trials is limited, as virtually all of the stents studied in these trials are no longer in clinical use. Once receiving FDA approval, newer, more advanced stent designs typically replaced earlier-generation stents in the marketplace because of enhanced deliverability and/or radiopacity, rather than because of any perception of improved acute or late outcomes. Several investigator-initiated studies did nevertheless demonstrate the superiority of thinner-strutted stent platforms over thicker-strut stents, not just in terms of deliverability, but also with respect to restenosis. However, particularly following the introduction of DES, the anti-restenotic effects of which in general dwarf design-specific differences in BMS (see below), the majority of studies with present BMS platforms have been either comparative DES versus BMS studies or nonrandomized approval registries of iterative BMS technologies.

**INDICATIONS FOR CORONARY STENTING**

Stents may be used either on a routine (planned) basis or after failed balloon angioplasty for acute or threatened vessel closure (“bail-out” stenting). One of the major benefits of stenting is the ability to reverse abrupt closure due to dissection and recoil, thus eliminating the need for high-risk emergency bypass surgery. These data, coupled with the fact that routine stent implantation compared to balloon angioplasty provides superior acute results and greater event-free survival in almost every patient and lesion subtype studied to date has for the most part relegated balloon dilation to the rare lesion that is too small (<2.0 mm) for stenting, or to which a stent cannot be delivered because of excessive vessel tortuosity or calcification, or in patients in whom thienopyridines are contraindicated.

The utility of routine stent implantation as a modality to reduce acute vessel closure and late restenosis was first demonstrated in the STRESS and BENESTENT-I trials, which enrolled patients undergoing PCI of discrete, focal lesions. As a result, the types of lesions treated in these trials (discrete de novo lesions coverable by one stent, with reference vessel diameter [RVD] 3.0 to 4.0 mm) became known as “Stress/ Benestent” lesions, to differentiate them from more complex stenoses. Despite initial concerns regarding potentially diminished efficacy of coronary stents (which were more costly than balloon angioplasty alone) with more generalized use of these devices, abundant randomized and nonrandomized data now exist comparing stenting to balloon angioplasty across a range of patient and lesion subsets, and they almost universally demonstrate an advantage to coronary stenting over conventional balloon angioplasty or other approaches using procedures such as atherectomy. As a result, stents are used in the vast majority of PCI procedures.
performed today, and balloon angioplasty alone is reserved for cases where stents cannot be delivered, where stents are too big for the target lesion, or for rare niche indications (e.g. ostial side branch disease at a bifurcation, some cases of in-stent restenosis, or cases where patients cannot tolerate the antiplatelet regimens required after stent implantation).

**DRUG-ELUTING STENT OVERVIEW**

**Limitations of Bare-Metal Stents**

Stent implantation has been the prevailing treatment for most patients with coronary artery disease since the late 1990s as a result of the more predictable acute and late angiographic results of stenting compared with conventional balloon angioplasty and other adjunctive technologies such as atherectomy. With improvements in stent deliverability and reductions in stent thrombosis through modifications of technique and adjunctive pharmacotherapy, the primary limitation of BMS as the default adjunctive therapy to balloon angioplasty for patients undergoing coronary revascularization by PCI was in-stent restenosis. While coronary stents increase acute luminal diameters to a greater extent than balloon angioplasty (leading to greater acute luminal gain), the vascular injury caused by stent implantation elicits an exaggerated degree of neointimal hyperplasia, resulting in greater decreases in luminal diameter (late lumen loss) compared to balloon angioplasty alone.6 While these two factors can offset each other, the mean incremental gain in luminal dimensions with stenting compared with balloon angioplasty alone is greater than the mean incremental increase in late loss, resulting in a larger net gain in minimal luminal dimensions over the follow-up period. This observation was formulated as the “bigger is better” concept by Kuntz and colleagues, who demonstrated an association between better acute results following stent placement with a lower rate of subsequent restenosis—a finding that was replicated independent of the stent device selected.34,35 Nonetheless, despite attempts to maximize acute gain through an upfront “bigger is better” stent optimization strategy, rates of clinical restenosis following BMS implantation approached 20% to 40% within 6 to 12 months, with even higher rates observed among the highest-risk patient and lesion subsets. As such, coronary restenosis became known as the “Achilles’ heel” of coronary stenting, with significant resources devoted to the study of its prevention and treatment.

DES, which maintain the mechanical advantages of BMS while delivering an antirestenotic pharmacologic therapy locally to the arterial wall, have been shown to effectively and safely reduce the amount of in-stent tissue that accumulates after stent implantation, resulting in significantly reduced rates of clinical and angiographic restenosis. In numerous randomized trials, the reduction in neointimal hyperplasia that occurs with DES compared to that with BMS has been shown to result in a marked reduction in binary angiographic restenosis and target lesion revascularization (TLR).36-38 The initial results of the pivotal randomized trials that led to device approval have been replicated and validated in numerous subsequent trials and real-world registries across the spectrum of disease and lesion subtypes.39,40 As a result, DES are currently implanted in the majority of the >2 million patients undergoing PCI each year.

**Components of Drug-Eluting Stents**

The three critical components of a DES that must be optimized to ensure its safety and efficacy are (1) the stent itself (including its delivery system); (2) the pharmacologic agent being delivered; and (3) the drug carrier, which controls the drug dose and pharmacokinetic release rate (Figure 31.4).

**Stent Design**

The stent component of DES has typically consisted of a predicate BMS without specific modifications. Indeed, first-generation DES designs often appropriated “off-the-shelf” stent designs in order to expedite device development and regulatory approval. Subsequent DES have incorporated newer, more flexible designs, with resultant improvements in device delivery and performance.41,42 Ideally, stent geometry should be optimized for homogeneous drug distribution (which involves considerations of closed versus open cell designs, interstrut distances, etc.). Consistent circumferential stent-to-vessel wall contact should be ensured to ensure drug delivery. As a result, the stent should be conformable to angulated segments, while at the same time minimize geometric distortion. The stent should also have sufficient radiopacity to facilitate precise lesion coverage (while avoiding excessive stent overlap or interstent gaps). Side branch access should be maintained, and the stent should be low profile, flexible, and deliverable to reach and treat complex anatomies. Additionally, newer dedicated DES designs have included modifications aimed at either optimizing local drug delivery while reducing total drug dose (e.g. abluminal wells engineered into the stent struts), or modifying the stent surface to facilitate direct drug delivery and/or arterial healing following implantation (without a drug carrier vehicle per se).

![Figure 31.4](image-url) Components of drug-eluting stents.
Pharmacology

Following promising cell culture and in vitro development, the antirestenotic properties of a wide range of pharmacologic agents have been tested in humans (Figure 31.5). The two most clinically effective classes of agents have been the “rapamycin-analogue” (or “-limus”) family of drugs and paclitaxel. The principal mechanism of action of rapamycin (also known as sirolimus), and its analogues (including zotarolimus, everolimus, biolimus A9, novalimus, and amphilimus) is inhibition of the mammalian target of rapamycin (mTOR), which prevents cell cycle progression from the G1 to S phase. Two other rapamycin analogues that have been used on DES platforms—tacrolimus and pimecrolimus—have a different mechanism of action, binding directly to FK-binding protein (FKBP)-506 and thereby inhibiting the calcineurin receptor with downregulation of cytokines and inhibition of smooth muscle cell activity; unlike the mTOR inhibitors, these agents have not been demonstrated to be beneficial. The other agent that has been used effectively in coronary DES (and more widely now in drug-eluting balloons and in peripheral DES applications) is paclitaxel. By interfering with microtubule function, paclitaxel has multifunctional antiproliferative and antiinflammatory properties, prevents smooth muscle migration, blocks cytokine and growth factor release and activity, interferes with secretory processes, is antiangiogenic, and impacts signal transduction. At low doses (similar to those in DES), paclitaxel affects the G0-G1 and G1-S phases (G1 arrest) resulting in cytotasis without cell death.

Polymers and Drug Delivery Systems

Early DES programs were plagued by the inability to predictably deliver a specific dose of active drug over the right time frame to the arterial wall. In order to more effectively regulate the dosing of antirestenotic agents, a drug carrier vehicle became necessary. In many respects, formulating and optimizing the drug carrier vehicle have proven even more complex than identification of the drug itself. Properties that must be considered for a controlled release vehicle include its biocompatibility, solubility, diffusivity and porosity, molecular size, weight and distribution, elongation, functional requirements, degradation products, durability, relative hydrophobicity, purity, availability, adhesion, crystallinity, sterilization, solvent solubility, biostability, miscibility, bioabsorbable versus permanent nature, evaporation rate, thermal properties, resistance to humidity and temperature extremes, compatibility with specific drugs, approval for implant use, processability (which relates to shelf life), and packaging requirements.

Numerous polymer-based drug delivery systems have since been developed, and are DES-specific (discussed below). While the polymer is instrumental in regulating the pharmacokinetics of drug delivery to the arterial wall (which is necessary for reduced neointimal hyperplasia), the polymer may also elicit deleterious vascular responses. Specifically, histopathologic studies have demonstrated hypersensitivity and eosinophilic inflammatory reactions and delayed endothelialization with first-generation DES that were not previously seen with BMS. Whether these vascular responses in humans are directly related to the polymer or to toxicity from the drug
itself is not well known, but in animal models these effects can be attenuated by modification of the polymer vehicle.\textsuperscript{53} It is believed that inflammation and delayed endothelialization play a role in the development of late stent malapposition, aneurysm formation, stent thrombosis and restenosis.\textsuperscript{50,54,55} For these reasons, there has been great interest in developing inert and biocompatible polymers, bioabsorbable/biodegradable polymers, and even polymer-free DES.

Generations of Drug-Eluting Stents

DES are often classified into several generations of development (Table 31.2). First-generation devices include the two DES that were initially approved for clinical use by most regulatory bodies, each of which utilized an early (currently outdated) BMS stent platform with early durable polymers (not specifically designed for biocompatibility) in order to deliver either sirolimus or paclitaxel. Second-generation devices (currently used in the vast majority of DES procedures) have incorporated more deliverable, thinner-strut stents with polymers that have been designed for biologic compatibility. Most second-generation DES utilize -limus (rapamycin) analogues. Future-generation DES will continue to undergo iteration, with further modifications of the base stent and use of biodegradable/bioabsorbable or polymer-free drug-carrier vehicles.

<table>
<thead>
<tr>
<th>Generation</th>
<th>Drug</th>
<th>Polymer</th>
<th>Stent</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>Sirolimus or Paclitaxel</td>
<td>Not Specifically Designed for Biocompatibility</td>
<td>Early BMS Platforms</td>
</tr>
<tr>
<td>Cypher™</td>
<td>Sirolimus</td>
<td>Biostable mix of poly-n-butyl methacrylate and polyethylene–vinyl acetate</td>
<td>Bx Velocity™</td>
</tr>
<tr>
<td>TAXUS™ Express</td>
<td>Paclitaxel</td>
<td>Styrene-isobutylene-styrene (SIBS)</td>
<td>Express</td>
</tr>
<tr>
<td>TAXUS™ Liberté</td>
<td>Paclitaxel</td>
<td>Styrene-isobutylene-styrene (SIBS)</td>
<td>Liberté\textsuperscript{a}</td>
</tr>
<tr>
<td>ION™ (TAXUS™ ELEMENT)</td>
<td>Paclitaxel</td>
<td>Styrene-isobutylene-styrene (SIBS)</td>
<td>Element (platinum-chromium)\textsuperscript{a}</td>
</tr>
<tr>
<td>Second</td>
<td>Limus Analogues</td>
<td>Biocompatible Polymers</td>
<td>More Flexible, Thinner-Strut BMS</td>
</tr>
<tr>
<td>Endeavor™</td>
<td>Zotarolimus</td>
<td>Phosphorylcholine</td>
<td>Driver (cobalt alloy)</td>
</tr>
<tr>
<td>Xience V™ and Xience PRIME™</td>
<td>Everolimus</td>
<td>Vinylidene fluoride and hexafluoropropylene</td>
<td>Multi-Link Vision and Multi-Link 8 (cobalt-chromium)</td>
</tr>
<tr>
<td>Promus Element™</td>
<td>Everolimus</td>
<td>Vinylidene fluoride and hexafluoropropylene</td>
<td>Element (platinum-chromium)</td>
</tr>
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<td>Zotarolimus</td>
<td>Biolinx polymer</td>
<td>Integrity (cobalt alloy)</td>
</tr>
<tr>
<td>Biomatrix™</td>
<td>Biolimus A9</td>
<td>Abluminal poly-L-lactic acid (bioabsorbable)</td>
<td>Juno (stainless steel)</td>
</tr>
<tr>
<td>Nobori™</td>
<td>Biolimus A9</td>
<td>Abluminal poly-L-lactic acid (bioabsorbable)</td>
<td>S-stent</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Liberté and, in particular, Element BMS platforms are newer BMS platforms but are included in the first-generation due to the presence of the original TAXUS™ polymer.

The Cypher™ Sirolimus-Eluting Stent

The first DES to attain approval for human use was the Cypher™ stent (Cordis, Johnson and Johnson), with initial first-in-human studies as well as subsequent clinical trials.
leading to its approval in Europe in 2002 and in the United States in 2003. Production of this stent was recently halted, but some description of the technology and initial studies that led to device approval is of historical interest, as the introduction of this stent ushered in the DES era of interventional cardiology. Sirolimus (rapamycin) is a highly lipophilic, naturally occurring macrocyclic lactone, which was first isolated from Streptomyces hygroscopicus found in a soil sample from Easter Island (also known as Rapa Nui) and was initially developed as an antifungal agent. Shortly thereafter, it became apparent that this agent also was a potent immunosuppressive, and was initially approved by the FDA (as Rapamune) for prevention of renal transplant rejection in 1999. The primary mechanism of action of inhibition of neointimal hyperplasia in sirolimus is thought to be related to its ability to bind to FKBP-12 in cells; the sirolimus–FKBP-12 complex then binds to and inhibits activation of mTOR, preventing progression in the cell cycle from the late G1 to S phase.43 Sirolimus has been demonstrated to have a marked effect on suppression of neointimal hyperplasia with low toxicity following sirolimus-eluting stent (SES) implantation in initial small and large animal studies.56,57

The stent platform for the Cypher™ SES was the Bx Velocity™ stent, a thick-strutted slotted tube with a closed cell design constructed from 316L stainless steel. The stent was coated with biostable (nonerodible) polymers consisting of poly-n-butyl methacrylate and polyethylene–vinyl acetate that are loaded with 140 \( \mu \)g/cm\(^2\) sirolimus. The slow-release (SR) formulation of the Cypher™ SES employed in clinical practice used a basecoat of blended polymers loaded with sirolimus as well as a topcoat of polymer alone (without sirolimus) that acted as a diffusion barrier, controlling the rate of drug release from the basecoat into the vessel wall. Approximately 80% of the sirolimus loaded on the stent was released within the first month after stent implantation.

In 1999, human experience with the Cypher™ SES was initiated at the Institute Dante Pazzanese of Cardiology in São Paulo, Brazil, and the Thoraxcenter, Rotterdam, The Netherlands, with the first-in-man (FIM) study in 45 patients with symptomatic de novo native coronary lesions <18 mm in length with RVD 3.0 to 3.5 mm. In this study, SES demonstrated marked suppression of neointimal hyperplasia measured by IVUS and quantitative coronary angiography at 4 months, and 1, 2, and 4 years.58 Serial angiography and IVUS have now been performed at 7 years, showing continued vessel patency without further late loss (Figure 31.6). These data led to the conduct of the larger RAVEL trial, in which 238 patients outside the United States with relatively simple de novo coronary lesions were randomized to either the Cypher™ SES or the uncoated Bx Velocity stent.36 The SES essentially eliminated late loss compared with BMS (mean of -0.01 mm versus 0.80 mm, \( P < 0.001 \)), with a corresponding reduction in the rate of angiographic restenosis (0% versus 26%, \( P < 0.001 \)).

On the basis of these data, the larger pivotal SIRIUS trial was conducted in the United States.29 SIRIUS was a 1058-patient randomized trial comparing the Cypher™ SES to the uncoated Bx Velocity in patients with vessel diameters

Figure 31.6 Seven-year follow-up of one of the initial sirolimus-eluting stent implantations from Institute Dante Pazzanese of Cardiology in São Paulo, Brazil, demonstrating sustained patency of the initially stented segment.
yses, treatment with SES has resulted in sustained reductions with a multitude of randomized trials and observational studies in patients with a primary endpoint, the rate of target vessel failure (TVF, a percent volumetric obstruction at 8 months) was reduced in clinical restenosis endpoints with similar rates of death, in 9.7% of Cypher™ SES patients versus 0% of Bx Velocity patients. By IVUS, the in-stent percent volumetric obstruction at 8 months was reduced from 33.4% with the Bx Velocity to 3.1% with the SES (P < 0.001), although late stent malapposition was present in 9.7% of Cypher™ SES patients versus 0% of Bx Velocity patients (P = 0.02).

On the basis of these results, in April 2003 the Cypher™ SES became the first DES approved by the FDA, and this stent became one of the most studied devices in modern history, with a multitude of randomized trials and observational studies assessing its efficacy and safety. In their aggregate, these data demonstrate extremely low levels of in-stent late loss with SES (averaging ~0.15 mm across studies), with an approximate 7% to 8% risk reduction in angiographic restenosis and clinical revascularization of the target lesion (TLR) compared to BMS. Longer-term follow-up with this device extending to 5 years and beyond has confirmed these findings. In these analyses, treatment with SES has resulted in sustained reductions in clinical restenosis endpoints with similar rates of death, MI, and stent thrombosis compared with BMS. In part due to the availability of newer stent platforms and designs, the manufacturer of this stent recently announced that the device would no longer be manufactured and sold, ending the stent’s tenure as the oldest DES in current clinical use.

The Taxus™ Paclitaxel-Eluting Stent

The other first-generation DES that came to market soon after approval of SES was the TAXUS™ paclitaxel-eluting stent (PES). Paclitaxel, a highly lipophilic diterpenoid compound, was first isolated in 1963 from the pacific yew tree (Taxus brevifolia) and developed for its potent antineoplastic properties. Its principal action is to interfere with microtubule dynamics, preventing their depolymerization. This leads to widespread dose-dependent multicellular activity of the drug, including antiproliferative and antiinflammatory properties, reduced smooth muscle migration, blocking of cytokine and growth factor release and activity, interference with secretory processes, antiangiogenic effects, and impaired signal transduction. At low doses (similar to those in DES applications), paclitaxel affects the G0-G1 and G1-S phases (G1 arrest) resulting in cytostasis without cell death (probably via induction of p53/p21 tumor suppression genes). Systemic paclitaxel was shown to inhibit restenosis in a rat carotid injury model at levels more than 100-fold lower than that required for tumor cytotoxicity. Neointimal area was greatly reduced in a rabbit balloon-injury experiment using local paclitaxel administration and stent-based paclitaxel elution from polymer-based systems has been shown to profoundly reduce intimal hyperplasia in rabbit iliac arteries for up to 6 months with dose-dependent efficacy and toxicity.

The TAXUS™ PES (Boston Scientific, Natick, MA) consists of paclitaxel contained within a polyolefin derivative biostable polymer (styrene-isobutylene-styrene, referred to as SIBS (Translute™)), originally coated on the Nir stent and subsequently on the Express open-cell slotted tube stainless steel stent platform (PES(E), the device from which most of the randomized clinical trial data for this stent was derived). The base BMS has further evolved from the Express stent to the newer Liberté stent (PES(L), a more flexible, thinner-strutted open-cell stainless steel slotted tube stent, and finally to a platinum-chromium Element stent. Depending on the relative ratio of paclitaxel to polymer, the stent may be formulated with varying release kinetics. The clinically available formulation of the TAXUS™ PES is the SR formulation, although the moderate-release (MR) formulation has also been tested in moderate-sized clinical trials. The SR stent has relatively more polymer to drug (paclitaxel concentration of 1 μg/mm²), with a coat thickness 18 μm, and approximately 8% in vivo paclitaxel elution in 30 days. The drug is eluted in a rapid burst phase over the initial 48 hours, followed by a slow, sustained release for the next 10 to 30 days, with the remainder sequestered in the bulk of the polymer matrix below the surface without pathways to the external environment (thus permanently retained on the stent).

**Figure 31.7** Primary results of the SIRIUS trial, the pivotal approval trial of the sirolimus-eluting stent, demonstrating superiority of the sirolimus-eluting stent in reducing restenosis-related endpoints. SES, sirolimus-eluting stent; BMS, bare-metal stent; MACE, major adverse cardiac events; TVF, target vessel failure; TLR, target lesion revascularization; MI, myocardial infarction.
The TAXUS clinical program evaluated the clinical safety and efficacy of the TAXUS™ PES in several clinical trials. TAXUS I and II evaluated the performance of the PES on the NIR stent platform in focal de novo disease, whereas TAXUS IV, V, and VI investigated the PES(E) stent in more complex lesions. All studies have used the SR formulation, except for one arm of the TAXUS II trial and TAXUS VI. Collectively, these trials demonstrate a marked decrease of binary restenosis with PES compared to BMS, with an approximate 60% to 75% reduction in the need for TLR, an effect that has been consistent across a range of patient and lesion subtypes. The study that ultimately led to device approval in the United States in 2004 was the TAXUS IV trial, which enrolled 1,314 patients with single de novo lesions with visually estimated lengths of 10 to 28 mm in native coronary arteries with an RVD of 2.5 to 3.75 mm. Patients were assigned to either a PES(E) stent or Express BMS control. The primary endpoint of TVR assessed at 9 months was reduced with the PES(E) from 12.0% to 4.7% (P < 0.001) (Figure 31.8). Follow-up angiography at 9 months demonstrated marked reductions in mean in-stent late loss (0.39 versus 0.92 mm, P < 0.001), and the rate of binary in-segment restenosis (7.9% versus 26.6%, P < 0.001). By IVUS, the in-stent percent volumetric obstruction at 8 months was reduced from 29.4% with the BMS to 12.2% with PES(E) (P < 0.001), and late stent malapposition at 9 months was present in 1.1% of PES(E) patients versus 2.2% of BMS patients (P = 0.62).

The PES(E) has been studied in numerous randomized trials and observational analyses, across a range of patient indications and lesion subsets. These studies have demonstrated consistent reductions in measures of neointimal hyperplasia and resultant reductions in clinical restenosis endpoints compared with BMS. Longer-term follow-up with this device has extended to 5 years and beyond, confirming the sustained efficacy of this stent. In these analyses, treatment with PES has resulted in sustained reductions in clinical restenosis endpoints, with similar rates of death, MI, and stent thrombosis with PES and BMS. Additionally, a series of comparisons between the first two approved devices (SES and PES) was reported in order to determine whether superiority could be established for a particular DES. In summary, the totality of evidence appears to indicate similar performance of SES and PES in routine de novo coronary artery lesions, despite a lower amount of neointimal hyperplasia with SES as assessed by IVUS and angiography. Given the greater degree of late loss suppression with the SES, it was hypothesized that in the highest restenotic risk patients and lesions, this stent would hold an advantage over PES. Without a large-scale adequately powered randomized trial, however, these potential benefits remain unproven.

The commercially available PES has undergone several iterations, but is still generally considered a “first-generation” DES due to its use of an original polymer to elute paclitaxel. The PES(L) stent (using the same drug and polymer formulation as the PES(E), but with an improved stent platform) was approved for clinical use based upon the TAXUS ATLAS program, in which nonrandomized data from several PES(L) single-arm studies were compared to the treatment arms from prior TAXUS trials with the PES(E). More recently, the PES(L) has been replaced by the TAXUS™ Element stent (again, using the same drug and polymer formulation as the original TAXUS™ Express SR, but with an iterated stent platform using a platinum chromium alloy). The TAXUS™ Element stent (or ION stent) is the current commercially available version of PES in the United States. Approval of this stent required completion of the PERSEUS trial, which evaluated 1,262 patients with de novo “workhorse” atherosclerotic coronary lesions allocated in a 3:1 randomization to TAXUS™ Element versus PES(E). The TAXUS™ Element was demonstrated to be noninferior to PES(E) with respect to the primary endpoint of 12-month target lesion failure (TLF: 5.6% versus 6.1%, respectively) as well as the secondary endpoint of percentage diameter stenosis at 9-month angiographic follow-up (3.1% versus 3.1%, respectively). No differences in clinical outcomes were observed between the two randomized groups in this trial. The TAXUS™ Element stent has additionally been evaluated in smaller vessels in a prospective, single-arm trial comparing 224 patients treated with this stent with 125 lesion-matched historical Express BMS control subjects from the TAXUS V trial. In this analysis, the TAXUS™ Element was superior to the Express BMS with respect to late lumen loss (0.38 mm versus 0.80 mm, P < 0.001), and TLF (7.3% versus 19.5%, P < 0.001).

Figure 31.8
Primary results of the TAXUS-IV trial, the pivotal approval trial of the paclitaxel-eluting stent, demonstrating superiority of the paclitaxel-eluting stent in reducing restenosis-related endpoints. PES, paclitaxel-eluting stent; BMS, bare-metal stent; MACE, major adverse cardiac events; TVF, target vessel failure; TLR, target lesion revascularization; MI, myocardial infarction.
SECOND-GENERATION DRUG-ELUTING STENTS

Despite the demonstrated efficacy of first-generation SES and PES as observed in the initial and subsequent randomized trials of these devices, late reactions to first-generation DES polymers as well as delayed endothelialization and adverse vessel responses were described, potentially resulting in the most devastating complication of stent placement, namely late stent thrombosis. In order to mitigate some of the abnormal vessel responses associated with first-generation DES, several new devices have been introduced, with specific modifications implemented upon first-generation technology. These so-called second-generation DES (currently used in the majority of PCI) have incorporated more deliverable, thinner-strut stents with polymers that have been specifically designed for biologic compatibility. Discussed below are clinical data relating to the most-studied second-generation devices, namely, everolimus-eluting stents (EES; Xience V/Promus and everolimus-eluting platinum chromium stent (Promus Element)); zotarolimus-eluting stents (ZES; Endeavor and Resolute); and biolimus A9-eluting stents (BES; Biomatrix).

Everolimus-Eluting Stents (Xience V™/Promus™)

In the EES (manufactured by Abbott Vascular (Santa Clara, CA) and distributed as the Xience V and now Xience PRIME stents, and also originally distributed by Boston Scientific as the Promus stent), everolimus (100 μg/cm²) is released from a thin (7.8 μm), nonadhesive, durable, biocompatible, fluorocopolymer consisting of vinylidene fluoride and hexafluoropropylene monomers, coated onto a low-profile (81 μm strut thickness), flexible, cobalt chromium stent. (The original Xience V base stent platform has been updated in the Xience PRIME stent to the Multi-link 8 BMS platform, a more deliverable version of the Vision platform). The release kinetics of EES are similar to that seen with sirolimus from the SES (~80% of the drug released at 30 days, with none detectable after 120 days). The polymer is elastomeric, and experiences minimal bonding, webbing, or tearing upon expansion. Fluoropolymers have additionally been shown to resist platelet and thrombus deposition in blood-contact applications. The EES polymer has also been demonstrated to be noninflammatory in porcine experiments. Preclinical studies have demonstrated more rapid coverage of the stent struts with functional endothelialization with EES compared to SES, PES, or ZES.

In the small SPIRIT First trial, the EES was shown to markedly reduce the extent of angiographic late loss at 6 and 12 months compared to the otherwise identical cobalt chromium Vision BMS. Subsequently, the EES has been studied in multiple randomized trials comparing this device to PES (the predominant comparator), SES, ZES, and BMS (Table 31.3). The large SPIRIT IV trial, enrolling 3,687 patients with stable coronary artery disease undergoing PCI of up to three lesions in three vessels, was a pivotal FDA approval study of the EES, randomizing patients to EES versus PES(E). While this study had broader inclusion criteria than first-generation DES approval studies, patients with unstable acute coronary syndromes, MI, thrombus, chronic occlusions, vein graft lesions, and true bifurcation lesions were excluded. The primary endpoint of TLF (a composite of cardiac death, target-vessel MI, or ischemia-driven TLR) was significantly lower at 1 year with EES compared to PES (3.9% versus 6.6%, P = 0.0008). Rates of stent thrombosis (0.3% versus 1.1%, P = 0.003), MI (1.9% versus 3.1%, P = 0.02), and TLR (2.3% versus 4.5%, P = 0.0008) were also lower with EES compared to PES. Longer-term follow-up of SPIRIT IV to 3 years has demonstrated sustained reductions in TLF, MI, and stent thrombosis with EES over PES (0.8% versus 1.9%), but narrowing of the initially observed difference in TLR with each stent (6.2% versus 7.8%, P = 0.06). However, both all-cause mortality (3.2% versus 5.1%, P = 0.02) and death or MI (5.9% versus 9.1%, P = 0.001) were reduced with EES compared to PES. These data from SPIRIT IV parallel results from the unrestricted “all-comer” COMPARE trial, in which 1,800 patients were randomized to EES versus PES(L). The primary endpoint of MACCE at 1 year (death, MI, or TVR) was lower with EES compared to PES (6.2% versus 9.1%, P = 0.02), driven by reductions in stent thrombosis (0.7% versus 2.6%, P = 0.002), MI (2.8% versus 5.4%, P = 0.007), and TLR (1.7% versus 4.8%, P = 0.0002). Notably, between 1 and 3 years in this high-risk study cohort (in which only ~15% of patients were maintained on dual antiplatelet therapy), fewer stent thrombosis, MI, and TLR events occurred with EES compared to PES.

In contrast to the marked differences observed between EES and PES, smaller differences have been observed between EES and SES in several randomized trials. In the SORT OUT IV trial, 2,774 unselected patients were randomized to EES versus SES and followed through the Danish Civil Registration System. Similar 9-month outcomes were observed between EES- and SES-treated patients although definite stent thrombosis occurred in fewer EES- than SES-treated patients at both 9 and 18 months (18 months: 0.2% versus 0.9%). In the 2,314-patient BASKET-PROVE multicenter trial comparing EES, SES, and BMS (the otherwise identical cobalt chromium Vision BMS) in large coronary arteries requiring >3.0 mm stents, EES, SES, and BMS were associated with similar rates of cardiac death or nonfatal MI at 2 years and the rate of TVR was similar between EES and SES. However, the rate of TVR was significantly lower with both EES and SES compared to BMS (3.1% for EES, 3.7% for SES, 8.9% for BMS), even in larger arteries with low rates of restenosis. The majority of comparative trials between EES and SES have demonstrated largely similar angiographic outcomes with EES and SES except for the ESSENCE-DIABETES trial, in which EES was associated with lower rates of angiographic late loss and binary restenosis in diabetic patients at 8 months compared
**Table 31.3** Randomized Controlled Trials of Everolimus-Eluting Stents

<table>
<thead>
<tr>
<th>Trial Acronym and Reference</th>
<th>Study Cohort</th>
<th>EES Versus</th>
<th>Number Randomized (Planned Angiographic Follow-Up)</th>
<th>Latest Follow-Up to Date</th>
<th>Principal Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPIRIT First(^78,90)</td>
<td>Noncomplex CAD</td>
<td>BMS</td>
<td>60 (all)</td>
<td>5 y</td>
<td>EES versus BMS resulted in markedly reduced late loss and neointimal volume obstruction.</td>
</tr>
<tr>
<td>SPIRIT II(^82)</td>
<td>Noncomplex CAD; up to 2 lesions</td>
<td>PES(E)</td>
<td>300 (all)</td>
<td>5 y</td>
<td>EES versus PES(E) resulted in lower 6-month angiographic in-stent late loss (0.11 ± 0.27 mm versus 0.36 ± 0.39 mm, (P &lt; 0.0001)).</td>
</tr>
<tr>
<td>SPIRIT III(^93,91)</td>
<td>Noncomplex CAD; up to 2 lesions</td>
<td>PES(E)</td>
<td>1,002 (564)</td>
<td>5 y</td>
<td>EES versus PES(E) resulted in lower 8-month angiographic in-segment late loss (0.14 ± 0.41 mm versus 0.28 ± 0.48 mm, (P = 0.004)), noninferior 9-mo rates of TVF (72% versus 9.0%, (P = 0.31)), and reduced rates of MACE at 1 y (5.9% versus 9.9%, (P = 0.02)) and 5 y (13.7% versus 20.2%, (P = 0.007)).</td>
</tr>
<tr>
<td>SPIRIT IV(^42,85)</td>
<td>Noncomplex CAD; up to 3 lesions</td>
<td>PES(E)</td>
<td>3,687 (none)</td>
<td>3 y</td>
<td>EES versus PES(E) resulted in lower 1-y rates of TLF (3.9% versus 6.6%, (P = 0.0008)) and ischemia-driven TLR (2.3% versus 4.5%, (P = 0.0008)), with similar rates of cardiac death or target-vessel MI (2.2% versus 3.2%, (P = 0.09)). EES also resulted in lower rates of MI and stent thrombosis. At 3 y, these results were maintained although the difference in TLR was no longer significant (6.2% versus 7.8%, (P = 0.06)). 3 y mortality and death or MI were reduced with EES compared to PES (text).</td>
</tr>
<tr>
<td>COMPARE(^80,92)</td>
<td>All-comers</td>
<td>PES(L)</td>
<td>1,800 (none)</td>
<td>3 y</td>
<td>EES versus PES(L) resulted in lower 1-y rates of the primary composite endpoint death, MI or TVR (6.2% versus 9.1%, (P = 0.02)). EES also resulted in lower rates of MI, stent thrombosis, and TLR (text). Between 1 and 3 y, EES resulted in less stent thrombosis, MI, and TLR events.</td>
</tr>
<tr>
<td>SPIRIT V Diabetes(^79)</td>
<td>Diabetes</td>
<td>PES(L)</td>
<td>324 (all)</td>
<td>1 y</td>
<td>EES versus PES(L) resulted in lower 9-mo rates of angiographic in-stent late loss (0.19 ± 0.37 mm versus 0.39 ± 0.49 mm, (P = 0.0001)).</td>
</tr>
<tr>
<td>Trial Acronym and Reference</td>
<td>Study Cohort</td>
<td>EES Versus</td>
<td>Number Randomized (Planned Angiographic Follow-Up)</td>
<td>Latest Follow-Up to Date</td>
<td>Principal Findings</td>
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<tr>
<td>BASKET-PROVE\textsuperscript{93}</td>
<td>Large coronary arteries (≥ 3.0 mm stents)</td>
<td>SES, BMS</td>
<td>2,314 (none)</td>
<td>2 y</td>
<td>EES and SES resulted in lower rates of TVR compared to BMS (3.1% and 3.7% respectively versus 8.9%). There were no differences between the three stent types in the rates of death, MI, or stent thrombosis at 2 y.</td>
</tr>
<tr>
<td>EXECUTIVE\textsuperscript{81}</td>
<td>MVD, otherwise noncomplex CAD</td>
<td>PES(L)</td>
<td>200 (all)</td>
<td>9 mo</td>
<td>EES versus PES(L) resulted in lower 9-mo angiographic in-stent late loss (0.11 ± 0.27 mm versus 0.36 ± 0.39 mm, ( P = 0.008 )).</td>
</tr>
<tr>
<td>ISAR-TEST-4\textsuperscript{95,94}</td>
<td>Simple and complex CAD</td>
<td>SES</td>
<td>1,304 (all)</td>
<td>3 y</td>
<td>EES versus SES resulted in nonsignificantly different rates of in-segment late loss at 24 mo (0.29 ± 0.51 mm versus 0.31 ± 0.58 mm, ( P = 0.59 )). At 3 y, the rates of clinical outcomes were similar between EES and SES (for TLR: 12.8% versus 15.5%, ( P = 0.15 )).</td>
</tr>
<tr>
<td>SORT OUT IV\textsuperscript{87}</td>
<td>Unselected patients</td>
<td>SES</td>
<td>2,774 (none)</td>
<td>18 mo</td>
<td>EES versus SES resulted in similar rates of the composite endpoint of death, MI, stent thrombosis, or clinically driven TVR at 9 and 18 mo (7.2% versus 7.6%, ( P = 0.64 )). Definite stent thrombosis at 18 mo was lower with EES (0.2% versus 0.9%, ( P = 0.03 )).</td>
</tr>
<tr>
<td>EXAMINATION\textsuperscript{95}</td>
<td>STEMI</td>
<td>BMS</td>
<td>1,504 (none)</td>
<td>1 y</td>
<td>EES versus BMS resulted in similar rates of composite death, MI, or revascularization, but lower rates of TLR (2.2% versus 5.1%, ( P = 0.003 )). Definite/probable stent thrombosis at 1 y was lower in EES patients (0.9% versus 2.6%; ( P = 0.01 )).</td>
</tr>
<tr>
<td>EXCELLENT\textsuperscript{89}</td>
<td>Noncomplex CAD</td>
<td>SES</td>
<td>1,443 (all)</td>
<td>9 mo</td>
<td>EES versus SES resulted in similar in-segment late loss at 9 mo (0.10 mm versus 0.05 mm, ( P ) for noninferiority = 0.02). Low rates of MACE were seen in both groups.</td>
</tr>
<tr>
<td>Trial Acronym and Reference</td>
<td>Study Cohort</td>
<td>EES Versus</td>
<td>Number Randomized (Planned Angiographic Follow-Up)</td>
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<tr>
<td>LONG-DES-III(^{86})</td>
<td>Long (≥25 mm) native coronary lesions</td>
<td>SES</td>
<td>450 (all)</td>
<td>9 mo</td>
<td>EES versus SES resulted in higher in-segment late loss (0.17 mm versus 0.09 mm, (P = 0.046)), but similar in-stent late loss and in-stent binary restenosis as well as other clinical endpoints at 9 mo.</td>
</tr>
<tr>
<td>ESSENCE-DIABETES(^{88})</td>
<td>Diabetes</td>
<td>SES</td>
<td>300 (all)</td>
<td>1 y</td>
<td>EES versus SES resulted in lower 8-mo angiographic in-segment late loss (mean 0.23 mm versus 0.37 mm, (P = 0.02)) and lower binary restenosis (0.9% versus 6.5%, (P = 0.04)). There were no differences in clinical outcomes between the two stents.</td>
</tr>
<tr>
<td>RESOLUTE All-Comers(^{84,97})</td>
<td>Unselected patients</td>
<td>ZES(R)</td>
<td>2,292 (460)</td>
<td>2 y</td>
<td>EES versus ZES(R) resulted in comparable 1-y rates of TLF (8.3% versus 8.2%, (P = 0.92)) and TLR (3.4% versus 3.9%, (P = 0.50)), although less definite stent thrombosis (0.3% versus 1.2%, (P = 0.01)) and definite/probable stent thrombosis (0.7% versus 1.6%, (P = 0.05)) were noted at 1 y. At 2 y, similar rates of clinical endpoints were observed, with a trend toward less definite/probable stent thrombosis (1.0% versus 1.9%, (P = 0.077)).</td>
</tr>
<tr>
<td>TWENTE(^{88})</td>
<td>Unselected patients</td>
<td>ZES(R)</td>
<td>1,391 (none)</td>
<td>1 y</td>
<td>EES versus ZES(R) resulted in similar rates of TVR (8.1% versus 8.2%, (P = 0.94)) and other clinical endpoints including stent thrombosis at 1 year.</td>
</tr>
<tr>
<td>PLATINUM(^{99})</td>
<td>1 or 2 de novo native lesions</td>
<td>Pt-Cr EES</td>
<td>1,530 (none)</td>
<td>1 y</td>
<td>EES versus Pt-Cr EES resulted in similar rates of TLF (2.9% versus 3.4%, (P = 0.60)) as well as other clinical endpoints at 1 y.</td>
</tr>
</tbody>
</table>

EES, everolimus-eluting stents (Xience V/Promus); BMS, bare-metal stents; PES(E), paclitaxel-eluting stents (Taxus Express platform); PES(L), paclitaxel-eluting stents (Taxus Liberté platform); ZES(R), zotarolimus-eluting stents (Resolute platform); Pt-Cr EES, platinum chromium EES; CAD, coronary artery disease; MVD, multivessel disease; MI, myocardial infarction; TLR, target lesion revascularization; TVR, target vessel revascularization; TLF, target lesion failure (cardiac death, target-vessel MI, or TLR); TVF, target vessel failure (cardiac death, MI, or TVR); MACE, major adverse cardiac events (cardiac death, MI, or TLR).
to SES. Excepting this trial’s results, whether clinically apparent efficacy differences between EES and SES are manifest in the highest-risk patient and lesion subsets remains unknown.

One intriguing attribute of EES that has emerged is the low rate of stent thrombosis observed with this stent. First demonstrated in SPIRIT IV and COMPARE, these findings have also been validated in several other studies, summarized in a metaanalysis of 13 randomized EES trials (N = 17,101) that demonstrated lower rates of ST with EES compared to non-EES DES. These data, combined with further observational validation of these findings, support the use of the second-generation EES over previously existing first-generation DES with respect to a safety advantage (in addition to efficacy). Further, whether EES can achieve lower or noninferior overall rates of stent thrombosis compared to BMS is an area of active interest, piqued by both preclinical data as well as studies such as the randomized EXAMINATION trial of 1,504 patients with ST-segment elevation myocardial infarction (STEMI), in which the rate of definite/probable stent thrombosis at 1 year was significantly lower in EES-treated patients compared to those treated with BMS (0.9% versus 2.6%; \( P = 0.01 \)). Similarly, in a large network metaanalysis of head-to-head DES trials (49 trials, \( N = 50,844 \)), the use of EES was associated with statistically significant reductions in 1- and 2-year stent thrombosis compared to other DES, as well as BMS. Whether EES can definitely reduce stent thrombosis compared to BMS is being actively tested in the randomized controlled HORIZONS-II trial.

Another iteration of EES has involved the use of everolimus eluted by the same stable fluoropolymer as in the original EES, but on a platinum chromium stent platform (Promus Element, Boston Scientific, Natick, MA). This stent was evaluated in the randomized PLATINUM trial, which randomized 1,530 patients undergoing PCI of one or two de novo native lesions to treatment with the standard EES versus the Promus Element stent. The rates of efficacy and safety outcomes were very similar with both stents in this trial, which ultimately led to FDA approval of this EES platform.

In summary, in a broad cross-section of patients undergoing PCI, EES have shown significant improvements in safety and efficacy outcomes over first-generation DES. The finding of lower rates of stent thrombosis with EES, particularly compared to predecessor DES systems and in some cases even compared to BMS is notable, and suggests that this stent may have set a new standard for DES safety, if these findings can be further validated in larger adequately powered clinical trials.

**Zotarolimus-Eluting Stents**

**Endeavor**

Although studied contemporaneously with first-generation SES and PES, the zotarolimus-eluting Endeavor stent (ZES(E), Medtronic, Santa Rosa, CA) was originally conceived as a “second-generation DES,” rapidly eluting zotarolimus (10 μg per 1 mm stent length) from a thin layer (5.3 μm) of the biocompatible polymer phosphorylcholine from a flexible, low-profile (91 μm strut thickness) cobalt chromium stent. Phosphorylcholine is a naturally occurring phospholipid found in the membrane of red blood cells, and is resistant to platelet adhesion. The potencies of zotarolimus, everolimus, and sirolimus are roughly comparable, and zotarolimus is somewhat more lipophilic. However, the release rate of zotarolimus from Endeavor (~90% within 7 days, 100% within 30 days) is significantly faster than everolimus and sirolimus are released from EES and SES stents respectively.

In the Endeavor I FIM study, ZES(E) was demonstrated to have a low rate of TLR (1%), despite a mean in-stent late lumen loss of 0.61 mm at 12 months. The ZES(E) was subsequently compared to its base BMS in the ENDEAVOR II randomized trial, conducted in 1,197 patients with noncomplex lesions. In this trial, ZES(E) was associated with lower rates of TVF and TLR at 9 months compared to BMS; these results were sustained at follow-up up to 5 years. Once again, 9-month angiographic in-stent late loss (at 0.61 mm) in this trial was greater than previously seen with either SES or PES, but compared to BMS, in-segment binary restenosis was reduced from 35.0% to 13.2% \( (P < 0.0001) \).

A series of head-to-head DES studies in the ENDEAVOR clinical trial program was launched with a 436-patient angiographic trial, ENDEAVOR III, which was designed to demonstrate noninferiority of ZES(E) to the Cypher SES. In this trial, the amounts of late loss and rate of restenosis at angiographic follow-up were significantly greater with ZES(E) compared to SES. Despite these findings, the overall rates of clinical restenosis endpoints were not dissimilar between treatment arms in this trial, and as such, the larger ENDEAVOR IV trial (\( N = 1,548 \)) was conducted with a primary clinical endpoint (rather than an angiographic one). In this trial, which randomized patients with noncomplex coronary lesions to treatment with ZES(E) versus PES, despite greater late loss and angiographic restenosis with ZES(E) compared to PES, ZES(E) had noninferior 9-month rates of TVF and comparable 12-month rates of TLR. Rates of TLR were lowest and in fact indistinguishable between both stents particularly among patients who were assigned to receive clinical follow-up alone (rather than routine angiographic follow-up) (Figure 31.9), emphasizing a somewhat “artificial” clinical trial phenomenon previously described as the “oculostenotic reflex.” The ENDEAVOR IV findings ultimately led to device approval of ZES(E) in the United States. The 5-year follow-up of this trial has been recently presented, demonstrating comparable rates of TLR for ZES(E) compared with PES (7.7% versus 8.6%; \( P = 0.70 \)). More notably, the ZES(E) demonstrated a superior late safety profile with lower very late stent thrombosis (0.4% versus 1.8%; \( P = 0.012 \)) and a lower overall incidence of cardiac death or MI (6.4% versus 9.1%; \( P = 0.048 \)) compared to PES at 5 years.

Several trials have compared ZES(E) to other DES in unrestricted patient populations. In the SORT OUT III trial, a trial notable for a design that employed follow-up through a nationwide clinical registry in Denmark, 2,333 patients
(nearly 50% of whom presented with acute coronary syndromes) were randomized to ZES(E) versus SES. In this trial, treatment with ZES(E) was associated with higher rates of 9-month major adverse cardiac events (MACE: cardiac death, MI, or TVR: 6% versus 3%, \( p = 0.0002 \)), as well as endpoints of MI, stent thrombosis, and TLR, differences which persisted at 18 months (with the exception of stent thrombosis). The ISAR-TEST-2 trial was a three-way 1:1:1 randomized trial in 1,007 patients of an investigational combination sirolimus/probulcol-eluting stent versus ZES(E) versus SES.111,112 Compared to SES, ZES(E) resulted in higher rates of late loss, angiographic restenosis (the primary endpoint), and TLR at 6 to 8 months, with similar rates of death, MI, and stent thrombosis. A larger study, the ZEST trial, randomized 2,645 patients with simple and complex coronary artery disease to ZES(E), SES, or PES.113,114 In this trial, while SES demonstrated the lowest degree of late loss and binary restenosis, ZES(E) was intermediate between SES and PES with respect to rates of MACE, TVR, and TLR. There were no significant differences in the 2-year rates of death, MI, or stent thrombosis between the two stents.

Overall, both the pivotal approval trials within the ENDEAVOR clinical program as well as the investigator-initiated clinical trials of ZES(E) demonstrate lesser neointimal suppression with this stent compared to either SES or PES, resulting in lesser performance of this stent with respect to angiographically measured trial endpoints. However, ZES(E) is clearly superior in efficacy to BMS, and likely comparable to other stent platforms in reducing clinical restenosis in less complex lesions, particularly in the absence of routine angiographic follow-up. The findings of very low rates of late adverse safety events including very late stent thrombosis as well as cardiac death or MI115 with ZES(E) is a notable positive attribute of this stent, particularly in light of the potential ongoing thrombotic risks of SES and PES.116 In this regard the large, randomized PROTECT trial has completed enrollment of 8,800 patients to ZES(E) versus SES, and is the first clinical DES study powered to demonstrate a difference in stent thrombosis between two stent platforms (with ascertainment of the primary endpoint at 3 years).

### Resolute

The Resolute stent (Medtronic Inc.) is similar to the Endeavor stent in that zotarolimus is eluted from the thin-strut cobalt-alloy BMS platform (in this case, the updated and more deliverable Integrity cobalt-alloy BMS). However, instead of the phosphorycholine coating of the Endeavor stent, the Resolute stent employs the BioLinx tripolymer coating, consisting of a hydrophilic endoluminal component and a hydrophobic component adjacent to the metal stent surface. This polymer serves to slow the elution of zotarolimus, such that 60% of the drug is eluted by 30 days and 100% by 180 days, making this the slowest rapamycin analogue-eluting DES.

In the single-arm RESOLUTE trial, ZES(R),117 the primary endpoint of in-stent lumen loss at 9-months was 0.22 mm, and the in-segment binary restenosis rate was 2.1%, both significantly less than seen with other studies of ZES(E) or BMS. Low rates of MACE, TLR, and ARC definite/probable stent thrombosis were observed. Two-year data from this study have demonstrated TLR, TVR, and TVF rates of 1.4%, 1.4%, and 7.9%, respectively, with no late stent thrombosis events.118

The large RESOLUTE All-Comers randomized trial of ZES(R) versus EES was conducted in 2,292 patients86; this trial sought to enroll a more selected patient population than in prior pivotal DES trials. The rate of the primary endpoint of TLF at 1 year was similar to ZES(R) and EES (8.2% versus 8.3%, \( P < 0.001 \)). In this trial, the rates of death, cardiac death, MI, and TLR were similar with both stents, but both definite and definite or probable stent thrombosis occurred less frequently with EES at 1 year. In-segment late loss at 13 months (after ascertainment of the primary clinical endpoints) was slightly greater with ZES(R) compared to EES (0.15 mm versus 0.06 mm, \( P = 0.04 \)), but there were no differences in rates of binary restenosis among the 460 patients undergoing angiographic follow-up. At 2 years, similar rates of clinical endpoints including TLF, TVF, MI, TLR, and TVR were observed, with a trend toward less stent thrombosis with EES (1.0% versus 1.9%, \( P = 0.077 \)), predominantly driven by events within the first year.7 Three patients in each group (0.3%) had very late stent thrombosis (thrombosis occurring beyond 1 year). One additional investigator-initiated randomized trial of ZES(R) and EES has been reported; in the TWENTE trial88 1,391 unselected patients were randomized between these two stents. Notably, “off-label” indications occurred in >75% of patients enrolled. At 1 year, the primary endpoint of TVF was similar with both
stents (8.1% versus 8.2%, P = 0.94), with no observed differences in other clinical endpoints, including stent thrombosis (definite/probable: 0.9% for ZES(R) versus 1.2% for EES).

In summary, the ZES (Resolute platform) is the first stent to demonstrate comparable overall safety and efficacy to the EES, although slight differences in angiographic and clinical outcomes between these stent platforms may exist. Larger studies and longer-term follow-up are required to assess whether these device-specific performance characteristics influence outcomes in actual clinical practice, and whether the long-term safety of this stent is maintained.

**Biolimus A9-Eluting Stents (BioMatrix)**

The BioMatrix (Biosensors International, Switzerland) stent (BES) elutes biolimus A9 (concentration 15.6 μg/mm), a semi-synthetic rapamycin analogue with similar potency but greater lipophilicity than sirolimus, from a stainless steel platform. The stent platform that originally was the S-stent is currently the Juno BMS platform, in the BioMatrix Flex iteration of BES. Of note, the Nobori DES (Terumo Medical Corporation, Japan) is a similar BES that releases biolimus using the same polymer system with a different BMS platform. The Nobori DES has demonstrated favorable results compared to SES in three modest-sized randomized trials.119,121 BES are unique, especially compared to the previously described first- and second-generation DES, in that biolimus A9 is eluted from PLLA, a biodegradable polymer which is applied solely to the abluminal stent surface. The biolimus A9 and PLLA are coreleased, and the polymer is converted via the Krebs cycle into carbon dioxide and water after a 6- to 9-month period. Conceptually, such a stent might not be prone to late inflammatory reactions as are occasionally seen with durable polymers, and thus result in improved outcomes after 1 year.

The BioMatrix BES was first tested in the randomized STEALTH trial in which 120 patients with single de novo coronary lesions received either a BES or a bare-metal S-stent.122 Treatment with BES resulted in lower in-stent late loss at 6 months (0.26 mm versus 0.74 mm for BMS, P < 0.001). The largest trial examining the safety and efficacy of BES was the LEADERS trial, which randomized 1,707 “all-comer” patients (55% of whom had acute coronary syndromes) to BES versus SES.123 Similar rates of all clinical endpoints were observed at 9 months with both BES and SES, including the primary study endpoint, which was the composite of cardiac death, MI, or TVR (9.2% versus 10.5%, P = 0.39). Among the 427 patients allocated to angiographic follow-up at 9 months, in-stent late loss and binary restenosis were similar with both stents. Longer-term follow-up of LEADERS to 4 years has been recently reported (Figure 31.10).124 Over the entire follow-up period, the rate of the composite primary endpoint of cardiac death, MI, or clinically indicated TVR was lower with BES compared to SES (19% versus 23%, P = 0.039), with gradual separation of respective event curves over time. Additionally, while overall definite/probable stent thrombosis rates were not significantly different (3% for BES versus 5% for SES, P = 0.20), the rate of very late definite/probable stent thrombosis was significantly lower with BES (6 events (1%) versus 20 events (2%), P = 0.005). Similar results were observed when assessing the endpoint of definite stent thrombosis.

Collectively, these data demonstrate that BES has similar efficacy as the first-generation devices, with a favorable safety profile that emerges particularly beyond 1 year. However, much larger and adequately powered studies will be required to determine whether BES, or other devices with bioabsorbable polymers, offer true and sustained clinical advantages to the best-in-class second-generation DES with durable polymers. Several studies investigating these hypotheses are ongoing.

![Figure 31.10](image-url)

Principal clinical endpoints at 1 year (left) and 4 years (right) from the randomized all-comers LEADERS trial of a biolimus A9-eluting stent compared to a sirolimus-eluting stent. BES, biolimus A9-eluting stent; SES, sirolimus-eluting stent; MACE (major adverse cardiac events) denotes cardiac death, myocardial infarction (MI), or clinically indicated target vessel revascularization; stent thrombosis refers to Academic Research Consortium (ARC) definite or probable events.
CONCERNS REGARDING SAFETY OF DRUG-ELUTING STENTS AND POOLED COMPARISONS OF DRUG-ELUTING STENTS AND BARE-METAL STENTS

The evidence base for initial DES approvals by the FDA consisted primarily of randomized controlled trials enrolling largely stable patients with relatively noncomplex, single, de novo coronary artery lesions. Data from these early studies demonstrated similar rates of death and MI among DES and BMS-treated patients.\(^{39,125}\) Yet, due to their potent efficacy, DES are used “off label” (in higher-risk patients and in more complex lesions) in 60% to 70% of cases,\(^{126}\) leading to concerns about the safety and appropriateness of the routine use of DES in the “real world.” Moreover, most randomized studies (especially those conducted early in the DES era) included primary outcomes of interest that focused upon stent efficacy, rather than absolute safety. As such, evidence of the safety of DES has come from two sources—randomized controlled trials, which are usually small to modest in size, and typically underpowered to assess safety endpoints such as death, MI, and stent thrombosis, as well as large-scale observational studies, which provide a broader look at the real-world use of DES and allow more generalizability and power.

A number of analyses have amalgamated trial data across clinical studies to increase overall sample size. In particular, these studies have attempted to address one of the prominent limitations of individual DES studies, namely the limited power to detect differences in low-frequency safety endpoints. In the largest and most comprehensive metaanalysis of first-generation DES versus BMS studies (including 9,470 patients from 22 randomized trials and 182,901 patients from 34 observational studies), the use of DES in randomized trials was associated with comparable rates of mortality and MI, with a 55% relative reduction in TVR (Figure 31.11).\(^{39}\) In the observational studies included separately in this analysis (Figure 31.12), significant heterogeneity was observed, and treatment with DES was in fact associated with significant reductions in overall death, MI, as well as TVR. The differences observed between the findings of randomized trials and observational studies included in this analysis highlight the difficulty in assessing nonrandomized active treatment comparisons through an observational study design. In another metaanalysis, Stettler and colleagues incorporated comparative data from SES versus BMS trials, PES versus BMS trials, and SES versus PES trials in a statistical “network” of trials to discern treatment effects across all

<table>
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<th>Study ID</th>
<th>Estimate (95% CI)</th>
<th>Weight (%)</th>
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<td>Typhoon</td>
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<td>Passion</td>
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<tr>
<td>BASKET (SES only)</td>
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<td>0.84 (0.36, 1.96)</td>
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<td>TAXUS V</td>
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</tr>
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</table>

Random Effects ($I^2 = 0.0\%$) 0.97 (0.81, 1.15), \(p = 0.72\)

Fixed Effects

Figure 31.11 Mortality in randomized trials comparing drug-eluting stents to bare-metal stents (from Kirtane et al., Circulation 2009), demonstrating similar overall mortality of both stent types. DES, drug-eluting stent; BMS, bare-metal stent.
Mortality in observational studies comparing drug-eluting stents to bare-metal stents (from Kirtane et al., Circulation 2009), demonstrating a reduction in mortality with drug-eluting stents. DES, drug-eluting stent; BMS, bare-metal stent.

In this analysis of 38 trials including data from 18,023 patients, TLR was lower with SES and PES compared to BMS, with similar mortality among patients treated with SES, PES, and BMS. In this analysis, a reduction in the hazard of MI was observed with SES compared to both BMS (hazard ratio [HR] 0.81, 95% credibility interval 0.66 to 0.97, $P = 0.030$) and PES (HR 0.83, 0.71 to 1.00, $P = 0.045$).

In addition to these and other analyses, numerous observational studies have focused upon the examination of low-frequency safety endpoints when comparing first-generation DES to BMS, across a wide range of clinical indications. More than 50 nonrandomized comparisons between DES and BMS have been published and/or presented to date. Aside from the initial publication of data from SCAAR registry\textsuperscript{128} that was subsequently revised with the addition of longer term follow-up,\textsuperscript{129} the majority of these studies have demonstrated favorable safety for DES compared to BMS. For example, in the largest such analysis of DES safety, which was conducted using data from 262,700 Medicare beneficiaries in the United States, the use of DES was associated with lower rates of death (13.5% versus 16.5%, $P < 0.001$) and MI (7.5% versus 8.9%, $P < 0.001$) with minimal differences in bleeding.\textsuperscript{130}

Despite the reassuring findings from these and other observational registries of unselected DES use, it is our opinion that data from these nonrandomized comparisons of DES versus BMS should be considered exploratory at best, and potentially misleading. This opinion is based upon several factors: (1) Nonrandomized treatment comparisons are subject to significant unmeasured confounding that cannot be adequately accounted for using conventional statistical methodology; (2) Mortality reductions have never been observed in randomized trials comparing first-generation...
DES to BMS; and (3) In propensity-matched observational analyses comparing DES to BMS, the majority of benefit of DES compared with BMS was evident within the first 30 days after implantation,\(^{113}\) a difference that does not appear to have an adequate pathophysiologic explanation. These limitations notwithstanding, the abundance of randomized trial and observational data with DES has been reassuring, demonstrating efficacy of DES in reducing clinical restenosis, and with no major safety concerns compared to BMS. As described in the earlier sections on second-generation DES, there are now emerging data demonstrating improvements in safety outcomes with ZES(E), EES, and BES compared to first-generation DES and even compared to BMS. These findings, in conjunction with superior and/or similar efficacy of second-generation DES, suggest that the comparison between the second generation DES and BMS may be hypothetically even more favorable than prior studies comparing first-generation DES to BMS. At present, however, this remains unproven as direct comparisons between second-generation DES and BMS are scant.

**BIOABSORBABLE DRUG-ELUTING STENTS**

All BMS and DES platforms in clinical practice today are permanent coronary prostheses. As described above, in order to mitigate adverse vascular responses to older DES, newer DES platforms have tried to achieve BMS-like biocompatibility through either inert durable polymers or bioabsorbable polymers. Building further upon this approach is the concept of a completely bioabsorbable scaffold (or bioabsorbable stent). This concept had been investigated prior to the DES era,\(^{132}\) but remained largely dormant until recent efforts to combine a bioabsorbable platform with the antirestenotic efficacy of DES.

Several bioabsorbable DES are currently undergoing clinical trials. The stent at the most advanced stage of investigation and with the most clinical data is the Bioabsorbable Vascular Solutions EES (BVS-EES, Abbott Vascular, Santa Clara, CA). The BVS-EES (Figure 31.13) is a polymeric bioabsorbable scaffold constructed of PLLA with a thin mixture of poly-D, L-lactic acid (PDLLA) that serves as the drug-carrier vehicle for everolimus at a concentration of 8.2 mcg/mm. The PDLLA enables controlled release of everolimus, with 80% elution by 30 days. The BVS-EES has an overall strut thickness of 150 μm in order to maintain structural integrity of the stent in coronary applications.

The BVS-EES was initially investigated in the ABSORB FIM study (ABSORB Cohort A) completed in 2006.\(^{133}\) In this nonrandomized, open-label study of 30 patients receiving BVS-EES in noncomplex de novo coronary lesions, device success was 94% with a MACE rate of 3.3% (one MI event and no TLR). Although a comparative study with cobalt chromium EES demonstrated similar acute recoil with BVS-EES to EES,\(^{134}\) in ABSORB, angiographic in-stent late loss was 0.44 mm, and appeared to be related in large part to late recoil of the scaffold\(^{135}\) rather than neointimal hyperplasia. Nonetheless, follow-up to 5 years has demonstrated a persistently low MACE rate (3.4%) without any further occurrence of late complications.\(^{136}\) After a manufacturing and design modification to the BVS-EES (in order to improve strut strength and enabling storage at room temperature), enrollment in Cohort B of the ABSORB trial ensued.\(^{137}\) The Cohort B patients (total of 101 patients) represent two separate groups of patients undergoing various modes of invasive and noninvasive follow-up (including angiography, IVUS, optical coherence tomography (OCT), and multislice computed tomography) at different timepoints (6 months and 24 months, and 12 months and 36 months). The cumulative rate of MACE at 18 months was reported to be 6.7%, comprising 3 MI events and 4 TLR events.\(^{138}\) There have been no observed stent thrombosis events in either cohort of the ABSORB trial. Furthermore, OCT analyses from Cohort B have demonstrated persistence of the mechanical scaffolding properties of BVS-EES despite evidence of reductions in strut core area.\(^{139}\) Strut malapposition has been rare, and strut coverage occurred in almost 97% of struts at 12 months. The ongoing ABSORB EXTEND trial in up to 1,000 patients with up to two de novo coronary lesions will further expand the clinical evidence base of the BVS-EES.

Aside from the intuitive appeal of fully bioabsorbable scaffolds, other potential advantages of this technology relate to a restoration of normal arterial vasomotion and arterial function (including resolution of side branch jailing and obstruction), visualization of coronary arteries via noninvasive means, and potential facilitation of repeat interventions, if needed. These advantages would theoretically come in addition to mitigating any adverse effects of existing permanent stent platforms (both DES and BMS).

**DRUG-ELUTING STENT SUMMARY**

In summary, significant progress has been made with second-generation DES compared to their first-generation counterparts in terms of enhanced deliverability (through
Achieving optimal stent outcomes requires operator skill in guide catheter, guidewire, and stent selection and usage. Understanding the utility of adjunctive imaging and physiologic lesion assessment catheters (e.g., IVUS, fractional flow reserve [FFR], OCT; see Chapters 24 and 25), lesion modification devices (e.g., atherectomy, thrombectomy), and distal protection devices (see Chapter 29) is also critical to optimizing stent results. Perhaps most important, however, intimate knowledge is required regarding the appropriate indications for stent implantation versus alternative medical therapy or surgical revascularization, identification and treatment of high-risk patients and lesions, appropriate use of adjunct pharmacotherapy, and the recognition and management of stent-related complications (see Chapters 4 and 5).

### Technical Aspects of Coronary Stent Implantation

#### Guide Catheter and Guidewire Selection

Optimal guide catheter selection is critical for the successful completion of most stent procedures and requires the operator to consider prior to the case the amount of backup support required and the luminal dimensions of the guide to accommodate the devices likely to be used. Stenting of noncomplex lesions is typically performed through 6F or even smaller (e.g., 5F) guiding catheters. Smaller-diameter guides, however, provide reduced backup support, a disadvantage that may necessitate active guide catheter manipulation (deep guide intubation), a technique that is usually safe when performed by experienced operators, although it may occasionally result in proximal coronary dissection requiring placement of additional stents.

If significant guide catheter backup support is anticipated (e.g., fibrocalcific or tortuous vessels, distal lesions, or chronic total occlusions [CTO]), or simultaneous delivery of multiple wires, stents, or use of atherectomy devices is planned, larger-dimension guiding catheters (typically 7F or 8F) or those with specialized shapes (e.g., Extra-Back Up or Voda shapes for the left coronary artery, and hockey stick or Amplatz shapes for the right coronary artery and SVGs) should be chosen. Larger guiding catheters may also be required for stenting of bifurcation lesions when a two-stent technique that requires contemporaneous delivery of both stents is required. An alternative to larger guide sizes to increase support is the use of a “mother-daughter” technique, or coaxial deployment of a smaller catheter through an existing guide catheter system.

Floppy wires should be used for most stent implant procedures, although at least medium shaft support is required to advance most stents. More complex guide-anchoring techniques or a second parallel (“buddy”) wire placed alongside the wire being used may be considered further aids to deliver the stent when difficulty advancing the stent over an extra-support wire is still encountered.

#### Stent Selection and Techniques to Optimize Acute and Long-Term Outcomes

Optimal stent selection and implantation technique will minimize procedural complications, reduce the risk of stent thrombosis, and enhance long-term freedom from restenosis. Key issues include selection of the appropriate stent (including stent diameter and length), implantation pressure, the decision whether to predilate versus direct stent, and whether to postdilate or implant additional stents to achieve an optimal result (Table 31.4). Balloon-expandable rather than self-expanding stents are almost universally used for coronary applications, given their simplicity and accuracy in positioning. Open cell designs are generally more trackable than closed cell stents and may be favored in tortuous vessels where conformability on bends is important or when stenting across bifurcation lesions (to reduce the risk of side branch closure and preserve side branch access). Closed cell designs, in contrast, may be desirable when uniform or optimal scaffolding is required, such as in ostial lesions. Excessive force should never be applied in trying to pass a stent across a rigid, nondilated lesion; such efforts are likely to be unsuccessful and increase the risk of stripping the stent from the balloon. If guide support is adequate and the stent does not easily pass across the lesion, it should be carefully withdrawn back into the guide catheter under fluoroscopic visualization and the lesion should be aggressively predilated before an attempt to readvance the stent is made.

The optimal pressure for stent implantation has been a matter of some debate. Colombo first demonstrated that high-pressure stent implantation techniques were important to achieve optimal stent expansion and to appose the stent completely to the vessel wall. Although Colombo initially achieved these results with the use of adjunctive IVUS imaging, acceptable results were also demonstrated with moderate-pressure implantation techniques without IVUS imaging. In a randomized trial of high (mean 16.9 atm) versus moderate (mean 11.1 atm) pressure for stent implantation in 934 patients, similar rates of stent thrombosis and restenosis were observed. In contrast, in a second randomized...
Table 31.4 Guidelines for Optimal Stent Selection and Implantation

1. **Choose the optimal stent length**
   
   A. Ensure adequate lesion coverage while avoiding excessively long stents, as stent length is a risk factor for periprocedural myocardial necrosis, stent thrombosis, and restenosis.

   B. Implant the stent from normal reference to normal reference if possible (starting 2 mm before and after the lesion shoulder), which will avoid edge dissections. An edge dissection, unless mild, often requires treatment with an additional short (8–10 mm) overlapping stent.

   C. In diffusely diseased vessels, a normal reference segment often cannot be identified. The most severe atherosclerotic segments should be stented so there are no major inflow or outflow lesions proximal or distal to any stenosis. Spot stenting is likely preferable to the “full metal jacket” Avoid stenting over potential graft anastomosis site (e.g. mid-distal LAD).

   D. For long lesions, use one long stent if possible. If multiple stents are required, they should overlap by ~2 mm to ensure complete lesion coverage but minimizing the total length of overlap.

2. **Choose the optimal stent diameter**
   
   A. Size the stent diameter with a ratio of 1.0–1.1:1 to the distal reference vessel diameter. Be cognizant that the size of the distal vessel can be underestimated due to proximal severe disease or spasm (e.g. in the setting of acute myocardial infarction).

   B. If the vessel is tapering, a larger noncompliant balloon can then be used to more fully expand the proximal stent segments.

   C. Be aware that within the same stent line, different-sized stents exist for different-diameter vessels. Oversizing stents designed for small vessels will lead to inadequate scaffolding and possibly strut fracture.

3. **Predilatation versus direct stenting**
   
   A. Direct stenting may be considered when guide catheter support is good to excellent. Lesions not generally amendable for direct stenting include those with excessive vessel or lesion tortuosity or calcification, diffuse disease or subtotal stenoses, bifurcations, acute myocardial infarction, or chronic total occlusions. While direct stenting is faster than predilatation prior to stenting, recognition of the potential for inadequate expansion is critical prior to deploying a stent that then cannot be expanded, which is a major risk factor for stent thrombosis and/or restenosis.

   B. If direct stenting is not feasible, predilatation should be performed with balloons undersized to the reference diameter by 0.5 mm, and with length shorter than the lesion so as to not extend the length of stenosis requiring stenting. If this degree of predilatation does not allow stent passage, larger and/or higher-pressure balloon inflations may be required.

4. **Implant and postdilate the stent at adequate pressure**
   
   A. Most stents (except those mounted on a very compliant delivery system) should be implanted using at least 12 atm of inflation pressure.

   B. Higher routine implantation pressures and/or requisite high-pressure postdilation with a noncompliant balloon (16–18 atm or greater) are preferred by many to optimize stent expansion and are often required in fibrocalcific lesions.

   C. In diffusely diseased vessels, consider implanting the stent at 10–12 atm to avoid edge dissections, and then postdilate the stent at higher pressures using a short noncompliant balloon positioned within the stent margins.

5. **Strive for an optimal angiographic stent result, defined as**
   
   A. A residual stenosis <10%

   B. No edge dissection greater than NHLBI type A

   C. TIMI grade 3 flow

   D. Patency of all side branches ≥2.0 mm in diameter

   E. Absence of distal thromboemboli, perforation, or other angiographic complications with associated chest pain, electrocardiographic changes, or hemodynamic instability

NHLBI, National Heart, Lung, and Blood Institute; TIMI, Thrombolysis in Myocardial Infarction.
trial, routine high-pressure (17.0 atm) versus low-pressure (9.9 atm) stent implantation resulted in greater initial and 6-month follow-up minimal stent cross-sectional areas.142

More important than the actual deployment pressure is the overall degree of expansion of the stent itself. Inadequate stent expansion has been linked to both stent thrombosis as well as restenosis.75,143,144 The use of compliance charts supplied by stent manufacturers can be misleading, as they reflect ex vivo sizing; in vivo, stent size is determined not only by the inflation pressure but also by the compliance of the vessel, and systematic undersizing of stents has been observed when stents are assumed to be sized based upon manufacturers’ compliance charts.145 Complete lesion coverage without edge dissections is also believed to be important, as is the elimination of inflow and outflow stenoses that can compromise flow and lead to stent thrombosis. Implantation of additional short stents may be required to cover edge dissections and achieve optimal lumen dimensions.146

With optimal stent implantation technique, stent thrombosis should occur in no greater than 1% of patients.147 Although routine high-pressure stent implantation and high balloon-to-artery ratios result in greater stent expansion and optimize late outcomes, care must be taken to avoid edge dissections and perforation.

The use of adjunctive imaging technologies including IVUS and OCT (see Chapter 25) can often be helpful to the operator in real time. These invasive imaging technologies facilitate the accurate assessment of true (media-to-media) vessel size prior to stent implantation, and can be useful post deployment in assessing how well the stent has expanded and whether there is any malapposition of stent struts. The prospective data on the use of IVUS-guided stent implantation, however, is mixed,148-151 partially due to the high level of experience of operators enrolling in trials of IVUS-guidance (these operators’ stent implantation techniques are often modified even in the absence of IVUS based upon their knowledge of IVUS-based parameters of stent implantation). There are emerging data on the use of other imaging technologies including OCT as an adjunct to stent implantation. At present, IVUS (and/or OCT) is currently used in <10% of patients undergoing stent implantation in the United States, a reflection of the learning curve this technique requires, difficulties in incorporating the information IVUS provides into treatment decisions, logistic issues, and lack of widespread reimbursement.

Like adjunctive imaging technologies, physiologic lesion assessment (measurement of either coronary flow reserve or FFR) has utility during coronary stent implant procedures (see Chapter 24). FFR can be used to identify the hemodynamic significance of intermediate lesions, thereby providing direct physiologic evidence to the operator who can then address the suitability of the lesion for treatment.152,153 The use of an FFR-guided strategy of stent implantation for patients with multivessel disease has been shown to improve outcomes over an angiography-alone guided strategy in a randomized clinical trial.154 The use of FFR in the FAME trial was not only associated with a lower rate of adverse events, but was also less costly due to a greater number of deferred lesions in the FFR-guided group.155 FFR can also be used to determine the adequacy of stent implantation; an FFR of < 0.95 correlates with an underdeployed stent by IVUS.156 Finally, FFR may also be useful in provisional stenting approaches to identify cases where distal or side-branch disease may be left alone, thereby avoiding the use of an additional stent.157

Role of Plaque Modification Prior to Coronary Stent Implantation

The amount of plaque present prior to and after stent implantation has been shown to be a strong determinant of subsequent restenosis,158 leading to the hypothesis that plaque debulking using either directional or rotational atherectomy devices prior to stenting would enhance event-free survival. Similarly, the circumferential extent of calcium is a strong determinant of inadequate stent expansion,159 and pilot studies initially demonstrated greater stent dimensions when stenting was preceded by high-speed rotational atherectomy.160,161 Unfortunately, randomized trials have been unable to demonstrate improved clinical or angiographic outcomes with atherectomy prior to stent implantation compared with stenting alone,162,163 particularly in light of the profound effects of DES on reduction of restenosis.

At present, rotational atherectomy prior to stenting is used in “niche” indications, primarily to treat heavily calcified lesions or those resistant to balloon crossing or predilation. In these cases, if rotational atherectomy is applied safely and with good operator technique, this technique can markedly improve the deliverability of coronary stents to the target lesion. Directional atherectomy may still play a role in selected cases of stenting in ostial, bifurcation, or left main lesions to reduce plaque shift and subsequent side-branch compromise (see Chapter 29), but at present, this technique is reserved almost exclusively for the treatment of peripheral arterial lesions (see Chapter 34). Similarly, the major contemporary role for excimer laser angioplasty is in the treatment of peripheral arterial lesions and in rare cases for recalcitrant coronary lesions or refractory stent underexpansion.

COMPLICATIONS OF CORONARY STENTING

Stent Thrombosis

The most feared complication following stent placement is stent thrombosis, which while fortunately rare (occurring in ~0.5% to 1% of patients within 1 year), in more than 80% of patients presents as acute MI. Treatment for stent thrombosis is almost always emergent repeat PCI, although optimal reperfusion is only achieved in two-thirds of patients.164 As a result, stent thrombosis has been associated with 30-day
mortality rates of 10% to 25%. Moreover, approximately 20% of patients with a first stent thrombosis experience a recurrent stent thrombosis episode within 2 years. Thus, understanding and preventing this complication is of paramount importance.

The most widely utilized definition and timing classification of stent thrombosis was developed by the Academic Research Consortium (ARC), with definite or probable stent thrombosis considered the best tradeoff between sensitivity and specificity (Table 31.5). Stent thrombosis is also classified as primary if it is directly related to an implanted stent, or secondary if it occurs at the stent site after an intervening TLR event. Primary stent thrombosis after BMS typically occurs within the first 30 days after implantation, although rarely can occur later. In contrast, primary stent thrombosis after DES can occur years afterward, with an annual incidence of 0.2% to 0.3% in patients with noncomplex coronary artery disease, and 0.4% to 0.6% after unrestricted use, particularly with first-generation DES (Figure 31.14). Thus, primary stent thrombosis rates during long-term follow-up are higher with most DES than BMS, with the differences emerging predominately beyond the first year after implant. However, after taking into account secondary stent thrombotic events after TLR procedures for restenosis (which occur more commonly after BMS than DES), the overall incidence of stent thrombosis (primary plus secondary) does not seem to be increased with DES compared to BMS, and the overall late rates of death and MI have been similar with DES and BMS. From a clinical perspective, the benefits of DES in reducing restenosis and subsequent MACE have been demonstrated to offset the small excess risk of late primary stent thrombosis with DES in an analysis of patients enrolled in the pivotal PES approval trials. Additionally, given the results of longer-term follow-up with second-generation devices including EES, ZES(E), and BES, which have demonstrated low rates of stent thrombosis compared to first-generation DES, whether these devices have the ability to further reduce stent thrombosis rates compared to BMS is an area of active investigation.

The mechanisms underlying stent thrombosis are multifactorial (Table 31.6), and include patient-related factors, procedural factors (including stent choice), and postprocedural factors (including type and duration of antiplatelet therapy). Stent thrombosis occurs more frequently in complex patients and lesions, especially in patients with acute coronary syndromes and thrombotic lesions, diabetes, renal insufficiency, diffuse disease, small vessels, and bifurcation lesions requiring multiple stents. Variability in the antiplatelet response to clopidogrel (either identified through loss-of-function mutations to the enzyme responsible for conversion of clopidogrel to its active metabolite or through testing of platelet responsiveness) has been identified as an independent risk factor for early stent thrombosis. While more potent dual antiplatelet therapies such as higher-dose clopidogrel, prasugrel, or ticagrelor can reduce the incidence of stent thrombosis, particularly in those at risk for resistance, these regimens are also associated with a greater risk of bleeding complications, and their use in unselected patients undergoing PCI is at present unproven. It is thus essential to carefully consider the individual patient’s risk of stent thrombosis (and MI) compared to bleeding before using these regimens.

Procedural factors associated with stent thrombosis include the stent type selected (whether BMS or DES, and even the specific DES used), as well as whether the stent is adequately expanded and apposed to the vessel wall and is

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**Table 31.5 Academic Research Consortium Definitions of Stent Thrombosis**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Definite</th>
<th>Probable</th>
<th>Possible</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>An acute coronary syndrome with angiographic or autopsy evidence of thrombus or occlusion within or adjacent to a stent.</td>
<td>Unexplained death within 30 d after stent implantation or acute myocardial infarction involving the target-vessel territory without angiographic confirmation.</td>
<td>Any unexplained death beyond 30 d after the procedure.</td>
</tr>
</tbody>
</table>

**Timing**

<table>
<thead>
<tr>
<th></th>
<th>Acute</th>
<th>Subacute</th>
<th>Early</th>
<th>Late</th>
<th>Very late</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Within 24 h (excludes events within the catheterization laboratory)</td>
<td>1–30 d</td>
<td>Within 30 d</td>
<td>30 d–1 y</td>
<td>After 1 y</td>
</tr>
</tbody>
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The rates of stent thrombosis may be decreasing with improvements in stent technology, imaging, and adjunct pharmacology. A large nonrandomized propensity-controlled study has suggested that IVUS guidance may reduce stent thrombosis at both 30 days and 1 year. As discussed above, less reactive and biocompatible polymers and improvements in stent design have significantly reduced the rates of early (EES) and late (EES, ZES(E), and BES) stent thrombosis. The role of potent antiplatelet therapy for the prevention of stent thrombosis, particularly in the early phase, is well established. While observational studies have uniformly documented that premature thienopyridine discontinuation within 6 months after DES placement is strongly associated with stent thrombosis, whether prolonged dual antiplatelet therapy beyond this time reduces stent thrombosis and/or death and MI is unknown, with some studies in support of this hypothesis and others against. In this regard the potential benefits of prolonged dual antiplatelet therapy, including the prevention of stent-related and nonstent atherosclerosis-related adverse events must be weighed against the persistent risk of ongoing major bleeding with combination therapy.

Three published randomized trials have tested this hypothesis (Figure 31.15). In the pooled REAL-LATE/ZEST-LATE trial, 2,701 patients who were MACE-free for at least 1 year after DES (SES, PES, or ZES) were randomized to an additional 2 years of clopidogrel along with aspirin or aspirin alone. There were no significant differences between the two groups in the late occurrence of the primary endpoint or cardiac death or MI, or of definite stent thrombosis, and paradoxically the composite endpoint of all-cause death, MI, or stroke was increased with prolonged clopidogrel use. The PRODIGY trial randomized 2,013 stented patients (treated with BMS, ZES(E), SES, or PES) to 6 versus 24 months of dual antiplatelet therapy with aspirin and clopidogrel, and demonstrated similar rates of adverse ischemic events (including stent thrombosis) with both strategies, and a greater incidence of hemorrhagic complications with extended duration therapy. Finally, the EXCELLENT trial randomized 1,443 patients after DES implantation (with SES or EES) to 6 versus 12 months of dual antiplatelet therapy, and also demonstrated similar rates of ischemic events, including stent thrombosis, with both strategies. The event rates from each of these studies, however, are small, and therefore none of these studies are adequately powered to demonstrate definitively the most optimal duration of dual antiplatelet therapy following DES implantation. Several additional randomized trials are ongoing to address the relative safety and efficacy of prolonged dual antiplatelet therapy, the largest and most meaningful of which is the Dual Antiplatelet Therapy (DAPT) Study, in which 20,645 patients free from MACE 1 year after SES, PES, EES, or ZES implantation are being randomized to aspirin alone or aspirin plus a thienopyridine (either clopidogrel or prasugrel), with follow-up for an additional 18 months.
Table 31.6  Potential Mechanisms of Stent Thrombosis

Patient-related factors relating to increased thrombogenicity:
- Smoking
- Diabetes
- Chronic kidney disease
- Acute coronary syndrome presentation
- Thrombocytosis
- High posttreatment platelet reactivity
- Premature discontinuation or cessation of dual antiplatelet therapy
- Surgical procedures (unrelated to the PCI)

Lesion-based factors relating to adverse rheology/thrombogenicity within stents:
- Diffuse coronary artery disease with long-stented segments
- Small vessel disease
- Bifurcation disease
- Thrombus-containing lesions
- Significant inflow or outflow lesions proximal or distal to the stented segment

Stent-related factors:
- Poor stent expansion
- Edge dissections limiting inflow or outflow
- Delayed or absent endothelialization of stent struts
- Thicker stent struts
- Hypersensitivity/inflammatory and/or thrombotic reactions to specific DES polymers (N.B. specific polymers may have a protective effect)
- Strut fractures
- Late malapposition/aneurysm formation
- Development of neatherosclerosis within stents with new plaque rupture

Treatment of Stent Thrombosis
Prompt reperfusion is critical when treating stent thrombosis, particularly when it presents as acute ST-elevation MI. While stent thrombotic events can be treated with fibrinolytic therapy, emergent PCI is typically the rule. Stent thrombosis may be treated with emergent thrombectomy (either aspiration or mechanical) or with balloon angioplasty alone, often in conjunction with administration of more potent antiplatelet regimens including glycoprotein IIb/IIIa inhibitors. The placement of additional stents should usually be avoided unless a mechanical reason for the initial thrombotic event is ascertained (e.g. edge dissection or residual untreated disease). The use of adjunctive imaging such as IVUS or OCT will often reveal a possible cause of stent thrombosis, such as stent underexpansion or malapposition, residual dissection, or significant inflow or outflow stenosis, and is thus recommended following thrombectomy. In the absence of a mechanical cause, hematologic evaluation should be performed to exclude a hypercoagulable state (including resistance to aspirin or clopidogrel) or thrombocytosis. Maintenance antiplatelet therapy is typically escalated in cases of stent thrombosis (e.g. clopidogrel is switched to prasugrel or ticagrelor, or cilostazol is added).

Restenosis
Restenosis is most commonly defined as renarrowing to a diameter stenosis >50%, either within the stent or within
5 mm proximal or distal to the stent margin. By increasing acute luminal gain\textsuperscript{34,35} and eliminating late recoil and negative vessel remodeling,\textsuperscript{211} BMS reduce the rates of restenosis compared to balloon angioplasty.\textsuperscript{6,7} However, stents induce more arterial injury than stand-alone balloon angioplasty, and therefore elicit a greater absolute amount of neointimal hyperplasia developing over the first 6 to 12 months after the procedure.\textsuperscript{212} As a result, BMS result in binary angiographic restenosis in 20% to 40% of lesions (with even higher rates observed depending on patient and lesion complexity). While restenosis most commonly presents with stable angina and exercise-induced ischemia within 1 year of stent implantation, it has become increasingly recognized that restenosis presents as an acute coronary syndrome in as many as 25% of patients, occasionally even with STEMI.\textsuperscript{312,313}

The causes of restenosis after stent implantation are multifactorial. In addition to excessive late neointimal hyperplasia, restenosis after BMS and DES has been associated with stent underexpansion,\textsuperscript{214-216} edge dissections, and residual untreated disease.\textsuperscript{217,218} geographic miss,\textsuperscript{219} and strut fractures.\textsuperscript{219,220} Some\textsuperscript{221} but not all\textsuperscript{222,223} studies have found an association between nickel allergy and restenosis after BMS or DES. Genetic mutations in the genes encoding mTOR or polymorphisms in the genes encoding proteins involved in paclitaxel metabolism may result in resistance to SES and PES respectively.\textsuperscript{224,225} Other genetic polymorphisms have also been associated with restenosis.\textsuperscript{226,227} Excessive inflammation from first-generation DES polymers (specifically eosinophilic reactions to PES and granulomatous reactions to SES) may provoke late restenosis.\textsuperscript{211,228}

Numerous studies have demonstrated that the most reproducible determinates of restenosis after BMS implantation are the presence of diabetes mellitus (especially if insulin is required), small RVD, and long lesion length.\textsuperscript{229-234} Other factors associated with restenosis are treatment of ostial and/or calcified lesions, true bifurcation lesions requiring main vessel and side branch stents, CTOs, and SVGs.\textsuperscript{235} The same factors are associated with (relatively) higher rates of DES restenosis, although to a lesser absolute scale because of the profound effects of DES in limiting the intimal hyperplastic response to stent implantation. Angiographic and clinical restenosis (as well as death, MI, and stent thrombosis) after DES occurs less frequently in FDA-approved “on-label” lesions (generally noncomplex lesions for which safety and efficacy have been established by large-scale randomized trials) than in less studied and more complex “off-label” lesions,\textsuperscript{126,236} although in nearly all cases DES have been shown to reduce TLR compared to BMS.\textsuperscript{39,237,238} As discussed above, newer DES platforms (especially EES, ZES(R), and BES) have been shown to possess improved efficacy and safety. In addition, by facilitating the operator’s ability to achieve larger lumen areas, IVUS may reduce restenosis and improve clinical outcomes after BMS.\textsuperscript{39,240} No randomized trial has been adequately powered to demonstrate a reduction in TLR with IVUS after DES implantation, although the recently reported AVIO trial demonstrated that the postprocedural minimal luminal diameter was significantly greater with IVUS guidance.\textsuperscript{151}

The incidence of angiographic restenosis after BMS implantation peaks within approximately 6 months; thereafter, continued organization of the extracellular matrix results in slight luminal enlargement, and serial angiographic and IVUS studies have rarely shown late restenosis.\textsuperscript{241,242} More recently late neatherosclerosis with plaque rupture within the stented segment has been described as a possible cause of restenosis occurring years after BMS.\textsuperscript{243} In contrast, a small amount of incremental angiographic late loss has been described for several years after SES and EES implantation, although reports on very late loss after PES have been conflicting.\textsuperscript{106,244-248} These observations imply the existence of low-grade chronic vascular inflammation from either the polymer or lack of healing. However, when compared to their BMS counterparts (or with EES versus PES in the SPIRIT trials), there has been little evidence demonstrating late loss to be of clinical relevance during extended follow-up of 2 to 5 years.\textsuperscript{111,116,170,244,249-251} In the largest randomized trial examining the issue of “late catch-up” (SIRTAx), 1,012 patients

![Graph showing outcomes in three randomized trials of extended-duration dual antiplatelet therapy versus standard-duration therapy after stenting.](image-url)
were randomized to PES versus SES and followed for 5 years, with angiographic follow-up performed systematically at 8 months and 5 years. Incremental late loss between these two time periods occurred with both stents, although more so with SES than PES. At 1 year the rate of TLR was less with SES than PES, a benefit that was somewhat mitigated at 5 years. However, because routine angiographic follow-up was performed at regular intervals in this trial, the degree to which routine angiographic follow-up itself (rather than true clinical restenosis events) triggered late TLR procedures is unknown. Nonetheless, a small degree of angiographic late loss may be expected with durable polymer-based DES, and may contribute to late adverse events in a small proportion of patients.

Patients who develop in-stent restenosis are at high risk for recurrence after percutaneous treatment, especially if the pattern of restenosis is diffuse. IVUS and/or OCT imaging is highly useful in patients with restenosis to differentiate neointimal hyperplasia from stent underexpansion, geographic miss, strut fracture, and other rare occurrences such as chronic recoil and stent embolization which require directed approaches to successfully manage. Isolated restenosis at the stent edge can often be effectively treated with balloon angioplasty only or an additional short stent. Treatment options for diffuse BMS restenosis due to neointimal hyperplasia have been extensively studied. In the BMS era, neither cutting balloons, directional or rotational atherectomy, nor repeat BMS proved better than balloon angioplasty for diffuse in-stent restenosis. However, in selected cases, the use of a cutting balloon or another force-focused device may be useful in that it minimizes balloon slipping and potentially affords a better initial angiographic result. Vascular brachytherapy with either locally applied beta or gamma radiation was effective in reducing recurrent restenosis within 1 year, but was logistically complex, and the resultant vascular toxicity with prolonged inflammation and obliteration of normal cell lines resulted in high rates of late stent thrombosis (especially when new BMS were implanted) and restenosis. Following the introduction of DES, two multicenter randomized trials demonstrated that SES and PES significantly reduced angiographic restenosis and improved event-free survival compared to either beta or gamma vascular brachytherapy in patients with BMS restenosis.

Treatment of in-stent restenosis with DES has been shown to be superior to balloon angioplasty alone in the randomized ISAR-DESIRE trial. Angiographic follow-up at 6 months demonstrated recurrent restenosis after balloon angioplasty in 44.6% of patients versus 14.3% for SES (P < 0.001) and 21.7% for PES (P = 0.001), with TVR rates of 33%, 8%, and 19% respectively (P < 0.001 and P = 0.02 compared to balloon angioplasty, respectively). Based on the results of this and other trials, DES (with either PES or –limus analogue stents) has become the standard of care for nearly all cases of BMS restenosis due to intimal hyperplasia. For patients who are refractory to PCI-based strategies to treat restenosis, coronary artery bypass grafting (CABG) should be considered.

The optimal treatment for DES restenosis typically involves treatment with a second DES. (An emerging strategy to treat both BMS and DES restenosis is the use of drug-eluting balloons, which are presently not approved for use in the United States). Compared to BMS restenosis, DES restenosis (particularly with more potent DES) tends to be focal and is diffuse in less than one-quarter of patients. If the stenosis is isolated to the margin or the stent, or is focal within the stent, either balloon angioplasty or implantation of a short DES is often selected. Management of diffuse DES restenosis has been less studied. In the CRISTAL trial, 197 patients with diffuse restenosis (mean length ~14 mm) of either an SES or PES were randomized to treatment with SES versus balloon angioplasty. Follow-up at 12 months demonstrated a significantly larger minimal lumen diameter (MLD) with SES compared to balloon angioplasty only (2.14 ± 0.62 mm versus 1.71 ± 0.55 mm, P < 0.0001, with a trend toward less TLR (5.9% versus 13.1%, P = 0.10). Many operators consider diffuse in-stent restenosis after DES (if IVUS demonstrates adequate stent expansion) to represent “drug failure” and will treat with a different class of agent (e.g. PES after SES failure). However, in the ISAR-DESIRE-2 trial, 450 patients with SES restenosis were randomized to SES versus PES. At 6 to 8-month follow-up there were no differences between SES and PES in late loss (0.40 ± 0.65 mm versus 0.38 ± 0.59 mm; P = 0.85), binary restenosis (19.6% versus 20.6%; P = 0.69), or TLR (16.6% versus 14.6%; P = 0.52).

Some operators have adopted a strategy of balloon angioplasty for focal restenotic lesions, and DES use for more diffuse restenotic lesions. In a randomized trial (N = 162 patients) of cutting balloon angioplasty versus SES for focal (<10 mm) restenotic lesions and SES versus EES for diffuse (>10 mm) restenotic lesions, use of SES was shown to reduce restenosis compared to cutting balloon angioplasty (3.1% versus 20.6%, P = 0.06) for focal lesions, with no differences observed between SES and EES for more diffuse lesions. Finally, recurrent diffuse DES restenosis represents a major clinical challenge. Options that may be considered include cilostazol, brachytherapy, and oral rapamycin. Ultimately, CABG surgery may be required in patients with recurrent DES restenosis.

Other Complications of Coronary Stent Implantation

A review of all complications that can occur during or after PCI is beyond the scope of this chapter (see Chapters 4 and 28). However, several risks that are unique to or are increased in frequency with coronary stenting compared with balloon angioplasty should be appreciated.

Side Branch Compromise/Occlusion

Side branch compromise after stent implantation most commonly results from shifting of plaque during stent deployment.
or high-pressure dilatation (though coronary spasm may contribute). This has been termed the “snowplow” effect. The incidence of side branch compromise after coronary stent implantation is greater than after balloon angioplasty alone. Side branch compromise and/or occlusion occurs with a greater frequency when both the parent vessel and side branch are diseased.272 Stent-induced occlusion of a large side branch may result in significant myocardial ischemia and infarction, though in most patients the long-term prognosis is excellent, and most initially occluded side branches are patent at late angiographic follow-up.273,274

Side branch compromise and/or occlusion should be anticipated whenever a stent is placed across a bifurcation. If the side branch is large (≥2.5 mm in diameter), or is ≥2.0 mm in diameter and diseased at its ostium, it should be protected with a second guidewire prior to PCI. Many operators elect to wire and protect all side branches ≥1.5 to 2.0 mm using a “keep-it-open” strategy in order to avoid loss of any side branches. If the origin of the branch is narrowed, it is often beneficial to predilate it prior to stent implantation in the main branch, although this approach can increase the necessity of a second stent in the side branch, particularly if it results in dissection of the side branch ostium. Predilation of bifurcations are most commonly performed with conventional balloon angioplasty, but alternatives include use of focused force devices or debulking techniques such as atherectomy, although these approaches have not been clearly shown to preserve side branch patency beyond that achieved by balloon angioplasty alone. Once the side branch is protected with a second wire (and predilated if necessary), a stent may be placed in the main vessel across the branch origin, temporarily “jailing” the wire. This usually preserves patency of the side branch should occlusion otherwise occur and serves as a locator for the side branch origin.275 If additional angioplasty is planned, a third wire should then be passed through the stent struts into the narrowed side branch, after which the jailed wire is removed. The likelihood of a jailed wire becoming “stuck” is rare if the parent vessel stent is implanted at ≤12 atm of pressure, but jailing a long segment of wire in the parent vessel should be avoided, and hydrophilic wires should be used cautiously because of the risk of stripping the polymer coating on its withdrawal. Alternatively, if there is minimal narrowing at the origin of the side branch at baseline or after balloon dilatation, a stent may be placed in the main vessel across the side branch origin with the option of wiring the side branch should it become compromised after stent placement.

If the side branch significantly narrows after predilatation of either limb of the bifurcation, or the result is not acceptable after predilation (which typically depends on the plaque burden, extent of calcification, and angle or origin of the side branch from the parent), a second stent should be implanted in the side branch using one of numerous techniques. With all these dual-stent techniques, however, the stent thrombosis rate is increased compared with a single-stent approach, and the restenosis rate within the second stent at the side branch origin is increased compared relative to the main branch (even with DES). As such, the single-stent strategy is preferable if an acceptable balloon-only (or simple jailed wire) result in the side branch can be obtained.277

### Stent Embolization

Embolization of the stent from the stent delivery system may occur during antegrade passage in a fibrocalcific or tortuous vessel, or upon withdrawal of the device after failure to cross a lesion (often when the edge of the stent snaps on the tip of the guide catheter or on another plaque proximal to the lesion itself). Risk factors for stent embolization include heavy vessel calcification, pronounced vessel tortuosity, diffuse disease, and attempting to deliver a stent to a distal lesion through a previously implanted proximal stent.276 When the original Palmaz-Schatz stent was hand-mounted on a conventional angioplasty balloon and no sheath was used, stent embolization occurred in 8.4% of patients.277 Over the years, the development of tighter stent-to-balloon crimping processes in concert with lower-profile, more flexible devices has resulted in the incidence of this complication decreasing to <1% to 2%.279,280 Stent embolization into the peripheral vasculature usually has no adverse clinical sequelae, but may rarely cause limb ischemia or a cerebrovascular event. Conversely, intracoronary stent embolization is associated with significant rates of coronary thrombosis, coronary artery occlusion, and subsequent MI, with mortality rates as high as 17%. If the stent can be removed through percutaneous (nonsurgical) techniques, the majority of patients have a satisfactory outcome.281,282

Success rates for percutaneous retrieval of lost stents from the coronary tree have ranged from 40% to 70% of patients in contemporary series.279,280,281 There are several basic strategies that can be employed to address stent embolization. If the coronary guidewire is still through the stent and has been maintained in the distal coronary artery, a low-profile balloon can sometimes be advanced through the stent, allowing the stent to be repositioned across the target lesion and expanded. If the stent cannot be repositioned, the balloon can be placed distal to the stent and inflated to trap the stent between the balloon and guiding catheter, and then all components can be withdrawn together into the femoral sheath. If guidewire position has been lost and the unexpanded stent is located in a proximal portion of the coronary artery or has embolized into a peripheral artery, it can sometimes be removed using snare devices or forceps. If the stent is displaced from the wire more distally within the artery, a snare or series of wires can be wrapped around it to attempt to ensnare it. Alternatively, a second stent may be expanded adjacent to the dislodged stent to trap and crush it against the vessel wall, effectively excluding it from the lumen. If the stent cannot be removed or effectively “excluded” from the coronary lumen, strong consideration should be given to coronary artery bypass surgery (with possible retrieval of the stent), although high mortality rates have been described in this situation.
Coronary Perforation

Although the routine use of high-pressure postdilatation improves stent expansion, the significant barotrauma imparted to the vessel may result in frank perforation, particularly if oversized or particularly compliant balloons are used either for deployment or postdilatation. In a retrospective analysis, Ellis and colleagues documented a 0.5% incidence of perforation among 12,900 procedures. From most contemporary series with stents, perforation has been reported in 0.2% to 1.0% of patients, though mild perforations are likely underreported. Risk factors for perforation include female gender, advanced age, lesion calcification and angulation, CTOs, and adjunctive atherectomy use. Device oversizing is also a risk for perforation; Colombo reported that the use of markedly oversized balloons (balloon-to-artery ratio >1.2 in the absence of IVUS guidance) has a risk of perforation and vessel rupture ranging from 1.2% to 3.0%. An angiographic classification of the severity of coronary artery perforation has proven useful in determining prognosis and guiding treatment. A type I or concealed perforation is the most common type, and usually requires observation in case delayed tamponade occurs, but no additional specific therapeutic measures. A type II or limited perforation usually appears as a stain or blush at the site of the arterial tear, and can usually be managed with prolonged balloon inflations with or without reversal of anticoagulation. Serial echocardiography, both immediately postprocedure and 24 hours later is indicated to ensure the absence of a growing pericardial effusion. Of note, patients with a history of prior bypass surgery usually have extensive mediastinal adhesions, and perforations are rarely greater than type II. Type III or free-flowing perforations typically appear as a continuous jetlike dye extravasation and may rapidly result in hypotension and tamponade requiring emergency pericardiocentesis. When a type III perforation is visualized, the angioplasty balloon should immediately be inflated at the site of coronary rupture to obtain immediate hemostasis.

Most small perforations can be sealed with prolonged balloon inflations and reversal of unfractionated heparin anticoagulation with protamine, unless a platelet glycoprotein IIb/IIIa receptor antagonist has been given. If the perforation is not readily closed with these measures and is severe, pericardiocentesis with drain placement should be performed to treat/prevent pericardial tamponade, and deployment of PTFE-covered stents provides reliable sealing, usually obviating the need for emergency surgery. Given their porous nature, two overlapping PTFE-covered stent grafts may occasionally be required for hemostasis. Additionally, because these devices are prone to higher rates of restenosis and/or stent thrombosis, high-pressure postdilatation is critical to optimize their results, even if the perforation is sealed. If a stent graft is unable to be delivered to the site of the perforation (as these are bulky devices), emergency surgery is usually required, though the associated rates of morbidity and mortality in this setting are high.

Infectious Endarteritis

Placement of a foreign body endovascular prosthesis carries the rare, albeit theoretical, risk of bacterial endarteritis. In an experimental porcine model, following the induction of transient bacteremia, a significant number of recently placed coronary stents cultured positive for bacteria. The risk of suppurrative endarteritis in stented coronary arteries is extremely rare, however, with only a handful of documented cases in the literature. Although periprocedural antibiotic therapy is thus not routinely recommended, antibiotic prophylaxis may be considered if sterile technique has been breached or if the patient requires invasive procedures associated with transient bacteremia during the first 4 weeks following stenting, though the utility of this approach has never been demonstrated.

Allergic Reactions

Allergic reactions following coronary stent implantation are rare, and can result from allergy to either contrast dye used during the stent procedure, the antiplatelet regimen administered, or in even rarer cases, to the stent device itself. The majority of allergic reactions to contrast dye and the antiplatelet regimen can be managed with the use of antihistamines and corticosteroids; in the case of allergy to the antiplatelet regimen, there is a low rate of cross-reactivity between agents, and switching to a different agent (e.g. prasugrel or ticagrelor) can eliminate the symptoms. With respect to the stent device itself, there do not appear to be adverse reactions to stent implantation even in patients with a history of a metal allergy. In a series of 29 allergic patients who underwent coronary stent implantation, similar rates of adverse clinical outcomes were observed when compared to a matched patient population without metal allergy.

Acute ST-Segment Elevation Myocardial Infarction (See Chapter 30)

Prompt reperfusion with either fibrinolytic therapy or PCI has been demonstrated to improve myocardial salvage and reduce mortality for patients with acute STEMI. Compared to fibrinolytic therapy, timely reperfusion with PCI results in improved myocardial salvage and reduced rates of recurrent ischemia, reinfarction, stroke, and death. Several studies have examined the use of stents compared to balloon angioplasty in patients with STEMI. In a metaanalysis of studies comparing the use of BMS with balloon angioplasty alone, implantation of BMS in STEMI was shown to result in similar rates of mortality and reinfarction, but reduced rates of TVR (Figure 31.16). In light of these results and the fact...
### Table 31.16

<table>
<thead>
<tr>
<th>30-day events</th>
<th>Bare metal stents</th>
<th>Balloon angioplasty</th>
<th>RR [95% CI]</th>
<th>RR [95% CI]</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>Mortality</td>
<td>3.0%</td>
<td>0.97</td>
<td>[0.74, 1.27]</td>
<td>0.83</td>
</tr>
<tr>
<td>Reinfarction</td>
<td>2.0%</td>
<td>2.2%</td>
<td>0.92</td>
<td>[0.66, 1.27]</td>
<td>0.61</td>
</tr>
<tr>
<td>TVR</td>
<td>3.1%</td>
<td>5.1%</td>
<td>0.60</td>
<td>[0.47, 0.77]</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6-12 month events</th>
<th>Mortality</th>
<th>5.1%</th>
<th>5.2%</th>
<th>0.98</th>
<th>[0.79, 1.10]</th>
<th>0.82</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reinfarction</td>
<td>3.7%</td>
<td>3.9%</td>
<td>0.94</td>
<td>[0.74, 1.20]</td>
<td>0.61</td>
<td></td>
</tr>
<tr>
<td>TVR</td>
<td>11.3%</td>
<td>18.4%</td>
<td>0.62</td>
<td>[0.55, 0.69]</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

BMS better PTCA better

---

that stent implantation can optimize acute procedural results (maximizing lumen gain, and reducing abrupt closure and/or recoil), however, stent implantation within or adjacent to a fibroatheroma may result in delayed endothelialization, and appropriate stent sizing can be difficult in cases of STEMI due to recent occlusion of the vessel with resulting layering thrombus, distal vessel spasm, and a desire to not oversize stents for fear of no reflow and distal embolization. These factors, combined with the heightened thrombotic state of patients with STEMI, are potential explanations for the relatively higher rates of stent thrombosis that have been reported after stent implantation in STEMI, although this risk can be somewhat ameliorated with more potent antiplatelet agents.

Following the introduction of DES, there have been at least 15 randomized trials comparing the use of DES versus BMS in patients with STEMI. The largest of these trials was the HORIZONS-AMI trial, which randomized 3,002 patients with evolving STEMI to PES(E) versus BMS at 123 international centers. The primary efficacy and safety endpoints were the 12-month rates of ischemia-driven TLR and MACE (a composite of death, reinfarction, stroke, or stent thrombosis), respectively. Routine angiographic follow-up at 13 months (beyond the primary endpoint) was performed in 1,249 patients. At 12 months, PES compared to BMS reduced the rates of ischemia-driven TLR (4.5% versus 7.5%, HR [95% confidence interval [CI] = 0.59 [0.43, 0.83], P = 0.002) with similar rates of MACE (8.1% versus 8.0%, HR [95% CI] = 1.02 [0.76, 1.36], P = 0.92). The 13-month rates of angiographic binary restenosis were reduced from 22.9% with BMS to 10.0% with PES (RR [95% CI] = 0.44 [0.33, 0.57], P < 0.001). In-stent late loss was reduced with PES from 0.82 ± 0.70 mm to 0.41 ± 0.64 mm (P < 0.001), with comparable rates of infarct artery reocclusion, ulceration, ectasia, and aneurysm formation between the two stent types. The greatest reduction in TLR was evident in patients with one or more risk factors for restenosis (RVD <3.0 mm, lesion length >30 mm, or insulin-treated diabetes mellitus), whereas patients without any of these variables had similarly low rates of TLR with BMS as with PES. Clinical follow-up from HORIZONS-AMI at 3 years has been reported, and demonstrated nonsignificantly different rates of death, reinfarction, stent thrombosis, and MACE with PES and BMS. At 3 years TLR was reduced from 15.1% with BMS to 9.4% with PES (HR [95% CI] = 0.60 [0.48, 0.76], P < 0.001), although the absolute benefit of PES was less pronounced in patients in whom routine angiographic follow-up was not performed (12.7% with BMS versus 8.7% with PES, HR [95% CI] = 0.67 [0.48, 0.93], P = 0.01).

The findings from HORIZONS-AMI parallel the amalgamated experience of randomized trials of DES versus BMS in STEMI. Collectively enrolling almost 8,000 patients, and with follow-up ranging from 3 to 5 years, these trials have demonstrated similar rates of death, reinfarction, and stent thrombosis with both stent types, and relative reductions in TVR with DES compared to BMS. Of note, the most updated metaanalysis of these trials demonstrated a significant interaction between DES versus BMS use and time with respect to the endpoint of stent thrombosis: DES were associated with a greater risk of very late (but not overall) stent thrombosis. Additionally, while the rates of angiographic and clinical restenosis (TLR or TVR) have been consistently reduced with DES compared to BMS in STEMI, many of these studies incorporated routine angiographic follow-up, which may artificially overestimate the absolute benefits of DES compared to BMS (the “oculostenotic reflex”). Further, the overall rates of events related to restenosis are
typically lower among patients with STEMI, partly due to the lesion composition (favoring thrombus over plaque) and also because restenosis in an infarcted territory is less likely to manifest clinically. As such, the overall clinical benefit of DES relative to BMS is somewhat attenuated on an absolute level, and is determined by the patient’s baseline risk of restenosis (Figure 31.17). Due to the thrombotic risk of these patients, maintenance of dual antiplatelet therapy is of particular importance among STEMI patients, in whom future adherence with antiplatelet medications may be difficult to assess. Premature discontinuation of dual antiplatelet therapy within 1 year after DES implantation in STEMI has been strongly associated with subsequent mortality. As such, a detailed risk-benefit analysis of DES versus BMS use in STEMI is warranted.

**Patients with Diabetes Mellitus**

Patients with diabetes have higher rates of angiographic and clinical restenosis than those without diabetes. In general, the pivotal trials in which DES were randomized to BMS revealed comparable relative safety and efficacy with DES in patients with diabetes compared to those without diabetes, although with greater absolute reductions in TLR and TVR in diabetic patients given their higher baseline risk. As a result, DES are typically favored for coronary revascularization over BMS, if PCI is chosen as a revascularization strategy.

The most appropriate choice of specific DES among patients with diabetes is unknown. Most prior studies have shown comparable rates of in-stent late loss with PES in patients with diabetes versus those without diabetes, suggesting that the multiple pathways with which paclitaxel interferes with restenosis (by affecting microtubular function) makes its action relatively independent of the diabetic state. Considerable controversy has existed, however, whether the greater suppression of late loss from stents which elute potent –limus analogue is preserved in patients with diabetes, given that the effect of rapamycin in interfering with the cell cycle is regulated by glycosylation-dependent enzymes. In this regard, several small-to-moderate sized studies have provided conflicting results. For example, among 379 patients with diabetes randomized to SES versus PES(E) in the REALITY trial, the rates of restenosis and clinical events were comparable with both stents. In contrast, in the randomized 250-patient ISAR-Diabetes trial, SES compared to PES resulted in a greater reduction in late loss at 6 months, but nonsignificantly different rates of TLR at 9 months.

This issue has more recently been addressed in a pooled patient-level analysis of 1,869 patients from the SPIRIT II, SPIRIT III, SPIRIT IV, and COMPARE trials of EES versus PES. In this analysis, while EES was associated with superior outcomes compared to PES among nondiabetic patients, in patients with diabetes, the rates of composite adverse events at 1 year (and their components) were almost identical between the two stent types. A strongly positive interaction (P < 0.0001) was present between diabetes and the stent platform with respect to 1-year events, confirming the observation of a statistically superior effect of EES over PES in nondiabetic patients (and similar outcomes in diabetic patients). While there are limited randomized data in diabetic patients with other –limus analogue DES, the ZES(R) recently received a specific FDA indication for use in patients with diabetes based upon the overall performance of the stent in patients with diabetes. Pooling the results of the ZES(R) clinical trial program, 878 patients with diabetes were treated with ZES(R), with a 12-month rate of target vessel failure of 7.8%, which was superior to a historical performance goal of 14.5%. Thus, potent rapamycin analogue-eluting stents have been demonstrated to be effective in patients with diabetes.

**Figure 31.17** HORIZONS-AMI: Rates of 12-month ischemic target lesion revascularization according to risk strata (from Stone et al., JACC 2010). The risk of ischemic target lesion revascularization is similar in both stents in patients at low risk for restenosis but more pronounced among patients at intermediate and high risk. HR, hazard ratio.
Often the most critical revascularization decision in patients with diabetes mellitus is the mode of revascularization, i.e., whether to perform PCI or CABG. A metaanalysis of four randomized trials has demonstrated comparable 5-year rates of death, MI, or stroke in patients with diabetes treated with BMS or CABG; however, the rate of repeat revascularization procedures was significantly greater among BMS-treated patients. In the CARDia trial, 510 patients with diabetes mellitus and multivessel disease were randomized to PCI (with either BMS (31%) or SES (69%) – DES were used after SES became available) versus CABG. The primary endpoint of all-cause death, MI, or stroke at 1 year occurred in 10.5% of patients treated with CABG versus 13.0% of patients treated with PCI (HR [95% CI] = 1.25 [0.75 to 2.09], P = 0.39). When comparing patients treated during the time in which SES were available, the 1-year event rates were 12.4% versus 11.6% for CABG versus SES (HR [95% CI] = 0.93 [0.51 to 1.71], P = 0.82). Whereas CARDia was too underpowered to be definitive and has only reported 1-year follow-up, the ongoing FREEDOM trial, which is enrolling more than 2,000 diabetic patients to SES or PES versus CABG with a follow-up of 6.75 years, will provide important evidence-based guidance for this high-risk subgroup of patients with multivessel disease.

For patients with diabetes who undergo PCI, specific issues that require foresight by the operator include the treatment of diffuse disease and disease in small vessels. Because the relative and absolute risks of restenosis and stent thrombosis are higher in diabetic patients, assiduous attention to procedural technique and details is critical. Specific attention should be paid to appropriate stent length (using the least amount of stent length in order to cover obstructive lesions) and optimization of stent lumen area to minimize the effects of a more aggressive intimal hyperplastic response.

Multivessel and Left Main Disease

Although they are distinctly different conditions, revascularization decisions for patients with left main and multivessel disease are often considered together because historically the default strategy for these lesion subtypes has been CABG. Patients with multivessel disease treated with PCI have higher rates of restenosis and stent thrombosis than those with single-vessel disease, especially when diffuse disease, small vessels, CTOs, and bifurcation lesions requiring treatment are present. In contrast, while restenosis and thrombosis are relatively rare after stenting the relatively short, large-caliber left main segment, PCI failure in the left main jeopardizes a sufficiently large amount of myocardium to entail a high risk of mortality.

While there have been several trials examining the use of PCI versus CABG for multivessel disease, the majority of these trials have been conducted prior to the introduction of DES. A widely cited metaanalysis by Hlatky et al. was performed using individual patient data from 10 randomized trials of PCI versus CABG in 7,812 total patients with multivessel disease. However, the majority of included trials were of balloon angioplasty alone compared to CABG; BMS were used in only four of these trials, and no study included in this analysis utilized DES. Among patients enrolled in trials using BMS, follow-up up to 5 years has demonstrated comparable rates of death, MI, or stroke between BMS and CABG (16.7% versus 16.9%, P = 0.69), with no heterogeneity noted in patients with diabetes versus those without diabetes or with double- versus triple-vessel disease. However, the 5-year rates of unplanned revascularization were significantly higher with BMS compared to CABG (29.0% versus 7.9%, P < 0.001).

Prior to the introduction of DES, there had been no randomized trials of PCI versus CABG in patients with unprotected left main disease, because observational studies had shown a high rate of procedural failure and late sudden cardiac death with balloon angioplasty, and unacceptably high restenosis and MACE rates with BMS in this anatomic subgroup. In a small prospective trial, Erglis et al. randomized 103 patients with left main disease to BMS versus PES, and demonstrated that PES resulted in significantly lower 6-month rates of binary restenosis (6% versus 22%, P = 0.02) and MACE (13% versus 30%, P = 0.04). The ISAR left main investigators then randomized 650 patients with left main disease to PES versus SES, and found comparable 1-year rates of composite death, MI, or TLR (13.6% versus 15.8%, P = 0.44), definite stent thrombosis (0.3% versus 0.7%, P = 0.57), and restenosis (16.0% versus 19.4% P = 0.30) with the two stent types. In another small randomized trial, the LEMANS investigators assigned 105 patients to either PCI with BMS or DES (the latter used in only 35% of patients) versus CABG. The primary endpoint of change in LVEF 12 months after the procedure was significantly greater with PCI than with CABG. PCI also had a significantly better early safety profile.

The most contemporary and relevant examination of the relative safety and efficacy of DES versus CABG in multivessel and left main coronary artery disease is the SYNTAX trial, which randomized 1,800 patients with either triple vessel disease (N = 1,095) and/or left main disease (N = 705) to PES(E) versus CABG, with the primary aim of demonstrating noninferiority of PES to CABG. The primary endpoint of SYNTAX, the 1-year composite rate of all-cause mortality, stroke, MI, or unplanned repeat revascularization, however, occurred significantly less commonly with CABG than with PES, and thus noninferiority could not be claimed (Figure 31.18, left). However, the major differences in the primary study endpoint were driven by greater rates of repeat revascularization with PCI compared to CABG (although the difference between PCI and CABG was greatly reduced with PES than in the earlier era with BMS). When considering the composite endpoint of death, MI, or stroke, there were no differences between the two study arms, and similarly, the rates of death or MI individually were similar between PCI and CABG. However, the 1-year rate of stroke was significantly lower with PCI than
The SYNTAX trial was a randomized controlled trial comparing coronary artery bypass graft surgery (CABG) with PCI using paclitaxel-eluting stents (PES) for patients with three-vessel disease and left main disease. The primary endpoint was a composite of death, myocardial infarction (MI), stroke, or unplanned repeat revascularization. The trial included 1,800 patients, with 819 patients assigned to CABG and 879 patients to PCI. The 4-year results showed a significant improvement in the primary composite endpoint with CABG compared to PCI, particularly in patients with triple-vessel disease and high SYNTAX scores. CABG was associated with a lower all-cause mortality (8.8% vs. 11.7%, p = 0.048) and a lower rate of MI (3.8% vs. 8.3%, p < 0.001). A borderline interaction (p = 0.11) was present between the randomization arm and the primary 1-year endpoint for patients with left main versus triple-vessel disease in SYNTAX, with CABG showing better outcomes in triple-vessel disease patients. The SYNTAX score, an anatomic-based risk score, was used to stratify patients based on their risk, with CABG being more beneficial for patients with high or intermediate SYNTAX scores. The results of PCI in patients with complex coronary artery disease may be further optimized by using better stents and pharmacotherapy, as seen in the ongoing EXCEL trial, which randomized 3,100 patients with unprotected left main disease and a low to moderate SYNTAX score to PCI with everolimus-eluting stents (EES) or CABG.
Table 31.7 Four-Year Outcomes from the SYNTAX Trial, Stratified by Triple Vessel Versus Left Main Disease, According to Syntax Score Tertile

<table>
<thead>
<tr>
<th></th>
<th>Low SYNTAX Tertile</th>
<th></th>
<th>Intermediate SYNTAX Tertile</th>
<th>PES</th>
<th>CABG</th>
<th>P value</th>
<th></th>
<th>High SYNTAX Tertile</th>
<th>PES</th>
<th>CABG</th>
<th>P value</th>
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<tr>
<td></td>
<td>PES</td>
<td>CABG</td>
<td>P value</td>
<td>PES</td>
<td>CABG</td>
<td>P value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triple vessel disease</td>
<td>n=181</td>
<td>n=171</td>
<td>30.4% 24.7% 0.27</td>
<td>n=207</td>
<td>n=208</td>
<td>&lt;0.001</td>
<td>n=155</td>
<td>n=166</td>
<td>37.9% 21.2% &lt;0.001</td>
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<tr>
<td>MACCE</td>
<td>15.8% 14.8%</td>
<td></td>
<td>18.6% 12.4%</td>
<td>22.3% 11.0% 0.008</td>
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<tr>
<td>- Death, MI, or stroke</td>
<td>9.0% 8.7%</td>
<td></td>
<td>18.6% 12.4% 0.048</td>
<td>14.5% 6.5% 0.02</td>
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<tr>
<td>- Death</td>
<td>8.2% 4.9%</td>
<td></td>
<td>10.5% 3.1% 0.004</td>
<td>7.9% 1.9% 0.01</td>
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</tr>
<tr>
<td>- MI</td>
<td>1.2% 3.9%</td>
<td></td>
<td>2.5% 3.6%</td>
<td>5.1% 2.6% 0.31</td>
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<td></td>
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<tr>
<td>- Stroke</td>
<td>21.2% 11.6% 0.02</td>
<td></td>
<td>21.0% 8.3% &lt;0.001</td>
<td>26.7% 11.2% &lt;0.001</td>
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<tr>
<td>Left main disease</td>
<td>n=118</td>
<td>n=104</td>
<td>26.0% 28.4% 0.60</td>
<td>n=103</td>
<td>n=92</td>
<td>42.6% 26.3% &lt;0.003</td>
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</tr>
<tr>
<td>MACCE</td>
<td>12.3% 14.2%</td>
<td></td>
<td>14.8% 20.3%</td>
<td>23.1% 18.5% -</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Death, MI, or stroke</td>
<td>7.1% 9.2%</td>
<td></td>
<td>8.0% 14.7%</td>
<td>17.9% 10.5% 0.06</td>
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</tr>
<tr>
<td>- MI</td>
<td>4.3% 3.1%</td>
<td></td>
<td>6.0% 4.6%</td>
<td>10.9% 6.1% -</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Stroke</td>
<td>1.8% 4.1%</td>
<td></td>
<td>1.0% 3.6%</td>
<td>1.6% 4.9% -</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Revascularization</td>
<td>18.2% 16.8%</td>
<td></td>
<td>20.2% 17.0%</td>
<td>31.3% 11.8% &lt;0.001</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

MI, myocardial infarction; MACCE, major adverse cardiac or cerebrovascular events (death, MI, stroke, or revascularization); PES, paclitaxel-eluting stents; CABG, coronary artery bypass graft surgery.

Chronic Total Occlusions

Clinical and angiographic restenosis rates after both balloon angioplasty and stent implantation are increased following PCI of CTO compared to nonoccluded stenoses, due principally to an increased incidence of diabetes, greater lesion length, plaque mass, and calcification.329,330 Additionally, during crossing of CTO lesions, wires and devices are sometimes advanced in the subintimal space; without stenting, these segments are likely to reocclude. Stenting of CTO lesions has thus become the default strategy when PCI is planned, and the use of DES is preferred. In a 200-patient randomized trial of SES versus BMS, the use of SES resulted in significant reductions in binary angiographic restenosis (7% versus 36%, P < 0.001) and TLR (4% versus 19%, P < 0.001), with reductions in clinical restenosis maintained at up to 4 years of clinical follow-up.331 A large number of retrospective, nonrandomized, and historically controlled comparisons of DES and BMS have similarly demonstrated approximately 60% reductions in clinical restenosis endpoints with DES compared to BMS. However, despite similar hazards of mortality and MI with DES compared to BMS in a meta-analysis aggregating this data, a trend toward increased stent thrombosis was observed with first-generation DES (RR: 2.79, 95% CI: 0.98-7.97, P = 0.06), merits some concern.332 Additionally, SES has been associated with a 16% rate of stent fracture when used in CTO lesions, particularly in long overlapping segments of disease.190 Studies are ongoing to determine whether these results may be improved upon by second-generation stents which are more fracture-resistant, such as EES and ZES(R).333 A number of advances in CTO technique have renewed the interest in tackling these lesions, which historically have had the lowest rates of procedural success among all lesions undergoing PCI. Critical issues related to stenting of CTO lesions include adequate selection of CTOs that are in viable and/or ischemic myocardial territories, minimizing stent overlap and overall stented length as much as possible, avoidance of stent implantation in diffusely diseased distal territories, and optimization of lumen area in vessels that are chronically underfilled (and therefore can appear smaller...
than they actually are in the reperfused state). Finally, prior to CTO recanalization and stent implantation, it is critical to ascertain the ability of a patient to adhere to dual antiplatelet therapy because stent thrombosis of recanalized CTO lesions will likely result in acute MI due to regression of collaterals supplying the CTO territory.314

**Bifurcation Lesions**

Bifurcation lesions represent 20% or more of stenoses undergoing angioplasty, and PCI of coronary bifurcation lesions is associated with increased procedural complications and worsened long-term outcomes. Due to the higher rates of clinical restenosis at bifurcation lesions, the use of DES for the main vessel of a bifurcation lesion has become the standard of care for bifurcation disease. For true bifurcation lesions (atherosclerotic involvement of both the parent and side branch), the major decision is whether to undertake a provisional or dual-stent strategy. With **provisional stenting**, the main vessel is stented (often after optimal predilatation of the side branch), and the side branch is dilated or stented only for a truly unacceptable result (typically a diameter stenosis >50% or severe dissection). A strategy of provisional stenting of the side branch is the generally accepted current approach to bifurcation disease unless there is significant high-grade and lengthy disease within the side branch.335,336 This approach is also usually preferred if the parent vessel is large and the side branch relatively small. Alternatively, when both the parent vessel and side branch are large (≥2.5 mm), especially when the side branch arises at a shallow angle, planned stenting of both branches may be considered. Various approaches to dual stenting of bifurcation lesions have been developed and are briefly outlined below (Figure 31.19).337

**T-Stent Technique**

A stent is deployed at the ostium of the side branch, followed by a second stent in the parent vessel. Unless the angle of origin of the side branch is 90°, however, the operator is faced with the dilemma of whether it is better to leave a portion of the ostial side-branch lesion unstented or risk having part of the stent protrude into the parent vessel (making subsequent advancement of the parent vessel stent difficult or impossible). A modification of this technique to maximize ostial side branch coverage is the T-and-protrusion technique, where the main branch stent is deployed first, followed by stenting of the side branch with a balloon angioplasty catheter in the main vessel. The side-branch stent is brought back to protrude slightly into the main branch to maximize ostial coverage, and is then deployed, impinging on the main branch balloon, making a “T.” A kissing balloon inflation (into the main branch and side branch simultaneously) is then performed to ensure adequate flow into both branches without compromise.

**“Culotte” Stent Technique**

A stent is deployed into the side branch with extension into the proximal aspect of the parent vessel. A wire is then passed through the side struts of this stent and into the distal parent vessel. After balloon dilatation, a second stent is passed through the side struts into the distal, so that the proximal ends of the first and second stents overlap in the proximal vessel. This technique is the most technically complex, but offers excellent scaffolding and coverage of the bifurcation.

**“Crush” Stent Techniques**

After predilatation of both limbs, two stents are positioned simultaneously in the side branch and main branch. The side-branch stent extends into the proximal main vessel 2 to 3 mm (or less in the “mini-crush”); the parent branch stent extends at least several millimeters more proximally. The side-branch stent is inflated first, trapping the main-branch stent delivery system. After confirmation of patency without dissection in the side branch, the side-branch guide wire and stent delivery system are removed, and the main-branch stent is implanted, “crushing” the side-branch stent. Following this, the side-branch stent is rewired and simultaneous kissing balloon inflations are performed (it is generally recommended that all bifurcation stent techniques be completed by kissing balloon technique). There have been many modifications of this technique, including modified sequences of stent implantation such as in the “reverse crush,” which is applicable when side-branch stenting was not initially planned. In this case, after main branch implantation, a second stent is placed in the side branch extending into the proximal parent vessel (within the previously placed stent), and a balloon angioplasty catheter is placed in the main vessel. The side-branch stent is then deployed, impinging on the balloon. After removal of the side-branch stent delivery system and wire, the main-branch balloon is then inflated to crush the proximal portion of the side-branch stent, and a final kissing balloon inflation is performed. Balloon crushing of the side-branch stent can also be used as the initial approach (prior to main branch deployment) in the “step crush” technique, a technique that is useful when smaller guide and sheath sizes are used). Other modifications include performance of additional kissing balloon inflations prior to main branch deployment (e.g. “double-kissing crush” technique) which can improve procedural outcomes.338

The crush technique is simpler than the culotte technique and affords excellent coverage of the carina; however, a randomized trial of the two techniques demonstrated a trend toward more frequent periprocedural enzymatic elevation with the crush technique but similar rates of late events with both techniques.339 Recrossing the crushed side-branch stent with a guidewire and balloon can be challenging and time consuming, however, but is essential because late outcomes are significantly improved following a simultaneous kissing balloon inflation with this technique.340
**Simultaneous Kissing Stents/V-Stenting**

Two stents are deployed simultaneously over separate guide-wires: one in the parent vessel and one in the side branch. For simultaneous kissing stents, both stents extend side by side in the main vessel proximal to the bifurcation (for V-stenting, these stents are deployed at the ostia of both branches, minimizing the length of the “carina”). Although this technique offers the advantage of simplicity and control of both vessels, a new, more proximal carina is created in the center of the proximal parent vessel, which is unlikely to endothelialize fully and can be very difficult to wire if repeat PCI is required. Also, placement of an additional stent is problematic should a proximal dissection occur.

**Bifurcation Summary**

An exhaustive review of the pros and cons of these techniques is beyond the scope of this chapter. However, as a general rule, a provisional strategy to bifurcation lesions is preferred as it can result in safer procedural outcomes, and, by minimizing the amount of stent at the carina, can minimize the risks of subsequent stent thrombosis. When treating bifurcation lesions provisionally, it is generally recommended to wire and protect all side branches ≥1.5 to 2.0 mm using a “keep-it-open” strategy in order to prevent and/or facilitate management of side branch compromise and occlusion (see stent complications section above). If an upfront two-stent strategy is selected, a familiarity with the techniques is necessary, because the majority of these dual-stent techniques are technically complex, require use of a larger (7F or 8F) guiding catheter, and can pose difficulty in reaccessing the parent vessel or side branch through overlapping metallic elements.

A variety of novel strategies for the treatment of bifurcation disease with drug-eluting balloons is also currently
undergoing evaluation, but current data using drug-eluting balloons in native coronary stenoses have been mixed. Additionally, several dedicated drug-eluting bifurcation stent systems have been designed and are under investigation. Bifurcation stent systems can be classified as those that facilitate access to the side branch to simply the PCI procedure, versus novel stents designed to address the unique geometric challenges of the bifurcated stenosis. Initial experiences with the Axxess self-expanding nitinol stent (Biosensors International, Switzerland) (coated with the bioabsorbable polymer PLLA which elutes the antiproliferative rapamycin analogue biolimus A9) have demonstrated low rates of restenosis of both the main vessel and side branch in both true bifurcation lesions as well as in the distal bifurcation of the left main coronary artery. This “reverse cone” stent is designed to adapt to and cover the main parent vessel and the bifurcation carina, and is used in conjunction with dedicated DES of one or both branches when necessary. Preliminary data have also been published on the use of the Stentys™ paclitaxel-eluting side branch access stent and the Taxus Petal™ dedicated bifurcation stent; further clinical data are awaited in order to determine the long-term advantages of these stents for the treatment of bifurcation disease.

Saphenous Vein Grafts

The most common cause of recurrent ischemia following CABG surgery is atheromatous degeneration within the body of an SVG, and BMS have been associated with improved outcomes compared to balloon angioplasty in SVG intervention. While DES have the potential to further lower rates of restenosis of the target lesion within SVGs, disease progression at nontarget sites within SVGs is frequent, and additionally, due to the large caliber of most SVGs, the “tolerated late loss” within SVG lesions is typically greater than in native coronary vessels. Two small randomized trials of DES versus BMS for critical SVG stenoses were conducted early in the DES experience, and demonstrated lower rates of angiographic restenosis with DES. With extended follow-up to a median of 32 months in one of these studies, however, the antirestenotic advantage of SES compared to BMS was lost, and SES was associated with higher mortality. A more recent larger randomized trial, the ISAR-CABG trial, randomized 610 patients to either BMS, SES, PES, or biodegradable polymer SES. At 1 year, the use of all DES versus BMS was associated with reductions in TLR (7% versus 13%, P = 0.01) as well as composite death, MI, and TLR (15% versus 22%, P = 0.02), with no differences observed in overall mortality or stent thrombosis. Further follow-up of this trial will help to critically assess the occurrence of late safety outcomes.

At present, for patients that can tolerate longer-term regimens of dual antiplatelet therapy, DES are typically preferred for either focal disease in large graft conduits or for diffuse graft degeneration (if native coronary artery PCI or repeat surgery is not an option). Notably, a small pilot study of prophylactic “sealing” of moderate, noncritical SVG lesions with PES in order to prevent disease progression within SVGs was superior to medical therapy alone, suggesting a possible preventive role for DES in degenerating SVG lesions prior to their becoming critical. A large randomized trial is required, however, before such an approach is undertaken.

CONCLUSION: CURRENT PERSPECTIVES AND FUTURE DIRECTIONS

The development and evolution of the coronary stent has resulted in remarkable progress in the lesser invasive treatment of coronary artery disease. Over the past two decades, coronary stenting has emerged as the dominant technology for catheter-based coronary revascularization. The availability of stents with excellent deliverability and scaffolding, the demonstration that stenting improves acute and long-term outcomes in a wide variety of lesion types, the development of effective and better-tolerated pharmacologic regimens to prevent stent thrombosis, and now the marked suppression of restenosis with antiproliferative bioactive coatings have facilitated the application of stenting to almost every patient and lesion subset. However, although infrequent, stent thrombosis and restenosis still occur with even the best DES, and the reliance on long-term, dual antiplatelet therapy is a major limitation for many patients. Novel DES approaches aimed at tackling this issue under active development and current study include further investigation of second- and third-generation durable polymer platforms with the ability to passivate the vascular endothelium, dual-agent DES that may also confer improved safety and/or efficacy, biodegradable polymer and polymer-free stents designed to minimize reactions to the drug carrier, and finally, fully bioabsorbable scaffolds that offer the potential to eliminate late stent thrombosis. Further enhancements to stent design will additionally allow these devices to continue to improve with respect to deliverability and ease of use, and novel adjunctive drugs and devices may further facilitate the use of PCI for the most complex patients and coronary anatomies. As such, the coronary stent is certain to remain the foundation for the minimally invasive treatment of coronary atherosclerosis for the foreseeable future.

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Chapter 31 Coronary Stenting


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General Overview of Interventions for Structural Heart Disease

MAURO MOSCUCCI, JOHN D. CARROLL, and JOHN G. WEBB

As Courmand stated in his Nobel Prize acceptance speech in 1956 for his work on the pulmonary circulation, “the cardiac catheter was … the key in the lock.” Over the next 40 years, the lock that was opened has played a fundamental role in our understanding of the pathophysiology of cardiovascular disease. Since then, the cardiac catheter has further evolved into a therapeutic tool that is allowing us to tackle cardiovascular disease in a way that was probably unthinkable at the time of Courmand’s lecture. More recently, the historic evolution of cardiac catheterization, coronary angiography, percutaneous coronary interventions, and vascular interventions has been paralleled by the development of the exciting field of interventions for structural heart disease, defined as a broad range of congenital or acquired pathologies involving the myocardium and cardiac valves. The introduction of valvuloplasty in the 1980s after the initial work in the 1950s by Rubio-Alvarez et al., and the more recent development of new technology for closure of intracardiac shunts and for percutaneous valve repair and replacement have led to a new frontier in interventional cardiology. This chapter provides a general overview of this developing field. The reader is referred to other sections of this textbook for more detailed information on techniques and indications of specific interventions.

CLASSIFICATION OF INTERVENTIONS FOR STRUCTURAL HEART DISEASE

Interventions for structural heart disease can be classified into six broad categories: (1) closure of congenital and acquired cardiac defects; (2) percutaneous valve interventions; (3) myocardial interventions or direct interventions on the heart muscle; (4) creation of new conduits and new communications between cardiac chambers; (5) pericardial interventions; and (6) miscellaneous interventions (Table 32.1). Each intervention requires an in-depth knowledge of the pathophysiology and cardiac anatomy of the condition being treated, the acquisition of specific technical skills, and knowledge of indications for the procedure performed as well as of potential complications and bailout techniques.

Closure of Congenital and Acquired Cardiac Defects

This category includes closure of atrial and ventricular septal defects, closure of perivascular ductus arteriosus, and closure of ventricular pseudoaneurysms (Figure 32.1). Beyond standard cardiac catheterization competency, additional knowledge base includes a full understanding of atrial and ventricular anatomy, understanding of indications and contraindications for closure, knowledge of occluder devices, specialized guidewires, and arterial sheath, and the development of technical skills needed for access to ventricular septal defects and ventricular pseudoaneurysm. Details on techniques and indications are listed in Chapters 35 and 45.

Percutaneous Valve Interventions

The pioneering work done in the 1950s by Rubio-Alvarez on tricuspid and pulmonic valvuloplasty was followed 30 years later by the development of percutaneous mitral and aortic balloon valvuloplasty. The long-term results with mitral valvuloplasty were encouraging and were confirmed in head-to-head comparisons with surgical commissurotomy. Thus, today mitral valvuloplasty is considered a valid alternative to surgical commissurotomy (see Chapter 33). In contrast, the initial enthusiasm for aortic valvuloplasty in the adult was met by disappointing intermediate- and long-term results, leading to a class IIb indication for aortic valvuloplasty in the
Table 32.1 General Classification of Interventions for Structural Heart Disease

<table>
<thead>
<tr>
<th>Classification</th>
<th>Procedures</th>
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</table>
| Closure of congenital and acquired cardiac defects | - Atrial septal defect closure  
- Ventricular septal defect closure  
- Patent foramen ovale closure  
- Acquired post-myocardial infarction ventricular septal defects closure  
- Post-myocardial infarction pseudoaneurysm closure  
- Patent ductus arteriosus closure |
| Percutaneous valve interventions | - Pulmonic valvuloplasty  
- Transcatheter pulmonary valve replacement  
- Tricuspid valvuloplasty  
- Mitral valvuloplasty  
- Aortic valvuloplasty  
- Percutaneous mitral valve repair  
- Transcatheter aortic valve replacement  
- Closure of paravalvular leaks. |
| Myocardial interventions | - Interventions with cell-based therapy  
- Alcohol septal ablation for hypertrophic cardiomyopathy |
| Intervention for the creation of intracardiac shunts | - Blade atrial septostomy  
- Balloon atrial septostomy  
- Balloon atrial septostomy for pulmonary hypertension  
- Balloon atrial septostomy to vent left ventricle in patients on percutaneous cardiopulmonary bypass |
| Pericardial interventions | - Pericardiocentesis  
- Balloon pericardiostomy  
- Epicardial access through the pericardial space |
| Miscellanea interventions | - Percutaneous cardiopulmonary bypass  
- Left atrial appendage exclusion  
- Transcatheter embolization of extracardiac shunts |

2008 focused update of the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease. "Class IIb. 1. Aortic balloon valvotomy might be reasonable as a bridge to surgery in hemodynamically unstable adult patients with AS who are at high risk for AVR. (Level of Evidence: C) 2. Aortic balloon valvotomy might be reasonable for palliation in adult patients with AS in whom AVR cannot be performed because of serious comorbid conditions." The recent introduction of transcatheter aortic valve replacement has created a revolution in the management of patients with aortic stenosis, and it has resulted in a resurgence of aortic valvuloplasty as a key component of transcatheter aortic valve replacement (Chapter 33). Similar developments are occurring for the management of mitral valve disease through percutaneous mitral valve repair and replacement (see Chapter 33), and also for the pulmonic valve (see Chapters 33 and 35). Thus, percutaneous valve interventions are emerging as an alternative to surgery in high-risk patients, and as a new option for patients who otherwise are not surgical candidates.

The growth of percutaneous valve interventions has been paralleled by a growth in interventions for the management of paravalvular leaks. It has been estimated that paravalvular leaks can occur in 5% to 17% of patients following surgical valve replacement. In addition, paravalvular leaks are a recognized occurrence following transcatheter aortic valve replacement. The clinical spectrum varies from asymptomatic status to heart failure and/or severe hemolysis. Reoperation in these patients is associated with high morbidity and mortality. Thus, there has been a large body of work attempting to address this problem with transcatheter techniques, and using a variety of devices from vascular coils to vascular plugs (Figures 32.2 and 32.3). Additional interventional skills required for the management of paravalvular leaks include proficiency in transseptal catheterization, access to the left ventricle through direct apical puncture, the ability to evaluate 3D echocardiographic and CT reconstructions of the defect (Figure 32.4), and familiarity with guidewire snaring and exteriorization techniques (Figure 32.5). Currently, there are no devices that have been developed specifically for the management of paravalvular leaks. It is hoped that the growing experience will lead to the development of dedicated devices.

Myocardial Interventions

This group includes alcohol septal ablation and the new field of interventions with cell therapies. Transcatheter ablation
of the septum with ethanol was first reported by Sigwart in 1995. The procedure entails inducing a controlled myocardial infarction by injecting absolute ethanol in the septal perforator branch supplying the area of the septum participating in the creation of left ventricular outflow tract (LVOT) obstruction. Confirmation of selection of the proper septal branch can be obtained by injecting in the septal artery echocardiographic contrast (Figure 32.6). The procedure has been shown to reduce the LVOT gradient and to provide symptomatic relief in patients with LVOT obstruction and with symptoms refractory to medical therapy. Criteria for selection of patients for septal reduction therapy with either surgical myectomy or alcohol ablation are shown in Table 32.2. Significant controversy still exists regarding the long-term risk of sudden death in patients undergoing alcohol septal ablation, although a recent meta-analysis has suggested that the benefits of alcohol septal ablation are similar to the benefits of surgical myectomy. Thus, the most recent 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy include alcohol septal ablation as a class Ila indication in patients with refractory symptoms who are not surgical candidates, and as a class IIb
Figure 32.2 Paravalvular leak closure with coils in a patient with severe hemolytic anemia. A. Right anterior oblique view of a prosthetic mitral valve. A hydrophilic wire has been advanced into the left ventricle a paravalvular mitral defect. The transesophageal echocardiogram probe can be seen in the top portion of the figure. B and C. Radiographic images after deploying the coils are shown. Both coils have been symmetrically deployed across the mitral valve ring. (Reproduced with permission from Moscucci M, et al. Coil embolization of a periprosthetic mitral valve leak associated with severe hemolytic anemia. Circulation 2001;104(16):E85–E86.)

indication for “eligible adult patients with hypertrophic cardiomyopathy (HCM) with severe drug-refractory symptoms and LVOT obstruction when, after a balanced and thorough discussion, the patient expresses a preference for alcohol septal ablation”. Given the complexity of HCM and the fact that alcohol ablation has a steep learning curve and unusual complications (Table 32.3), it has been recommended that alcohol ablation should be performed only by experienced operators within a multidisciplinary program, and in centers offering comprehensive care for patients with HCM. The
guidelines for the management of patients with HCM further define an experienced operator as “individual operator with a cumulative case volume of at least 20 procedures or an individual operator who is working in a dedicated HCM program with a cumulative total of at least 50 procedures.”

Cardiac cell-based therapy has emerged as a new exciting field that hopefully will provide novel therapeutic options for patients with dilated or ischemic cardiomyopathies. The reader is referred to Chapter 36, which provides a detailed description of cell therapy lines as well as methods for myocardial delivery.

Interventions for the Creation of Intracardiac Shunts

The development of the Fontan procedure was a major breakthrough in the management of patients with single ventricles, tricuspid atresia, and pulmonary atresia. It involves redirecting venous blood to the pulmonary arteries through an intracardiac or extracardiac cavopulmonary connection, or via an atrio pulmonary connection, thus bypassing the ventricle. Pulmonary blood flow will be driven by a pressure gradient between the venous circulation and the pulmonary circulation. Any alteration in pulmonary vascular resistance will result in an increase in venous pressure leading to right-sided heart failure and in some patients to protein-losing enteropathy secondary to the high venous pressure and bowel edema. In these patients, the creation of a small right-to-left shunt through a fenestration can be beneficial in reducing venous pressure and increasing cardiac output. The fenestration can be performed at the time of surgery or later percutaneously using balloon septostomy (see Chapter 35). Balloon atrial septostomy has also been used in patients with pulmonary hypertension to increase left ventricular filling at the expense of mild systemic

Figure 32.3 Paravalvular leak closure in a bioprosthetic mitral valve. In this case, given the size of the defect, two Amplatzer ventricular septal defect occluders were implanted (arrows). As shown by the position of the devices (arrows), the deployment was performed in a retrograde fashion using a transapical approach. (Courtesy of Claudia C. Martinez, M.D.)

Figure 32.4 Online 3D echocardiographic reconstruction during closure of a paravalvular mitral valve leak. An Amplatzer septal occluder is being deployed (single arrow). There is still a residual defect as shown by the double arrow. In cases like this, two devices can be used to achieve complete closure of the leak.
Closure of paravalvular leak with the anchor wire technique. Sequential device deployment (A): an extra support guidewire (arrowhead) is passed across the paravalvular defect, through the aortic valve, and is exteriorized through a femoral arterial sheath, creating an arteriovenous rail. An 8F Flexor Shuttle sheath (Cook Medical) is advanced across the paravalvular defect (arrow). B. A vascular plug (arrowhead) is deployed in the defect while the arteriovenous wire loop is maintained through the defect (arrow). C. A second vascular plug is deployed (arrow) alongside the first device, leaving the arteriovenous loop in position (arrowhead). D. Final position with two devices released (arrows) and the arteriovenous loop wire removed. (Reproduced with permission from Rihal CS, et al. Principles of percutaneous paravalvular leak closure. JACC Cardiovasc Interv 2012;5(2):121–130.)

Pericardial Interventions

Pericardiocentesis, balloon pericardiotomy, and pericardial access to the epicardium are described in Chapters 38, 39, and 44. Interventions for structural heart disease involve manipulation of catheters in cardiac chambers, which might be rarely complicated by the development of cardiac perforation. Thus, proficiency in pericardiocentesis should be part of the skill set of contemporary interventional cardiologists.

Miscellanea Intervention

This last group includes percutaneous cardiopulmonary bypass (see Chapter 27), left atrial appendage exclusion,
Intracatheter embolization of extracardiac shunts (see Chapter 35).

**TRAINING AND CREDENTIALING CRITERIA**

Training and credentialing criteria for structural heart disease interventions have not been fully developed, although there have been several consensus statements and position papers that have provided recommendations. Table 32.4 summarizes key competency criteria. For a detailed list of knowledge base elements and interventional skills related to each procedure, the reader is referred to an excellent recent expert consensus statement from the Society for Cardiovascular Angiography and Interventions endorsed by the American College of Cardiology Foundation. The consensus recommendation is that training in structural heart disease interventions or in interventions for adult with congenital heart disease should include at least 1 year of additional dedicated time, recognizing that learning in structural heart disease is a lifelong endeavor. Detailed credentialing criteria for each procedure listed in this chapter are yet to be defined. However, it should be noted that third-party payers, at least in the United States, have been developing criteria for

<table>
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<tr>
<th>Clinical, Hemodynamic and Anatomic Criteria for Selection of Patients for Septal Reduction Therapy in Patients with Hypertrophic Cardiomyopathy</th>
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<tr>
<td><strong>Clinical</strong></td>
</tr>
<tr>
<td><strong>Hemodynamic</strong></td>
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<tr>
<td><strong>Anatomic</strong></td>
</tr>
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</table>

LVOT, left ventricular outflow tract; NYHA, New York Heart Association; SAM, systolic anterior motion.
Table 32.3 Complications of Alcohol Septal Ablation

<table>
<thead>
<tr>
<th>Related to Cardiac Cath</th>
<th>Related to PCI</th>
<th>Related to ASA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>Contrast nephropathy</td>
<td>Dissection</td>
</tr>
<tr>
<td>MI</td>
<td>Atheroembolism</td>
<td>Perforation</td>
</tr>
<tr>
<td>Stroke</td>
<td>Local complications</td>
<td>Distal embolization</td>
</tr>
<tr>
<td>TIA</td>
<td>Hematoma</td>
<td>MI</td>
</tr>
<tr>
<td>Embolic events</td>
<td>Pseudoaneurysm</td>
<td>Death</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>Bleeding</td>
<td>Stroke</td>
</tr>
<tr>
<td>Perforation</td>
<td>AV fistula</td>
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<tr>
<td>Tamponade</td>
<td>Distal emboli</td>
<td></td>
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<tr>
<td>Allergic reactions</td>
<td>Arterial thrombosis</td>
<td></td>
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<tr>
<td>Infection</td>
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</tbody>
</table>

ASA, alcohol septal ablation; AV, arteriovenous; CHF, congestive heart failure; LAD, left anterior descending artery; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIA, transient ischemic attack; VSD, ventricular septal defect; V tach, ventricular tachycardia.


reimbursement, and that those criteria can have an effect on credentialing. For example, following approval by the Food and Drug Administration (FDA) of transcatheter aortic valve replacement, the Center for Medicare and Medicaid Services (CMS) has developed a national coverage determination that includes specific requirements for coverage (Table 32.5).36 It is expected that these criteria will be incorporated by most institutions in the credentialing process for operators performing transcatheter aortic valve replacement, and that as the field of structural heart disease interventions further evolves, new criteria will be developed.

**INFORMED CONSENT AND THE USE OF APPROVED DEVICES FOR NON-APPROVED INDICATIONS**

Interventions for structural heart disease might require the use of approved devices for a non-approved indication (off-label use).37 For example, specific devices for the closure of paravalvular leaks have not yet been developed, and a combination of coils, septal occluders, and ductal occluders has been used by several operators. The same applies to other procedures, such as closure of ventricular pseudoaneurysms. In the United States, the FDA does not regulate the practice of medicine and in particular, the Federal Food Drug and Cosmetic Act specifically states that “nothing in this Act shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship.” Thus, the off-label use of approved devices is implicitly allowed, as long as the general requirements for good medical practice as listed in the following statement are followed:

“Good medical practice and the best interests of the patient require that physicians use legally available drugs, biologics and devices according to their best knowledge and judgment. If physicians use a product for an indication not in the approved labeling, they have the responsibility to be well informed about the product, to base
In many circumstances, off-label use of approved device does not violate FDA or other regulatory bodies' rules, but the decision to reimburse is often independently made by insurance companies and government agencies such as CMS. For example, it is common for patients in the United States being referred for patent foramen ovale (PFO) closure to have coverage denied based on the lack of an FDA-approved device. Furthermore, CMS initial reimbursement for TAVR has followed FDA's indications for use that includes only transfemoral delivery of the Sapien device in inoperable patients or its use in an FDA-approved study. Disclosure of the off-label use is highly recommended and a well-executed and documented informed consent process is paramount. However, the FDA also specifies that the investigational use of an approved device, when the intent is to develop information about the safety of efficacy of the device in treating a specific condition, may require submission of an Investigational Device Exemption. For detailed information, the reader is referred to the FDA website listed in the references.
Table 32.4 Interventions for Structural Heart Disease: Knowledge Base and Interventional Skills

<table>
<thead>
<tr>
<th>Knowledge base</th>
<th>Interventional skills</th>
</tr>
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<tbody>
<tr>
<td>Natural history</td>
<td>Baseline cardiac catheterization skills</td>
</tr>
<tr>
<td>Cardiac Anatomy</td>
<td>Hemodynamics</td>
</tr>
<tr>
<td>Pathophysiology</td>
<td>Transseptal catheterization</td>
</tr>
<tr>
<td>Alternative treatment strategies to the interventional strategy</td>
<td>Direct left ventricular apical puncture</td>
</tr>
<tr>
<td>Practice guidelines from professional societies</td>
<td>Transhepatic access</td>
</tr>
<tr>
<td>Assessment of patient preferences and individualized patient-centric decision making</td>
<td>Intravascular ultrasound imaging and integration of multiple imaging modalities for navigation in cardiac chambers</td>
</tr>
<tr>
<td></td>
<td>Knowledge of available devices</td>
</tr>
<tr>
<td></td>
<td>Additional technical skills related to the specific procedure</td>
</tr>
<tr>
<td></td>
<td>Procedural complications and bailout techniques</td>
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</table>

Table 32.5 Qualification for Transcatheter Aortic Valve Replacement Programs Requested by the Center for Medicare and Medicaid Services within the National Coverage Determination

Qualifications to begin a TAVR program for heart teams without TAVR experience:

a. Cardiovascular surgeon with:
   i. ≥100 career AVRs including 10 high-risk patients; or
   ii. ≥25 AVRs in 1 y; or
   iii. ≥50 AVRs in 2 y; and which include at least 20 AVRs in the last year prior to TAVR initiation; and

b. Interventional cardiologist with:
   i. Professional experience with 100 structural heart disease procedures lifetime; or
   ii. 30 left-sided structural procedures per year of which 60% should be balloon aortic valvuloplasty. Atrial septal defect and patent foramen ovale closure are not considered left-sided procedures; and

c. Additional members of the heart team such as: echocardiographers imaging specialists, heart failure specialists, cardiac anesthesiologists, intensivists, nurses, and social workers

The hospital program must maintain the following:

a. ≥20 AVRs per year or ≥40 AVRs every 2 y; and
b. ≥2 physicians with cardiac surgery privileges; and

c. ≥1,000 catheterizations per year, including ≥400 percutaneous coronary interventions per year

Qualifications for heart teams with TAVR experience:

a. A cardiovascular surgeon and an interventional cardiologist whose combined experience maintains the following:
   i. ≥20 TAVR procedures in the prior year, or
   ii. ≥40 TAVR procedures in the prior 2 y; and

b. Additional members of the heart team such as: echocardiographers, imaging specialists, heart failure specialists, cardiac anesthesiologists, intensivists, nurses, and social workers.

CMS, Center for Medicare and Medicaid Services; TAVR, transcatheter aortic valve replacement.
THE ROLE OF INTERVENTIONS FOR STRUCTURAL HEART DISEASE IN PATIENT MANAGEMENT: MULTIDISCIPLINARY PROGRAMS AND THE CARDIAC TEAM

The recent expansion in the breadth of structural heart disease comes at a time when there is an expectation of high levels of scientific evidence such as randomized clinical trials to support changes of established clinical practice guidelines, regulatory approval is often more difficult, and surgical treatment for these conditions is well established with excellent and durable results. The interventionalist must be knowledgeable and able to assess patients for not only the intervention but also alternative treatments including medical therapy and surgical approaches. For example, patients with functional mitral regurgitation may be candidates for MitraClip therapy but do they have optimal medical management and are they not surgical candidates? These issues become more complex and outside of the traditional knowledge and skill set of interventional cardiology when using interventional strategies for primary prevention (left atrial appendage occlusion in atrial fibrillation) and secondary prevention (PFO closure following cryptogenic stroke).

Therefore, the evolution of interventions for structural heart disease has introduced the new concept of the cardiac team, with inclusion of interventional cardiologists, vascular surgeons, cardiac surgeons, imaging specialists, non-invasive cardiologists, intensivists, nurses, and cardiovascular technologists. The complexity of the procedure performed, the different types of vascular accesses and approaches that can be used, the need of the input from different subspecialists in the evaluation of best treatment options, and the integration of multiple imaging modalities within the hybrid cardiac catheterization suite make this multidisciplinary approach a critical component of interventions for structural heart disease. This new paradigm, which promotes appropriate and optimal patient’s care, is emphasized in several chapters in this textbook.

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38. http://www.fda.gov/RegulatoryInformation/Guidances/ucm126486.htm (last access date: 05/31/2013).
Although percutaneous intervention began with coronary angioplasty and other interventional tools (see Chapters 28 through 31), the concept of treating diseased heart valves began soon thereafter. The initial thrust was to open stenotic pulmonic, mitral, and aortic valves via balloon valvuloplasty for which the basic techniques and equipment have changed little over the last two decades. More recently, there has been a revolution in this area as exciting new therapies for percutaneous treatment of mitral regurgitation and percutaneous replacement of pulmonic and aortic valves have entered clinical testing and have been introduced in clinical practice. This chapter reviews the mechanisms, indications, techniques, and clinical results of balloon valvuloplasty of the mitral, pulmonic, and aortic valves and describes the novel catheter-based approaches for valve repair and replacement.

PERCUTANEOUS BALLOON MITRAL VALVULOPLASTY

Percutaneous mitral valvuloplasty is an important therapeutic tool in treating rheumatic mitral stenosis. Although the prevalence of rheumatic heart disease has declined significantly in the United States, this procedure still remains an important therapeutic option for the symptomatic patient with mitral stenosis. In the third world or developing countries where rheumatic heart disease remains prevalent, percutaneous mitral valvuloplasty is the treatment of choice for treating patients with mitral stenosis.1-3

Mechanisms

Percutaneous mitral valvuloplasty is more appropriately called percutaneous mitral commissurotomy because the balloon dilatation improves the valve orifice by separating the fused mitral commissures. As shown by echocardiographic, fluoroscopic, and anatomic studies, the expanding balloon splits fused commissures in the same manner as does surgical commissurotomy.4,5

Patient Selection

Patients should be selected for percutaneous mitral valvuloplasty based on both clinical and anatomic factors. In general, they should be symptomatic, and mitral valve area as measured by echocardiography and hemodynamics should be <1.5 cm². Unlike for valve surgery, the presence of pulmonary hypertension or abnormal left ventricular function is not a contraindication. Patients with anatomically suitable valves who have developed restenosis (commissural fusion) after prior surgical or balloon commissurotomy can also undergo percutaneous mitral valvuloplasty with results almost as good as those for previously untreated patients.6,7 Although the procedure can be performed in patients of almost any age, the best clinical results are observed in younger patients, with less predictable long-term results occurring in patients older than 70 years, who are more likely to have deformed and calcified valves. Percutaneous mitral valvuloplasty is a particularly valuable tool in treating the symptomatic pregnant woman with critical mitral stenosis. It can also be a lifesaving emergency procedure in the patient with mitral stenosis and refractory pulmonary edema or cardiogenic shock.8

Asymptomatic patients should be considered for percutaneous mitral commissurotomy when they develop...
pulmonary hypertension or new-onset atrial fibrillation.\(^9\) A pulmonary artery peak systolic pressure of >50 mmHg at rest or >60 mmHg with exercise in an otherwise asymptomatic patient represents disease severity that has reached the point where percutaneous commissurotomy should be considered (Figure 33.1).\(^9\) New atrial fibrillation is less clear an indication but should be considered, especially in patients with mitral valve morphology well suited for percutaneous commissurotomy.

**Contraindications**

Although the procedure can be performed at higher risk with thrombus localized to the left atrial appendage, thrombus within the left atrium itself is a contraindication to this procedure.\(^9\) Moderate or severe (>2+ on a scale of 0 to 4, determined angiographically) mitral regurgitation is also a contraindication to percutaneous mitral valvuloplasty. Patients with mitral stenosis and aortic or tricuspid valve lesions that require cardiac surgery should be referred for

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**Figure 33.1** Management strategy for Asymptomatic patients with mitral stenosis. *The writing committee recognizes that there may be variability in the measurement of mitral valve area (MVA) and that the mean transmitral gradients, pulmonary artery wedge pressure (PAWP), and pulmonary artery systolic pressure (PASP) should also be taken into consideration. \(^1\) There is controversy as to whether patients with severe mitral stenosis (MVA <1.0 cm\(^2\)) and severe pulmonary hypertension (pulmonary artery pressure >60 mmHg) should undergo percutaneous mitral balloon valvotomy (PMBV) or mitral valve replacement to prevent right ventricular failure. \(^2\) Assuming no other cause for pulmonary hypertension is present. AF, atrial fibrillation; CXR, chest X-ray; ECG, electrocardiogram; echo, echocardiography; LA, left atrial; MR, mitral regurgitation; 2D, 2-dimensional. (Reproduced with permission from: 2006 Writing Committee Members et al. *Circulation* 2008;118:e523–e661.)
surgery. Concomitant coronary disease can be treated with PCI in conjunction with valvuloplasty when the coronary anatomy is suitable. This can be done in one session or staged, with the clinically more severe lesion treated first.

Anatomic Factors in Patient Selection for Balloon Mitral Valvuloplasty

High-quality transthoracic and transesophageal echocardiography (TEE) is an essential part of proper patient selection. TEE prior to the planned valvuloplasty procedure excludes the presence of left atrial thrombus and moderate or severe mitral regurgitation. In addition to ensuring that there are no anatomic contraindications, echocardiography provides valuable information that helps the interventional cardiologist select patients and predict results. The ideal patient has pliable, noncalcified mitral leaflets and mild subvalvular disease. As the degree of subvalvular disease increases, the quality of the result with percutaneous mitral valvuloplasty decreases. Similarly, increasing degrees of calcification of the mitral valve diminish the effectiveness of mitral valve dilatation and increase the complication rate. Dilating mitral valves with commissural calcification may lead to leaflet tearing along noncommissural lines and is associated with a higher incidence of procedure-related mitral regurgitation. Heavy calcification of the valve and/or bicommissural calcification are also associated with poorer acute and long-term outcomes. When commissural fusion is symmetric, even in the presence of calcification, bicommissural splitting is more likely than when commissural fusion is asymmetric.

Valve deformity increases substantially with age. Older patients who present with mitral stenosis often have valves poorly suited for percutaneous mitral commissurotomy. In such cases, the goals of therapy must be considered individually for patient selection. Patients who are excellent candidates for mitral valve replacement, or those who have associated multivalve or complex coronary disease, may be better served by surgery. The very elderly, or patients with multiple comorbid conditions or prior median sternotomy, may have excellent palliation from percutaneous mitral commissurotomy despite a high degree of valve and subvalvular deformity and calcification. A prototypic example is the octogenarian patient with prior aortic valve replacement and coronary bypass surgery who presents with a heavily calcified mitral valve and severe symptomatic mitral stenosis. The results of percutaneous commissurotomy in these patients are clearly not as good as in younger patients with pliable valves, but the value of palliative therapy is substantial.

Many find the echocardiographic scoring system of Wilkins et al.15 useful in assessing patients for percutaneous mitral valvuloplasty. This echocardiographic classification system is shown in Table 33.1. Points are given for leaflet mobility, valve thickening, subvalvular thickening, and valvular calcification. The final score is determined by adding up the points from each category. Higher scores indicate more severe anatomic disease and less likelihood of a successful procedure. The maximum score is 16, and percutaneous mitral commissurotomy results are generally excellent in patients with an echo score of ≤8, indicating favorable anatomy, for example, pliable leaflets, mild or moderate subvalvular disease, and mild or absent valve calcification. A review of over 1,500 patients undergoing balloon mitral valvuloplasty was carried out using a logistic model to improve patient selection. As expected, younger patients with echocardiographic evidence of less severe disease had a better outcome.

Patients with significant valve deformity and echocardiographic scores of >8 should not be excluded a priori from consideration for percutaneous mitral valvuloplasty. There is no absolute contraindication to percutaneous mitral valvuloplasty in patients with higher echocardiographic scores, but patients with echocardiographic scores of >8 require an individualized approach. The duration of palliation in such patients may be less than that in patients with ideal valve anatomy, and the acute procedure success rate is lower. When valve deformity is associated with other clear indications for open heart surgery, the decision is relatively simple. This patient group includes patients with associated significant aortic stenosis or insufficiency, multivessel coronary artery disease, or severe tricuspid regurgitation in need of repair. When none of these indications are present or clear, percutaneous commissurotomy in patients with significant valve deformity can be a successful palliative therapy. This is an especially useful strategy in patients with borderline aortic insufficiency or stenosis, in whom a waiting period after mitral commissurotomy may allow for a more timely decision for double-valve replacement at a later date.

Technique

Several basic techniques of percutaneous mitral valvuloplasty (PMV) are in use. Retrograde transarterial techniques, used alone or in combination with antegrade (trans-septal puncture) techniques, have been used in some centers for single- and double-balloon PMV. They offer the advantage of not requiring trans-septal puncture or using only minimal dilatation of the intra-atrial septum. Disadvantages of these techniques include the risk of arterial injury because of the larger balloons used. In addition, the procedures can be technically difficult and time-consuming.

The most commonly used approaches are transvenous antegrade (i.e., trans-septal) techniques, using either a double-balloon or the Inoue balloon system. The Inoue balloon is the only device approved specifically for percutaneous mitral valvuloplasty in the United States and is the most commonly used device worldwide. Alternatively, a double-balloon technique can be used with two balloons advanced over separate guidewires from the femoral vein to the left atrium, across the mitral valve into the left ventricle. The two balloons are then inflated simultaneously across the mitral valve. Figure 33.2 illustrates the two-balloon technique. In this patient, the mitral valve was first dilated with a single balloon,
Table 33.1  Echocardiographic Scoring System<sup>a</sup> for Assessing Patients for Percutaneous Mitral Valvuloplasty

<table>
<thead>
<tr>
<th><strong>Leaflet Mobility</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Highly mobile valve with restriction of only the leaflet tips</td>
<td></td>
</tr>
<tr>
<td>2 Midportion and base of leaflets have reduced mobility</td>
<td></td>
</tr>
<tr>
<td>3 Valve leaflets move forward in diastole mainly at the base</td>
<td></td>
</tr>
<tr>
<td>4 No or minimal forward movement of the leaflets in diastole</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Valvular Thickening</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Leaflets near normal (4–5 mm)</td>
<td></td>
</tr>
<tr>
<td>2 Midleaflet thickening, marked thickening of the margins</td>
<td></td>
</tr>
<tr>
<td>3 Thickening extends through the entire leaflets (5–8 mm)</td>
<td></td>
</tr>
<tr>
<td>4 Marked thickening of all leaflet tissue (&gt;8–10 mm)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Subvalvular Thickening</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Minimal thickening of chordal structures just below the valve</td>
<td></td>
</tr>
<tr>
<td>2 Thickening of chordae extending up to one-third of chordal length</td>
<td></td>
</tr>
<tr>
<td>3 Thickening extending to the distal third of the chordae</td>
<td></td>
</tr>
<tr>
<td>4 Extensive thickening and shortening of all chordae extending down to the papillary muscle</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Valvular Calcification</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1 A single area of increased echo brightness</td>
<td></td>
</tr>
<tr>
<td>2 Scattered areas of brightness confined to leaflet margins</td>
<td></td>
</tr>
<tr>
<td>3 Brightness extending into the midportion of leaflets</td>
<td></td>
</tr>
<tr>
<td>4 Extensive brightness through most of the leaflet tissue</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Adding each of the components determines final score (maximum 16 points).


After which double balloons were used to achieve the desired hemodynamic result. When properly performed, the double-balloon technique results in excellent improvement in mitral valve area. Multiple studies have shown no significant difference in hemodynamic results (mitral valve gradient or mitral valve area) postprocedure between the double-balloon technique and the Inoue balloon system.

An adaptation of the double-balloon technique uses a monorail approach to deliver two balloons across the mitral valve over a single guidewire. The first valvuloplasty balloon with a short monorail segment is passed over the wire across the mitral valve, followed by a second conventional balloon that is then passed over the wire until it is parallel with the first balloon. There are no substantial differences in the mechanism of delivery of force by two balloons using this approach when compared with the conventional double-wire, double-balloon technique.

In the early surgical era of closed heart mitral commissurotomy, a metallic dilator, or commissurotome, was used via a left ventricular apical incision. Cribier et al. adapted this established surgical technique for percutaneous use. A 19F metallic commissurotome can be passed across the interatrial septum over a guidewire and used to accomplish mitral commissurotomy. There has been some evidence that bicommissural splitting can be accomplished more frequently with the metal commissurotome. Randomized comparisons of the Inoue balloon and metallic commissurotome have not demonstrated significant differences in long-term outcome. This device was never available in the United States and is no longer manufactured.

However, the Inoue balloon technique is faster and less cumbersome, and generally requires less fluoroscopy time than these other approaches. The Inoue balloon allows simple progressive upsizing of the balloon without withdrawing the balloon from the left atrium—an important advantage if larger balloon sizes are needed. The Inoue balloon system may, however, result in a slightly higher incidence of mitral regurgitation.
Inoue Balloon Technique

All antegrade approaches begin with the crucial first step of successful trans-septal catheterization. This technique, which is described in Chapter 6, not only requires successful access to the left atrium, but must also be performed through the appropriate part of the atrial septum to allow easy access to the mitral valve. After successful placement of a Mullins-type dilator and sheath into the left atrium and confirmation of its position by a hand injection of contrast, the patient is anticoagulated with heparin. Baseline hemodynamic measurements are then recorded, confirming the appropriateness of the degree of mitral stenosis for PMV. Subsequently, a special solid-core coiled 0.025-inch guidewire is introduced into the left atrium, and the Mullins sheath dilator system is removed. The femoral vein and interatrial septum are then dilated with a long 14F dilator over the coiled guidewire within the left atrium. The previously prepared, tested, and now slenderized Inoue balloon is then introduced over the guidewire into the left atrium. The Inoue balloon (Figure 33.3) is made of nylon and rubber micromesh. Owing to the variable elasticity along its length, the balloon inflates in three distinct stages as illustrated in Figure 33.3. This allows for stable positioning of the balloon catheter across the mitral valve, as described below.

After the slenderized balloon has been positioned within the left atrium, the stretching tube is removed, and a pre-shaped “J” stylet is introduced into the Inoue balloon. The distal portion of the balloon is inflated slightly to aid in crossing the valve and to prevent intrachordal passage. By maneuvering the balloon catheter while rotating and withdrawing the stylet, the balloon tip can be moved anteriorly and inferiorly toward the mitral orifice. Once the balloon catheter is placed across the mitral orifice, the distal portion of the balloon is inflated more fully and the catheter is pulled back gently to confirm that the inflated distal portion of the balloon is secure across the mitral valve. As further volume is added to the balloon, the proximal end inflates to lock the valve.
Chapter 33 Percutaneous Therapies for Valvular Heart Disease

Figure 33.3 The figure shows the Inoue balloon catheter. The top panel shows the length of the catheter. On the far left, at the hub, the stretching metal tube has been fully advanced, resulting in stretching and elongation of the balloon catheter, seen on the right side of the figure. This results in a minimized profile to facilitate passage through a femoral venous sheath or directly through the skin. In the second panel, the stretching metal tube on the far left has been pulled back, allowing the balloon to shorten and fatten. The stretching tube is pulled back in this manner after the balloon is passed across the atrial septal puncture. This is seen on the right side of the second panel. Panels 3 through 6 show the stepwise inflation characteristics of the balloon. In panel 3, the balloon is inflated. In panel 4, the distal portion has been inflated. This portion of the balloon can be “floated” or manipulated across the mitral valve from the left atrium to the left ventricle in a manner analogous to crossing the tricuspid valve with a right heart balloon floatation catheter. In panel 5, the balloon is further inflated to create a “dog bone” configuration. This allows the balloon to self-position within the mitral valve. Upon final inflation, as seen in panel 6, the waist of the balloon is fully expanded, ultimately resulting in commissural splitting.

The Inoue balloon comes in four sizes—24, 26, 28, and 30 mm, referring to the fully inflated maximal balloon diameter. The 24 mm balloon is not available in the United States. However, since actual balloon size is dependent on the volume used for inflation, the actual diameter can be varied over a range from 6 mm less than nominal up to the full rated diameter, as required. We generally estimate the expected maximal inflated balloon diameter using an empirical formula based on the height of the patient (one-tenth the height in centimeter plus 10 mm). It is important to start with a smaller balloon diameter, especially for valves that are very much thickened.
Figure 33.4 Balloon mitral valvuloplasty in a 42-year-old man who presented with dyspnea on exertion. 

A. Distal tip of the Inoue balloon has crossed the mitral valve. 

B. With the distal tip of the balloon filled, the catheter was withdrawn to straddle the mitral valve. 

C. Partial filling of the balloon. 

D. Complete filling of the Inoue balloon across the mitral valve. Following this dilation, the mitral valve gradient was reduced from 18 mmHg to 2 mmHg. 

E. A large V wave is seen prior to percutaneous mitral valvuloplasty. There is a large diastolic transmitral valve gradient. The filled arrows denote the peak of the V waves. No mitral regurgitation was noted at this point by either echocardiography or left ventriculography. 

F. Post mitral valvuloplasty, the transmitral gradient has been dramatically reduced, as has the V wave. Ventriculography and Doppler echocardiography at this point show no mitral regurgitation. (From Syed Z, Salinger MH, Feldman T. Alterations in left atrial pressure and compliance during balloon mitral valvuloplasty. *Cathet Cardiovasc Intervent* 2004;61:577.)
or rigid or have moderate amounts of subvalvular disease, to minimize the development of mitral regurgitation, which can develop suddenly with as little as a 1- to 2-mm increase in inflation diameter of the balloon.

The Inoue balloon is fundamentally different from conventional balloons, being volume driven. The balloon is precalibrated so that inflation with volumes labeled on the inflation syringe result in corresponding inflated diameters of the balloon. The pressure that the balloon is inflated to is thus different for different inflation volumes. A smaller maximal-size balloon, such as a 26-mm balloon, when inflated to its maximal size will be at a higher pressure than a balloon that has a larger capacity, such as a 30-mm balloon, inflated to the same diameter of 26 mm. The Inoue balloon has a low-pressure zone encompassing the first two-thirds of its range of inflation. The balloon pressure in this zone typically is approximately 2 or 3 atm. As the balloon is inflated to its last couple of millimeters of diameter with increasing inflation volumes, the balloon pressure rises toward 4 atm. Randomized trials have examined the effects of using balloons in the low-pressure zone as compared with using them in the high-pressure zone.27,28 With similar maximal inflated diameters, inflations in the low-pressure zone resulted in less mitral regurgitation than did inflations in the high-pressure zone. Thus, using a 30-mm balloon inflated to a maximum diameter of 28 mm will overall result in causing less mitral regurgitation than will using a maximal nominal 28-mm balloon inflated to 28 mm (in the high-pressure zone).

It is important to assess for increases in mitral regurgitation after each inflation before proceeding to the next inflation diameter. After each balloon inflation, the mean left atrial pressure should be expected to decrease in conjunction with a decrease in the transmitral pressure gradient. When the left atrial pressure remains unchanged both in magnitude and in morphology of the waveform after balloon inflation, it is likely that no progress has been made. If a persistent gradient is present, an additional inflation is warranted. The evaluation becomes more difficult when the left atrial pressure rises after a balloon inflation, or when the waveform changes with an increase in the amplitude of V wave. Decision making is all the more complicated because the presence and size of V waves in the left atrial pressure tracing is often misleading.

A V wave in the left atrial pressure tracing is dynamic. Large V waves are frequently seen in the left atrium in patients with mitral valve disease in the absence of mitral regurgitation reflecting alterations in left atrial compliance; thus, V waves are neither sensitive nor specific for the presence or importance of mitral regurgitation. In percutaneous commissurotomy, it is common to see a V wave diminish during the course of successive successful balloon inflations, reflecting left atrial decompression with improved left atrial compliance29 (Figure 33.4). Changes in the V wave must be assessed carefully during percutaneous commissurotomy procedures, but additional information obtained using techniques such as Doppler echocardiography or repeat left ventriculography is necessary to fully interpret these findings.

Following successful mitral valve dilatation, the Inoue balloon is reslenderized by reintroducing first the guidewire and then the stretching tube. The slenderized balloon is subsequently withdrawn from the body over the guidewire. If no sheath has been used, a 10F sheath is inserted into the femoral vein over the guidewire before removal of the wire. It is useful to leave the guidewire across the atrial septal puncture in the left atrium for 3 to 5 minutes after completion of the procedure, while monitoring the systemic arterial pressure. In rare cases, the trans-septal puncture can be made low in the right atrium, and rather than going through the atrial septum, the needle may traverse the right atrial wall and the transverse pericardial sinus, and then enter the inferior border of the left atrium. In this situation, a satisfactory left atrial pressure waveform is still obtained through the tip of the trans-septal needle, and the path of the puncture through the pericardial space is not apparent until the devices are removed at the conclusion of the procedure. If a wire is left in place at the end of the procedure and the blood pressure drops precipitously after a couple of minutes, with the wire in place, a small balloon catheter can be passed back across the puncture site and inflated to stabilize the patient while pericardial centesis is performed and plans for further management are made. This is a rare occurrence, but catastrophic when it does occur. This small step of leaving the wire across the puncture for just a few moments can be lifesaving in such a situation.

Immediate Results

Immediate results of mitral valvuloplasty are assessed by a combination of echo Doppler and hemodynamic measurements. Repeat evaluation of mitral valve area during the procedure by hemodynamic measurements can be performed with reasonable degrees of accuracy in catheterization laboratories equipped with systems featuring computer analysis. Some inaccuracy creeps into the Gorlin formula in the presence of an atrial shunt or mitral regurgitation.30 Nevertheless, in successful procedures, the mitral valve gradient will be observed to be substantially reduced.

Figure 33.5 illustrates a typical reduction in left atrial pressure and transmitral gradient immediately after balloon mitral valvuloplasty. The mitral valve orifice area will generally be increased to >1 cm²/m² body surface area (Table 33.2). By echocardiographic assessment in the laboratory, particularly by planimetry of the mitral valve orifice image in the two-dimensional echocardiogram short-axis view, another confirmation of improvement of mitral valve orifice area can be obtained. The accuracy of Doppler measurements during valvuloplasty can be variable, but color Doppler assessment is the method of choice for sequential evaluation of the degree of mitral regurgitation.37 When Doppler echocardiography is not available in the catheterization lab, serial left ventriculograms can be done to evaluate the degree of mitral regurgitation. The appearance of new mitral regurgitation or an increase of greater than one grade on the 0 to 4 classification of preexisting mitral regurgitation in general signals an end
Before valvuloplasty, there is a large transmirtal valve pressure gradient, filled in black in the first diastolic period in the prevavalvuloplasty tracing. After a 27-mm balloon inflation, the transmirtal valve pressure gradient is significantly reduced, and following a 28-mm diameter balloon inflation, the gradient is nearly resolved. (From Feldman T, Carroll JD, Herrmann HC, et al. Effect of balloon size and stepwise inflation technique on the results of Inoue mitral commissurotomy. *Cathet Cardiovasc Diagn* 1993;28:200.)

Long-Term Hemodynamic and Clinical Results

Numerous studies have demonstrated the effectiveness of balloon valvuloplasty in increasing mitral valve area. There is a consistent increase in mitral valve area to >1.5 cm², a decrease in left atrial pressure, and usually a slight increase in cardiac output. Over time, there is a gradual decrease in pulmonary artery pressure and pulmonary vascular resistance. Long-term follow-up of >4 years have been reported by several single-center registries. These registry analyses have shown quite satisfactory results (Table 33.3). In a larger multicenter series, the National Heart, Lung, and Blood Institute (NHLBI) Balloon Valvuloplasty Registry reported results in 736 patients older than 18 years who were followed for 4 years. The actuarial survival rates at 1, 2, 3, and 4 years were 93%, 90%, 87%, and 84%, respectively. The event-free survival (freedom from death, mitral valve surgery, or repeat balloon valvuloplasty) at 1, 2, 3, and 4 years was 80%, 71%, 66%, and 62%, respectively. Multivariate predictors of mortality were New York Heart Association (NYHA) functional class IV, echocardiographic mitral valve score of >12, systolic pulmonary artery pressure of >40 mmHg postprocedure, and left ventricular end-diastolic pressure of >15 mmHg. More recently, Boulet et al. reported long-term follow-up data for up to 20 years in 912 patients who had had successful mitral valvuloplasty, defined by a valve area of ≥1.5 cm² with mitral regurgitation of ≤2. During a median follow-up of 12 years, 561 patients (62%) were free of reintervention. In the 351 patients (38%) who underwent a reintervention, surgery was performed in 266 patients and repeat balloon valvuloplasty in 85 patients. Importantly, cardiovascular survival without surgery was 60 ± 7% at 10 years in the 85 patients who underwent repeat valvuloplasty. These data support the concept that percutaneous mitral balloon valvuloplasty is an effective therapy for mitral stenosis and that a repeat valvuloplasty can allow further postponement of surgery in a significant number of patients.

Comparison of Percutaneous Balloon Mitral Valvuloplasty and Surgery

Randomized comparisons of percutaneous balloon valvuloplasty with surgical commissurotomy have demonstrated similar acute and long-term results (Table 33.2). The equivalence of the various percutaneous commissurotomy approaches to each other, and of percutaneous...
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Mean Follow-Up</th>
<th>Procedure</th>
<th>No. of Patients</th>
<th>Age (years)</th>
<th>Average Score</th>
<th>Mitral Valve Gradient (mmHg)</th>
<th>Mitral Valve Area (cm²)</th>
<th>Restenosis (%)</th>
<th>Freedom from Reintervention (%)</th>
<th>NYHA FC I (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patel et al. (1991)</td>
<td>Immediate</td>
<td>PMBV</td>
<td>23</td>
<td>30 ± 11</td>
<td>6.0</td>
<td>12 ± 4 4 ± 3</td>
<td>0.8 ± 0.3 2.1 ± 0.7²</td>
<td>—</td>
<td>—</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CC</td>
<td>22</td>
<td>26 ± 26</td>
<td>6.0</td>
<td>12 ± 5 6 ± 3</td>
<td>0.7 ± 0.2 1.3 ± 0.3</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Turi et al. (1991)</td>
<td>7 mo</td>
<td>PMBV</td>
<td>20</td>
<td>27 ± 8</td>
<td>7.2</td>
<td>18 ± 4 10 ± 2</td>
<td>0.8 ± 2 1.6 ± 0.2</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CC</td>
<td>20</td>
<td>28 ± 1</td>
<td>8.4</td>
<td>20 ± 6 12 ± 2</td>
<td>0.9 ± 0.4 1.7 ± 0.2</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Arora et al. (1993)</td>
<td>22 mo</td>
<td>PMBV</td>
<td>100</td>
<td>19 ± 5</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>0.8 ± 0.3 2.3 ± 0.1</td>
<td>5</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CC</td>
<td>100</td>
<td>20 ± 6</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>0.8 ± 0.2 2.1 ± 0.4</td>
<td>4</td>
<td>—</td>
</tr>
<tr>
<td>Reyes et al. (1994)</td>
<td>3 y</td>
<td>PMBV</td>
<td>30</td>
<td>30 ± 9</td>
<td>6.7</td>
<td>—</td>
<td>—</td>
<td>0.9 ± 0.3 2.4 ± 0.4³</td>
<td>10</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CC</td>
<td>30</td>
<td>31 ± 9</td>
<td>7.0</td>
<td>—</td>
<td>—</td>
<td>0.9 ± 0.3 1.8 ± 0.4</td>
<td>13</td>
<td>—</td>
</tr>
<tr>
<td>Ben Farhat et al. (1998)</td>
<td>7 y</td>
<td>PMBV</td>
<td>30</td>
<td>29 ± 12</td>
<td>6.0</td>
<td>—</td>
<td>—</td>
<td>0.9 ± 0.2 1.8 ± 0.4</td>
<td>—</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OC</td>
<td>30</td>
<td>27 ± 9</td>
<td>6.0</td>
<td>—</td>
<td>—</td>
<td>0.9 ± 0.2 1.8 ± 0.3</td>
<td>—</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CC</td>
<td>30</td>
<td>28 ± 10</td>
<td>6.0</td>
<td>—</td>
<td>—</td>
<td>0.9 ± 0.2 1.3 ± 0.3</td>
<td>—</td>
<td>50</td>
</tr>
<tr>
<td>Cotrufo et al. (1999)</td>
<td>38 mo</td>
<td>PMBV</td>
<td>111</td>
<td>47 ± 14</td>
<td>7.6</td>
<td>—</td>
<td>—</td>
<td>1.0 ± 0.2 1.8 ± 0.3</td>
<td>28</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OC</td>
<td>82</td>
<td>49 ± 10</td>
<td>8.2</td>
<td>—</td>
<td>—</td>
<td>1.0 ± 0.2 2.3 ± 0.3</td>
<td>18</td>
<td>96</td>
</tr>
</tbody>
</table>

*Significant difference \( (P < 0.05) \) in increased mitral valve area by percutaneous mitral balloon valvotomy (PMBV) as compared with surgical commissurotomy. A dash indicates that data were not available.
CC, closed commissurotomy; FC, functional class; NYHA, New York Heart Association; OC, open commissurotomy; Post, postprocedure; Pre, preprocedure.
(Reproduced with permission from *Circulation* 2008;118:e523–e661.)
Table 33.3  Long-Term Results of Balloon Mitral Valvuloplasty for Mitral Stenosis

<table>
<thead>
<tr>
<th>Author (Reference)</th>
<th>No. of Patients</th>
<th>Mean Age (Years)</th>
<th>Follow-Up (Months)</th>
<th>Survival (%)</th>
<th>Freedom from Operation (%)</th>
<th>NYHA Class I–II and Freedom from Operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palacios^39</td>
<td>327</td>
<td>54</td>
<td>48</td>
<td>90</td>
<td>79</td>
<td>66</td>
</tr>
<tr>
<td>Cohen^40</td>
<td>146</td>
<td>59</td>
<td>60</td>
<td>76</td>
<td>51</td>
<td>–</td>
</tr>
<tr>
<td>Pan^41</td>
<td>350</td>
<td>46</td>
<td>60</td>
<td>94</td>
<td>91</td>
<td>85</td>
</tr>
<tr>
<td>Jung^42</td>
<td>606</td>
<td>46</td>
<td>60</td>
<td>94</td>
<td>74</td>
<td>66</td>
</tr>
</tbody>
</table>

NYHA, New York Heart Association.

Commissurotomy to surgical commissurotomy, suggests that commissurotomy by any method yields comparable results. Two prospective randomized studies of young patients in India and South Africa compared the clinical and hemodynamic results of percutaneous balloon valvuloplasty with those of closed surgical valvotomy. The valvuloplasty results compared favorably with those obtained surgically; in one study, better functional and hemodynamic results occurred in the patients treated with percutaneous balloon valvuloplasty. Another trial looked at 60 patients randomized prospectively to percutaneous balloon valvuloplasty versus open surgical commissurotomy. Initial mitral valve area increased from a mean of 0.9 to 2.1 cm² in the balloon valvuloplasty group and from 0.9 to 2.0 cm² in the surgical patients. However, after 3 years the patients treated with balloon valvuloplasty had a higher average mitral valve area (2.4 versus 1.8 cm²) and a greater likelihood of NYHA class I status (72% versus 57%).

Open surgical commissurotomy, closed surgical commissurotomy, and percutaneous balloon valvuloplasty were compared in a trial of 90 patients. Short- and long-term (7-year) outcomes were not as good with closed surgical commissurotomy as with the other two procedures. The increase in mitral valve area was larger after percutaneous balloon valvuloplasty (0.9 to 2.2 cm²) and open commissurotomy (0.9 to 2.0 cm²) than after closed commissurotomy (0.6 to 1.6 cm²). Early and late mortality and thromboembolism were similar for all the three groups. At 7 years of follow-up, NYHA class I status was observed in 87%, 90%, and 33% of patients in the balloon valvuloplasty, open commissurotomy, and closed commissurotomy groups, respectively. Freedom from repeat intervention at 7 years for the balloon valvuloplasty, open commissurotomy, and closed surgical commissurotomy patients was 90%, 93%, and 53%, respectively.

Complications

In skilled hands, the failure rate of the procedure should be <5%. Failure usually results from the inability to safely puncture the interatrial septum because of anatomic difficulties or, in some cases, to position the balloon catheter successfully across the mitral valve. Procedural mortality rate varies from 0% to 3% in most series. Hemopericardium related to trans-septal catheterization, atrial puncture, or, rarely, left ventricular apical perforation by the balloon or wires varies in incidence from 0.5% to 10%. Systemic embolization has been encountered in 0.5% to 5% of cases. These complications diminish with increasing operator experience.

Severe mitral regurgitation is fortunately uncommon, ranging in incidence from 2% to 9%, and is related to noncommissural leaflet tearing or chordal rupture. Leaflet tears are largely unpredictable and unpreventable, but chordal rupture can be minimized by careful application of the technique. Usually in these circumstances, one or both of the mitral commissures might have been too tightly fused to be split successfully by the balloon, and the leaflets might have torn along noncommissural lines. Most cases of severe mitral regurgitation occur in patients with unfavorable mitral valve anatomy. Same-day surgical mitral valve replacement is necessary in 2% to 3% of patients. Usually even severe mitral regurgitation is well tolerated for a time by the patient, and in the acute setting it is usually responsive to intravenous nitroglycerin or nitroprusside. In general, elective surgical replacement rather than repair of the valve will be necessary when severe mitral regurgitation occurs because of the severity of the underlying valvular and subvalvular disease.

PULMONIC VALVULOPLASTY

Pulmonary valve stenosis is a relatively common congenital defect. Mild to moderate pulmonary stenosis in children has generally a benign clinical course, with a high rate of survival into adulthood. Therefore, the adult interventional cardiologist will encounter previously undetected and untreated patients who are candidates for balloon valvuloplasty.
Pathophysiology
The typical patient with valvular pulmonic stenosis has a trileaflet valve, with varying degrees of fibrous thickening and fusion of the commissures. These restricted valve leaflets have a characteristic dome-shaped, or conical, appearance during systole on angiography or echocardiography. Bicuspid pulmonic valves are uncommon (<20%), and heavy calcification of the stenotic valve is rare. These features make the stenotic pulmonary valve well suited for balloon valvuloplasty. Other forms of congenital pulmonic stenosis not well suited for valvuloplasty include dysplastic valves (Noonan syndrome) and primary fibromuscular subvalvular narrowing.

Balloon valvuloplasty has evolved from a long surgical experience with mechanical valve dilatation, valvulotomies (Brock procedure), bougies, and finally, under cardiopulmonary bypass, direct incision of fused pulmonic valve commissures. Since the initial balloon valvuloplasty of the pulmonary valve in 1979 with an angiographic balloon catheter, larger-diameter, longer polyethylene balloon catheters have been developed to allow this procedure to be performed successfully and safely in children and adults. The Inoue balloon may be used as well. The proposed mechanism for successful balloon valvuloplasty is predominantly mechanical separation of congenitally fused commissures. Also, there appears to be in some patients minor tearing of valve leaflets and, occasionally, avulsion of the cusps.

Patients with moderate pulmonic stenosis and a gradient of 50 to 100 mmHg who have symptoms of exercise intolerance will probably benefit from balloon valvuloplasty. Patients with severe pulmonic stenosis, defined as a gradient of >100 mmHg, or those with evidence of right ventricular dysfunction may benefit from balloon valvuloplasty even in the absence of symptoms, because of the significant afterload that the obstructive pulmonary valve places on the right ventricle.

Technique
After selection of a symptomatic patient with a moderate or severe gradient across the pulmonary valve by echocardiographic and Doppler evaluation, pulmonary valvuloplasty begins with a careful measurement of the pulmonic valve annulus diameter on echo for balloon sizing. Right heart catheterization is done to document the pulmonary valve gradient and to exclude any significant supravalvular or subvalvular component. A 5F sheath may be placed in the left femoral artery for pressure monitoring, and the procedure is performed from the right femoral vein after the introduction of an 8F sheath. Right ventricular angiography is done in the anteroposterior and lateral projections to determine the exact location of the pulmonary valve and to confirm the sizing of the pulmonary annulus. In the lateral projection, right ventriculography demonstrates the morphology of the outflow tract. Subvalvular hypertrophy typically accompanies pulmonic stenosis; in some cases, a secondary subvalvular stenosis results. If on prevalvuloplasty right ventriculography subvalvular hypertrophy causes near obstruction, relief of the pulmonic stenosis with afterload reduction may allow for muscular obstruction to be accentuated after valvuloplasty. It is important to appreciate this preprocedure, since severe hypotension may result after successful pulmonary valvuloplasty as a consequence of subvalvular dynamic obstruction. This phenomenon is referred to as “suicide right ventricle.”

For sizing, we generally use a pigtail catheter with markers spaced 1 cm apart to facilitate assessment using quantitative coronary angiography. The single-balloon, double-balloon, or Inoue balloon technique may be used. For the dual-balloon technique in adult patients, balloon sizes approximating the diameter of the annulus, and then increasing in size, are chosen, if necessary, to abolish the gradient. It is often necessary to oversize the calculated annulus diameter by as much as 25%. Both balloons may be inserted via a single femoral vein, which necessitates a sheathless approach. Bilateral venous cannulation allows the use of sheaths. The Inoue balloon is large enough so that use of a single balloon, with a target inflated diameter 1.2 times larger than the pulmonic annulus, will suffice in most adult patients.

Following the angiographic localization of the pulmonary valve, the valve is crossed with a dual-lumen balloon flotation catheter. This catheter is useful for measuring the gradient from its end-hole lumen, as well as from its side-hole lumen, 5 cm from the tip. Pressure gradients can be measured through this catheter before and after balloon dilatation. Both lumens are passed distally into the pulmonary artery, and for the double-balloon technique two 0.038-inch heavy-duty exchange-length guidewires are passed into the distal pulmonary artery, one through the end-hole lumen and one through the side-hole lumen. The catheter is then removed, leaving the wires in place in the pulmonary artery exiting the body through the femoral vein. The pulmonary valvuloplasty balloons, having been previously purged of air and filled with diluted radiographic contrast, are then inserted one after the other in tandem into the femoral vein. They are then positioned one at a time, with the aid of both the external markers and the balloon markers, in such a way that the midportion of the valvuloplasty balloon is straddling the pulmonary valve. When both balloon catheters are in place, they are rapidly and simultaneously filled with the dilute radiographic contrast. The balloons are filled until the “waist” is seen to disappear on fluoroscopy. The balloon catheters are emptied and then withdrawn from the body sequentially over the two heavy-duty J wires. A 12F sheath is introduced into the femoral vein over the guidewires, and the dual-lumen catheter is reintroduced through the sheath and positioned across the pulmonary valve over one of the wires. That guidewire is then removed, and a careful determination made of the residual valvular gradient, if any.

In a successful balloon pulmonic valvuloplasty, the valvular gradient is almost always nearly abolished. However, on occasion the operator will encounter a previously undetected subvalvular gradient, after the valvular gradient has been
eliminated (the so-called suicide right ventricle). When the subvalvular gradient is severe enough to cause hypotension, beta-blockade and volume expansion must be rapidly instituted. This subvalvular gradient will usually diminish and disappear over the ensuing weeks, with regression of the right ventricular hypertrophy. Repeat dilatation of the pulmonary valve should be performed with larger balloons only when there is a persistent and significant valvular gradient. Repeat dilatation of the pulmonary valve for a subvalvular gradient is contraindicated.

Clinical Results and Complications

The impressive acute and long-term results of this procedure in adolescents and adults make balloon valvuloplasty the treatment of choice for valvular pulmonic stenosis. A pooled analysis involving 784 patients of all ages showed that clinical success was achieved with balloon valvuloplasty in 98% of patients. Procedural mortality was <0.5%, and the average peak valve gradient fell from 85 to 33 mmHg. Several series have looked at the long-term efficacy of balloon valvuloplasty. Chen and colleagues reported a series of 53 adolescent and adult patients, aged 13 to 55 years, treated between 1985 and 1995. The systolic pressure gradient across the pulmonary valve fell from 91 ± 46 to 38 ± 32 mmHg after the procedure. On late follow-up (average of 7 years), the gradient had fallen further. Seven of 53 patients developed pulmonary insufficiency immediately after the valvuloplasty, but none had this complication at late follow-up evaluation.

Procedural complications are rare in pulmonic valvuloplasty. It is generally planned as an outpatient procedure. Patients may have arrhythmias and occasional hypotension during balloon inflation. Transient right bundle branch block has also been observed. Despite the use of large balloon catheters, bleeding and vascular complications are infrequent because this procedure is done through the femoral vein.

Calcific Aortic Stenosis

The more typical patient encountered by the adult cardiologist is the elderly patient with acquired calcific aortic stenosis. Although experience with successful balloon valvuloplasty for this condition dates back to 1986, the procedure has a limited role at present because of limited durability owing to the high rate of recurrence or restenosis. Virtually all symptomatic patients with calcific aortic stenosis should undergo aortic valve replacement as the treatment of choice. There are, however, certain settings where balloon valvuloplasty may play an important palliative role in patients who are poor candidates for immediate valve replacement. These are listed in Table 33.4. Balloon aortic valvuloplasty is useful in

### Table 33.4

<table>
<thead>
<tr>
<th>Indications for Balloon Aortic Valvuloplasty in Adults</th>
</tr>
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<tbody>
<tr>
<td>Cardiogenic shock</td>
</tr>
<tr>
<td>Bridge to aortic valve surgery</td>
</tr>
<tr>
<td>Symptomatic critical aortic stenosis requiring emergency noncardiac surgery</td>
</tr>
<tr>
<td>Poor surgical candidate owing to high risk, e.g., age &gt;90 years</td>
</tr>
<tr>
<td>Diagnostic testing in low-gradient/low-output setting</td>
</tr>
<tr>
<td>Congenital aortic stenosis</td>
</tr>
<tr>
<td>Rheumatic aortic stenosis</td>
</tr>
<tr>
<td>Predilatation before transcatheter aortic valve implantation</td>
</tr>
</tbody>
</table>

Noncalcific Aortic Stenosis

Percutaneous balloon aortic valvuloplasty was first performed in children and young adults by Lababidi in 1984. Balloon dilatation resulted in a significant decrease in peak aortic valve
the patient presenting with cardiogenic shock owing to aortic stenosis and can serve as a successful bridge to definitive surgery in these hemodynamically unstable patients. It may also be used for palliation in patients with serious comorbidity conditions. The technique is also used in patients with critical aortic stenosis who require urgent noncardiac surgery, if it is felt that more conservative medical therapy presents excessive risk. Typical examples include patients undergoing hemicolecotomy for colon cancer or operations of a similar magnitude. Last, valvuloplasty may be useful as a diagnostic tool. Patients with low gradient, low cardiac output, and markedly depressed ejection fraction have poor outcomes with surgical valve replacement. Balloon valvuloplasty may be used to assess the potential for improvement in left ventricular function: those patients who do not improve represent a group that has underlying cardiomyopathy, while those who do improve after balloon dilatation generally have a good outcome with subsequent aortic valve replacement.

More recently, the indication for aortic balloon valvuloplasty has expanded with the introduction of transcatheter aortic valve implantation (TAVI); valvuloplasty is used increasingly as a bridge to TAVI. Also, predilatation of the aortic valve with aortic balloon valvuloplasty is a critical component of the standard TAVI protocol (see below).

Mechanism of Improved Aortic Orifice Area

Postmortem and intraoperative dilatations have demonstrated how balloon aortic valvuloplasty improves the adult aortic valve with calcific degenerative aortic stenosis. Balloon dilatation increases the mobility of leaflets, thus enlarging the aortic valve orifice. The mechanism of dilatation appears predominantly to be fracturing of the calcific aortic valve nodules. In addition, in some elderly patients there is rheumatic disease with superimposed calcification, and there may be separation of postinflammatory fused commissures that contributes to the results of dilatation. The likely mechanism of restenosis is fusion of the cracks or crevices in calcific nodules on the aortic leaflets. The balloon dilatation process rarely dislodges the amorphous calcific deposits, and embolization is rare. The fractured calcific nodules may heal with fibrosis, which is probably the most common occurrence, and in some cases even with ossification and true bone formation.

Technique

The retrograde aortic technique for balloon aortic valvuloplasty is the one most commonly used. One or both femoral arteries may be used. A 5F pigtail catheter is inserted from the left femoral artery and positioned in the ascending aorta for pressure monitoring and gradient determination. Right heart catheterization is done from the left femoral vein. A balloon flotation thermodilution catheter is placed in the pulmonary artery, which remains there throughout the procedure to allow determination of the cardiac output. A second venous puncture may be “stacked” under the first for a 5F sheath, for insertion of a temporary pacemaker, which is utilized for rapid right ventricular (RV) pacing during balloon inflation. Using the right femoral artery, a 6F sheath is introduced to allow left heart catheterization to be performed. A 0.035- or 0.038-inch straight-tipped guidewire is used to cross the aortic valve, which is advanced through an angled pigtail catheter, a left Amplatz catheter, or a specialized catheter designed to cross the aortic valve. The aortic valve gradient is measured and aortic valve area determined using the Gorlin formula. Patients may be heparinized prior to any attempt to cross the aortic valve.

Following these prevalvuloplasty baseline measurements, an extra-stiff 0.035-inch exchange-length (260 to 300 cm) guidewire, shaped with a pigtail or ram’s horn curve at its tip, is inserted into the left ventricle. The wire tip is shaped by pulling the wire between a finger and the edge of a hemostat, which helps it lie benignly in the left ventricular apex (without causing perforation or undue ventricular arrhythmia). The previously placed left ventricular catheter is removed, and a 10–14F sheath is placed over this wire into the femoral artery, depending on the size and type of balloon that has been selected. It is important that the groin be anesthetized adequately to avoid discomfort and possible vagal reaction during sheath exchange. Through the sheath, the previously prepared dilatation balloon is advanced over the guidewire. To keep its profile minimal, the balloon (purged of air) is kept completely deflated by constant negative pressure from a syringe and is introduced into the sheath with rotation.

Under fluoroscopy and using two operators, the extra-stiff guidewire is kept in the left ventricle as the balloon valvuloplasty catheter is advanced and positioned to straddle the aortic valve. Using the proximal and distal markers of the balloon, the operator attempts to place the midballon at the level of the calcific aortic valve. Figure 33.6 illustrates the unfilled balloon straddling the aortic valve.

In most normal-sized adult patients with an adequate aortic valve annulus, we begin with a 20- or 22-mm-diameter, 4- to 6-cm-long balloon. Measurement of the aortic annulus diameter from echocardiography, usually in a long-axis view, improves balloon size selection. A balloon-to-annulus ratio of about 1 is desirable. In very small or frail patients the operator can start with an 18-mm balloon or (very rarely) a 15-mm balloon. The balloon is filled with a contrast medium diluted 8 or 9 to 1 using either a very large syringe or an angioplasty end-deflator-type device. Care must be taken to maintain balloon position within the valve orifice to achieve an effective dilatation. The balloon catheter tends to jump either forward or backward with the force of ventricular systole. Therefore, the procedure is performed with rapid ventricular pacing. A pacing catheter is advanced into the right ventricle. Immediately before balloon inflation, rapid pacing at a rate between 180 and 220 beats/min is instituted. The rapid pacing results in a marked reduction in left ventricular ejection and prevents ejection of the balloon during inflation.
When the systemic pressure falls below 60 mmHg the balloon can be inflated and will usually remain in a stable position within the annulus. Pacing should be used only for a minimum amount of time to avoid causing myocardial ischemia. To achieve optimal balloon positioning, pacing, and balloon inflation requires significant coordination among the operators and the person running the pacemaker. We constantly monitor the ECG for arrhythmia and ischemia, as well as for aortic pressure. If tolerated clinically, the balloon can be left inflated for 15 to 20 seconds. It is then withdrawn into the aorta as it begins to deflate, maintaining guidewire position in the left ventricle. Pulling the balloon back immediately after full inflation is reached minimizes the duration of hypotension caused by obstruction of the aortic valve. A period of stabilization to allow blood pressure and ECG changes to return to baseline should be allowed before further dilatations.

It is often necessary to exert considerable force on these balloons to expand them fully and relieve the “waist” caused by the stenotic aortic valve, and it is difficult to achieve full inflation of these large balloons using the 20- or 50-ML syringe needed to provide adequate volume. If the balloon is connected to the larger syringe with a short pressure tubing and a high-pressure stopcock, the side arm of the stopcock can be attached to a 10-ML syringe filled with diluted contrast to inflate the balloon after the larger syringe has been used to its maximal volume. This maneuver of adding additional contrast to the balloon through the side arm of a three-way stopcock, however, can easily result in balloon rupture. A first balloon inflation with the large syringe only to test the patient's response to balloon inflation, followed by second and third inflations boosted to a maximum balloon diameter, is a careful approach to achieving optimal use of each balloon size. After several dilatations with a single balloon or after balloon rupture (not an infrequent occurrence), the balloon is withdrawn through the sheath, leaving the exchange-length, heavy-duty wire in place. It is frequently necessary to remove the arterial sheath along with the deflated valvuloplasty balloon, since valvuloplasty balloons do not always rewrap adequately to allow removal through the sheath.

A pigtail catheter is then reintroduced over the exchange-length guidewire back into the left ventricle, and measurements of the pressure gradient and cardiac output are repeated. The aortic valve area is calculated. Our usual goal is to achieve a valve area of at least 1 cm². If a desirable result has not been achieved, we may then change to a larger diameter balloon and repeat the procedure (a 14F sheath may be necessary to accommodate a 23- to 26-mm balloon). If an adequate result is still not achieved, a dual-balloon technique (using a pair of 15- or 18-mm balloons if aortic annulus size permits) can be attempted, although this requires accessing the contralateral femoral artery for introduction of the second balloon. Of course, the potential for aortic insufficiency increases with larger balloon sizes. Pressure is monitored through the side arm of the large arterial sheath during the procedure. Figure 33.7 illustrates the dual-balloon technique, and Figure 33.8 shows the progressive reduction in gradient...
Figure 33.7  

A. Balloon aortic valvuloplasty using the double-balloon technique in a 94-year-old woman who presented with syncope and heart failure. Full inflation of two 18-mm-diameter, 5.5-cm-long Scimed balloons across the stenotic aortic valve. B. A Mullins sheath has been passed through the left atrium across the mitral valve. The tip marker can be seen in the left ventricular inflow. Through the Mullins sheath, a 7F single-lumen balloon catheter has been advanced into the left ventricle and looped in the apex to point upward toward the aortic valve. The silhouette of the inflated balloon at the tip of the catheter can be noted just within the curve of the pulmonary artery catheter. C. A wire has been passed through the 7F balloon tip catheter, traversing the left ventricle and passing into the aortic arch and then the descending aorta. D. The proximal part of a 0.032-inch wire can be seen passing through a 14F sheath in the inferior vena cava (left). The J curve of the wire can be seen in the descending aorta (right). A microsnare has been passed over the distal end of the wire in the descending aorta. The snare will be anchored on the wire and left in place in the descending aorta to stabilize the wire for balloon passage through the left ventricle into the aortic valve. E. The inflated Inoue balloon is seen in the calcified aortic valve leaflets. The wire loop has been straightened in the left ventricle during inflation. After balloon deflation, the balloon will be pulled back into the left atrium and the loop reestablished in the left ventricle.
Figure 33.8 Balloon aortic valvuloplasty in an elderly patient with severe calcific aortic stenosis. A. Baseline pressure gradient across the stenotic aortic valve measured with one catheter in the left ventricle (LV) and a separate pigtail catheter in the ascending aorta (AA). There is a 58-mmHg mean gradient and an 80-mmHg peak-to-peak gradient across the valve. B. A reduction in the aortic valve gradient after a series of progressive single-balloon dilations of the aortic valve. C. A marked reduction in aortic valve gradient after dual-balloon valvuloplasty.
with single-balloon, followed by dual-balloon, valvuloplasty. Following a successful procedure, patients are placed in the recovery area or in the coronary care unit for continued observation. The femoral arterial sheaths are removed using suture closure devices, or with hemostasis maintained by a FemoStop™ device. Since prolonged compression is needed, rigid clamps should be avoided.

An alternative approach is to use an antegrade trans-septal route.69,70 After right femoral venous and trans-septal access, a balloon flotation catheter is used to pass through the left atrium and left ventricle, and into the aorta (Figure 33.7B). A wire is exchanged into the descending aorta (Figure 33.7C). An extra-support guidewire is passed into the descending aorta and snared from the arterial side for stability (Figure 33.7D). The valvuloplasty balloon catheter is then maneuvered over the guidewire antegrade and the balloon inflated in the aortic valve.

This technique is more complex than the retrograde approach. After trans-septal access is accomplished via a 14F venous sheath, a single-lumen balloon flotation catheter is passed across the mitral valve into the left ventricle. With the balloon inflated, preshaped curved guidewires can be introduced to encourage the balloon to make a curve around the left ventricular apex and take a course upward toward the aortic valve. The valve is crossed antegrade, sometimes with the balloon deflated to facilitate passage across the stenotic valve. Once in the ascending aorta, a guidewire can be advanced through the aortic arch into the descending aorta. Via a 6F or 7F arterial sheath, a 10-mm gooseneck snare is used to grasp the wire in the descending aorta. The wire can be either exteriorized and clamped on the arterial side or venous puncture may be "preclosed" with a percutaneous closure device or postclosed with superficial, temporary figure-of-eight sutures (see Chapter 6). A 6F closure device is adequate for this purpose. Also, a relatively larger balloon can be introduced in this manner as compared with the retrograde approach. The Inoue balloon can be inflated to 24 to 26 mm diameter without having to exchange balloons. The inflate/deflate cycle of the Inoue balloon is also more rapid than that of a conventional large balloon and thus results in a shorter period of hemodynamic instability during balloon inflations. The transcirculatory wire, however, can prop open the mitral or aortic valve in some patients, causing regurgitation with slowly progressive hypotension. In this situation, the technique must be abandoned and the retrograde approach used. Another advantage of the antegrade approach is nondependence on the arterial circulation for passage of catheters in a population where diffuse arterial disease is relatively common. Even so, some patients will exhibit a progressive decline or lack of recovery of systolic pressure after balloon inflations using either the antegrade or the retrograde technique, and it may then be wise to accept the result of the first balloon inflation. Larger valve areas have been obtained with the antegrade approach, possibly because larger balloons can be used or because the shape of the Inoue balloon better conforms to the sinus of Valsalva. Removal of the wire loop must be done with a catheter over the wire to protect the mitral and aortic valves from the "cheese cutter" effect of the bare wire.

Clinical Results and Complications

In the large Mansfield Scientific balloon aortic valvuloplasty registry, data were collected from 27 clinical centers across the United States and Europe from 6,742 patients with calcific aortic stenosis undergoing balloon aortic valvuloplasty between 1986 and 1987.71 Balloon aortic valvuloplasty resulted in an increase in aortic valve area from 0.5 ± 0.18 to 0.81 ± 0.18 cm², and a decrease in mean aortic valve pressure gradient from 60 ± 24 to 30 ± 14 mmHg. There was also an accompanying increase in cardiac output from 3.86 ± 0.55 to 4.01 ± 0.51 L/minute. Complications were experienced in 22.6% of patients, which included a procedural death rate of 4.9%, death within 7 days of 2.6%, emboli 2.2%, ventricular perforation 1.4%, and emergency aortic valve replacement 1.2%. The NHLBI balloon valvuloplasty registry enrolled patients from 1987 to 1989 at 24 clinical centers.72 Similar results were obtained, with balloon aortic valvuloplasty increasing aortic valve area from 0.5 ± 2 to 0.8 ± 0.5 cm², decreasing aortic valve pressure gradient from 57 ± 30 to 29 ± 13 mmHg, and increasing cardiac output from 3.9 ± 1.2 to 4.1 ± 1.2 L/minute.

The most common complication was local vascular injury, requiring surgical repair in 5.7% of patients.73 The requirement for transfusions has been significantly diminished by the use of percutaneous suture closure for the management of the large-caliber arterial puncture necessary for retrograde aortic valvuloplasty. Perclose devices must be preplaced after arterial access is obtained.74,75 After placing a 6F or 8F sheath in the femoral artery, the sheath is exchanged for a Perclose device, the sutures of which are deployed but not tied. A wire is replaced in the Perclose device, and an exchange is made
for a 12F or 14F sheath for valvuloplasty. At the conclusion of the procedure, a wire is replaced in the sheath so that vascular access can be protected while the Perclose knots are tied. If hemostasis is secure, the wire is removed and the knots tightened. If hemostasis with Perclose fails, the sheath can be replaced and a compression device can be used. In one report, this approach decreased the need for transfusions after aortic valvuloplasty from 23% to 0% of patients.75 Preclosure techniques may also be used in the same manner for large-bore venous punctures for antegrade aortic valvuloplasty, mitral valvuloplasty, or pulmonic valvuloplasty.

Overall complications include procedural death (2%), cardiac arrest (5%), emergency aortic valve replacement (1%), left ventricular perforation (2%), embolic stroke, and systemic emboli (1%). Ventricular arrhythmias and left bundle branch block are very commonly induced during the procedure; however, both are usually transient in nature. In patients with underlying bundle branch block, it is useful to place a temporary right ventricular pacemaker for aortic valvuloplasty procedures.

Long-Term Results

Restenosis with recurrent symptoms is common in the first year following balloon aortic valvuloplasty in the adult with calcific aortic stenosis.76-78 The mean duration of relief of symptoms is about 1 year. In the NHLBI-sponsored balloon valvuloplasty registry, the survival at 1, 2, and 3 years was 55%, 35%, and 23%, respectively, in the 674 patients undergoing balloon aortic valvuloplasty.72 The 1-year survival rate in the Mansfield registry of 492 patients was 64%, with an event-free survival rate of 43%.71,79 Therefore, it must be emphasized that, when at all feasible, definitive aortic valve replacement is the technique of choice for managing the adult patient with severe calcific aortic stenosis.

Short-term clinical improvements associated with balloon aortic valvuloplasty may be accompanied by improvement in systolic and diastolic left ventricular function in some patients.80 Patients with significantly depressed left ventricular function undergoing this procedure have a very poor long-term prognosis.81 In the patient with cardiogenic shock who has been stabilized with successful balloon aortic valvuloplasty, cardiac surgery with definitive aortic valve replacement should be undertaken soon after the patient stabilizes.63,82 Patients with a good acute clinical response are most likely to benefit from TAVI.83

Percutaneous valve replacement and repair today is one of the therapeutic options available for some patients with valvular heart disease.

Percutaneous pulmonic valve replacement

Percutaneous prosthetic treatment for pulmonic stenosis has been pioneered in children with congenital heart disease who have been previously treated with Fontan conduits in the pulmonary circulation. These conduits contain a porcine prosthetic valve that degenerates as the child grows. Reoperation for degeneration of the pulmonic prosthetic valve is frequently necessary in patients who have already undergone two or three prior surgical procedures for their congenital heart disease. As a nonsurgical alternative, Bonhoeffer et al. pioneered the use of a bovine jugular venous valve prosthesis for stent delivery,84-85 which led to the development of implantable pulmonary valves. The Melody valve (Medtronic) has been approved in the United States for pediatric patients with dysfunctional right ventricular outflow tract (RVOT) conduits and with a clinical indication for intervention represented by either moderate/severe regurgitation or stenosis with a mean RVOT gradient of ≥35 mmHg. The valve is made from a cow’s jugular vein valve sewn onto a metal stent. The Edwards Sapien valve is approved for aortic valve replacement in patients at high risk for surgery and is currently undergoing evaluation in clinical trials for intermediate-risk patients and for re-replacement in patients with degenerated tissue valves. For additional details on the Melody valve and on percutaneous pulmonic valve replacement the reader is referred to Chapter 35.

Percutaneous aortic valve replacement

Though the results of aortic valvuloplasty as a standalone therapy have been disappointing, the results of percutaneous aortic valve replacement have been outstanding.86-89 Cribier et al. in 2002 became the first to use equine pericardial leaflets placed on a balloon-expandable stent to treat aortic stenosis in elderly patients deemed nonsurgical or poor surgical candidates. Since then, the positive results of randomized clinical trials and registry analyses have led to the introduction in clinical practice of two different types of valve prosthesis.88-91 The Edwards Sapien valve was recently approved in the United States, whereas the Medtronic CoreValve is being evaluated in randomized clinical trials (Figures 33.9 and 33.10).

Valve Construction

The Edwards Sapien valve is made with bovine pericardial leaflets mounted on a balloon-expandable stent. It is currently available in two sizes in the United States: the 23-mm
SAPIEN XT and Edwards Sapien transcatheter heart valves (THVs) and their respective delivery systems. The figure illustrates the characteristics of the Sapien XT and Edwards Sapien valves, and the NovaFlex and RetroFlex 3 delivery systems (Edwards Lifesciences, Inc., Irvine, California). Sizes of the valves and diameters of the sheaths are shown. (Reproduced with permission from: Periprocedural and short-term outcomes of transfemoral transcatheter aortic valve implantation with the Sapien XT as compared with the Edwards Sapien valve. J Am Coll Cardiol Intv 2011;4(7):743-750.)

Figure 33.9  

Sapien XT and Edwards Sapien transcatheter heart valves (THVs) and their respective delivery systems. The figure illustrates the characteristics of the Sapien XT and Edwards Sapien valves, and the NovaFlex and RetroFlex 3 delivery systems (Edwards Lifesciences, Inc., Irvine, California). Sizes of the valves and diameters of the sheaths are shown. (Reproduced with permission from: Periprocedural and short-term outcomes of transfemoral transcatheter aortic valve implantation with the Sapien XT as compared with the Edwards Sapien valve. J Am Coll Cardiol Intv 2011;4(7):743-750.)

size for annulus size ranging between 18 and 22 mm and the 26-mm size for annulus size ranging between 21 and 25 mm. The Edwards Sapien valve has been approved for clinical use in the United States and in most other countries. A lower-profile delivery system (Sapien XT) was evaluated in the Partner II clinical trial and it should soon become available for clinical use in the United States, with two additional sizes being available and under evaluation (20 mm and 29 mm) (Figure 33.9, Table 33.5).92

The Medtronic CoreValve is also made of bovine pericardial leaflets, though mounted on a self-expanding stent (Medtronic, Minneapolis, MN). The valve is approved for clinical use in several countries outside the United States, and it is currently undergoing evaluation in clinical trials in the United States. It is available in a 26-mm size for annulus size ranging from 20 to 23 mm, in a 29-mm size for annulus size ranging from 23 to 27 mm, and in a 31-mm size for annulus size ranging from 27 to 29 mm (Table 33.5) (Figure 33.10). Given their rather different characteristics and shapes, each valve has specific positioning within the aortic annulus (Figure 33.11). Several other percutaneous aortic valve replacement devices are currently under development and entering clinical trials93 (Figure 33.12).
Patient Selection, Preparation, and Valve Delivery

Transcatheter aortic valve replacement presents a significant degree of complexity in terms of appropriate patient selection, identification of the optimal vascular access site for valve delivery, and accurate measurement of the aortic annulus for selection of the valve of appropriate size, in addition to the complexities related to aortic valvuloplasty and valve implantation.

Patient Selection

When compared with mechanical or bioprosthetic aortic valves approved for surgical implantation, data on percutaneous aortic valve durability are still limited. Therefore, current indications for transcatheter aortic valve replacement include patients who are not eligible candidates or who are considered at high risk for standard surgical aortic valve replacement. Several risk calculators have been developed for the assessment of surgical risk in patients undergoing coronary artery bypass surgery and valve replacement (Figure 33.13). As of today, the Society of Thoracic Surgeons (STS) score and the EuroScore are the most widely used risk calculators. High risk is defined as a EuroScore of >20% or an STS score of >8%, or presence of additional risk factors that might not be included in the EuroScore or STS score such as chest radiation therapy, porcelain aorta, hepatic cirrhosis, prior cardiac surgery, and any other major contraindication to open chest surgery.

Choice of Delivery Approach

Both antegrade and retrograde techniques have been utilized for delivery of the aortic valve prosthesis. The antegrade techniques include the transapical approach (see also Chapter 8) and the transvenous/trans-septal approach. The retrograde techniques include the transfemoral, subclavian, and direct transaortic approaches (see Chapter 8). Each approach has benefits and limitations. The profile of the aortic valve prosthesis was 24F in its initial iterations, which made the use of antegrade transvenous approach attractive, although delivery of a large prosthesis through the turns involved in traversing the left atrium and left ventricular apex en route to the aortic valve may be difficult. The retrograde approach through the femoral artery is limited by the size of the femoral artery (minimum 7 to 8 mm), and by the presence of aorto-iliac tortuosity and peripheral vascular disease. The transapical and transaortic approaches have the advantage of overcoming these limitations, thus allowing treatment of patients who otherwise might not be suitable candidates for percutaneous valve replacement because of peripheral vascular disease or a small femoral artery. In addition, the antegrade transvenous or transapical approaches can be used successfully in patients with heavily calcified or “porcelain” aorta. It is routine to obtain a CT of the distal aorta, iliac arteries,
Table 33.5 Transcatheter Valves and Delivery Systems

<table>
<thead>
<tr>
<th>Valve</th>
<th>Size (mm)</th>
<th>Annulus Diameter (mm)</th>
<th>Delivery Approach</th>
<th>Delivery System</th>
<th>Sheath Size (F)</th>
<th>Femoral Artery Size (mm)</th>
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<td>23–27</td>
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<td>Transfemoral/transaxillary/subclavian</td>
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<td>Ascendra 2</td>
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*Expandable delivery sheath, eSheath, is a new delivery sheath developed by Edwards Lifesciences that can expand during advancement of the valve and then retract to a smaller size.

and femoral artery for assessment of minimum vessel diameter (from the femoral artery entry site to the aorta) as well as the presence of calcification and tortuosity. Recommended minimum diameters of the ilio-femoral arteries for different delivery systems are listed in Table 33.5.

**Prosthesis Size Selection**

Sizing of the aortic annulus and assessment of the aortic root are critical components in the preparation for the procedure and are performed using transthoracic echocardiography, transesophageal echocardiography, and CT. Transesophageal echocardiography has been the preferred modality, although recent data support the use of CT angiography as a better approach. It should be noted that the aortic annulus has an oval shape and therefore measurements should be obtained for the two perpendicular diameters. Once the measurements are obtained, a valve that is generally 10% to 20% larger than the measured diameter should be selected.

**Deployment of the Valve**

Transcatheter aortic valve replacement includes all the steps of aortic valvuloplasty described above, with the addition of insertion of a larger arterial sheath and delivery of the valve itself. Aortic valvuloplasty is performed in preparation for
deployment of the valve. After removal of the valvuloplasty balloon, the valve delivery system is advanced over the guidewire and positioned across the aortic valve annulus. Appropriate positioning of the valve is critical, as a position of the valve either too high or too low can result in valve embolization, in the development of paravalvular leaks, or in obstruction of the origin of a coronary artery. The optimal view is the view that places the aortic valve annulus on edge and that results in alignment of the coronary and non-coronary cusps on a single line. In the past, multiple views used to be obtained with aortography. The introduction of multimodality imaging and the ability to import CT images in the cardiac catheterization suite have markedly improved the ability to identify the ideal view for valve deployment (Figure 33.14). More recently three-dimensional angiographic reconstruction of rotational aortic root angiography has emerged as a new modality for the identification of the optimal view for valve positioning in the cardiac catheterization laboratory.97

Clinical Results
The Placement of Aortic Transcatheter Valves (PARTNER) trial has provided landmark data on the effectiveness of transcatheter aortic valve replacement. In the first cohort reported (PARTNER Cohort B), 358 patients with aortic stenosis who were not considered to be candidates for surgery (defined as >50% risk of death or other major adverse events at 30 days based on STS score) were randomized to medical therapy versus transcatheter aortic valve implantation with the Edwards Sapien valve.88 At 1-year follow-up, the mortality rate was 30.7% in the TAVI group when compared with 50.7% in the standard medical therapy group (hazard ratio with TAVI, 0.55; 95% confidence interval [CI], 0.40 to 0.74; \( P < 0.001 \)). The benefit of TAVI was also observed when a combined endpoint including death from any cause or repeat hospitalization was analyzed (42.5% with TAVI versus 71.6% with standard therapy, \( P < 0.001 \)) and when New York Heart Association functional class was evaluated. In the PARTNER trial Cohort A, 699 patients with severe, symptomatic aortic stenosis and at high risk for traditional aortic valve replacement (STS score >10%) were randomized to either the Edwards Sapien valve implantation via transfemoral or transapical delivery or the standard surgical aortic valve replacement.89 The mortality rate was 3.4% in the transcatheter group and 6.5% in the surgical group (\( P = 0.07 \)) at 30 days and 24.2% and 26.8%, respectively, at 1 year (\( P = 0.44 \)). A trend toward a higher rate of major stroke was observed in the TAVI

Figure 33.13 Odds ratio of the variables included in different surgical risk models. (Reproduced with permission from Van Mieghem NM, Head SJ, van der Boon RMA, et al. The SURTAVI model: proposal for a pragmatic risk stratification for patients with severe aortic stenosis. EuroIntervention 2012; 7-online publish-ahead-of-print March 2012.)
Figure 33.14  A. CT 3D reconstruction of the aortic arch and aortic annulus in preparation for TAVI. The coronary and noncoronary cusps are aligned on a single line. B. Automatic segmentation and contouring of leaflets. (Courtesy of Mauricio Cohen, University of Miami.) (See also Chapter 3.)
group as compared with the surgical group at 30 days (3.8% versus 2.1%, \( P = 0.20 \)) and at 1 year (5.1% and 2.4%, respectively, \( P = 0.07 \)). Major vascular complications were significantly more frequent with TAVI, while the incidence of major bleeding and atrial fibrillation was significantly higher in the surgical group. At 2-year follow-up, the noninferiority of TAVI when compared with conventional aortic valve replacement was maintained. Several registry analyses have shown feasibility and overall excellent outcomes also with the CoreValve, which is currently undergoing further evaluation in the United States in randomized clinical trials.

### Complications

The complications of transcatheter aortic valve replacement include complications related to the aortic valvuloplasty and those related to the valve implantation. Vascular complications are the most common. Additional complications include stroke (see above), valve embolization (extremely rare), aortic annulus rupture, obstruction of the origin of a coronary artery (very rare), development of paravalvular leaks, and development of complete heart block requiring permanent pacemaker placement. Permanent pacing may be needed in up to 25% of patients receiving the self-expanding CoreValve device.

It is clear that percutaneous valve prosthetic devices will continue to evolve rapidly and that improvement in the profile of devices and delivery systems will occur incrementally. The durability of valve prostheses that have been crimped on a balloon and then compressed by a relatively high-pressure balloon expansion cannot be assumed to be similar to that of surgically implanted tissue valves, and experience with long-term results in these patients will take time to develop.

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**PERCUTANEOUS MITRAL VALVE REPAIR**

Even though we have already discussed the success of balloon valvuloplasty for the treatment of mitral stenosis, mitral regurgitation previously has been treatable only by surgical methods (placement of an annuloplasty ring, leaflet resection, chordal replacement, or the edge-to-edge Alfieri stitch repair). Percutaneous approaches to mitral valve repair have now been used successfully, and both annuloplasty and edge-to-edge repair approaches are under active investigation. Annuloplasty may be accomplished via the coronary sinus, the course of which parallels that of the mitral annulus, by placing devices that stretch or reshape the coronary sinus to cause contraction of the mitral annulus, with displacement of the posterior mitral annulus toward the septum. Several of these devices have shown efficacy in preclinical experience and are now entering clinical trials (Figures 33.15–33.16). Some of the challenges involved with this approach include the variability of the coronary sinus in its anatomic relation to the mitral valve annulus, the course of the circumflex coronary artery and its branches over or under the coronary sinus, and the potential for injury to the thin-walled sinus. To overcome those limitations, transventricular approaches are also under development, which involve plication of the mitral annulus percutaneously via annular sutures placed via a retrograde approach (across the aortic valve and into the space between the posterior leaflet and the lateral left ventricular wall) (Figures 33.17–33.19).

Another surgical approach for mitral valve repair involves the plication of the free edges of the two mitral leaflets using a suture or pledget, with a resultant bow tie or double-orifice mitral valve. This edge-to-edge repair technique was pioneered by Alfieri in the early 1990s. A percutaneous method to deliver a clip (MitraClip, Abbott Vascular, Menlo Park, CA) to the mitral leaflets via a trans-septal approach has been used successfully in a 40-patient Phase 1 trial (Figures 33.20–33.22). The resultant double-orifice repair is similar to surgical repair, ultimately maintained by fibrosis of the clip with a tissue bridge. The procedure is done using...
transesophageal echocardiographic guidance, so the results of clip placement can be evaluated during the procedure, in a manner analogous to the evaluation of the results of surgical repair on the operating table. In the event of adequate control of mitral regurgitation not being achieved, a second clip may be used, or the clip may be withdrawn with no apparent harm to the mitral leaflets. The randomized EVEREST II trial comparing percutaneous edge-to-edge mitral repair to surgical mitral repair showed that surgery is more effective in reducing mitral regurgitation, but that percutaneous repair is
safer and achieves both reductions in left ventricular chamber volumes and symptoms and improvements in quality of life that are similar to those achieved with surgery. Subgroup analysis from this trial showed that the best results for percutaneous repair were achieved in older patients with poor left ventricular function and functional mitral regurgitation. This had led to wider use of the MitraClip in poor surgical candidates with ischemic or dilated cardiomyopathy and functional mitral regurgitation. Early studies have shown a reduction in heart failure rehospitalization rates in this population. This is a group of patients with no other options for therapy. A randomized trial to compare MitraClip to medical therapy is underway for these high-risk, functional mitral regurgitation patients.

Figure 33.18 Direct annuloplasty with the Mitralign system. Pairs of pledgets have been placed to plicate the orifice (arrows). The lower panels illustrate cinching of the pledgets to decrease the mitral orifice circumference.

Figure 33.19 Direct annuloplasty with the Valtech annuloplasty ring. The ring is delivered via trans-septal access and anchored to the annulus with a screw mechanism, seen in the inset.
Fluoroscopic images of the steps of the MitraClip procedure. 

**A.** The arrow shows the clip in the left atrium (LA). LV, left ventricle; TEE, transesophageal echo probe. 

**B.** The open clip has been advanced into the left ventricle. 

**C.** The clip arms are everted to allow withdrawal back into the left atrium without chordal entanglement. 

**D.** The open clip has been readvanced into the left ventricle to attempt a better grasp of the leaflet edges. 

**E.** The clip has been closed to grasp the mitral leaflet free edges. 

**F.** The arrow shows the clip after release from the delivery system.

The two-clip MitraClip procedure. If there is a residual jet, a second clip can be passed adjacent to the first. On the left panel, a second clip has been passed on the anterolateral side of the first. The middle panel shows the second clip in a closed configuration, denoted by the arrow. On the right panel, the second clip has been released (circled). LA, left atrium; LV, left ventricle.
The MitraClip procedure is mostly transesophageal echo guided. Panel A shows the MitraClip above the leaflets in the left atrium (LA). In panel B the clip is in the left ventricle, ready to be pulled back to grasp the leaflets. In panel C the open arms of the clip have contacted the leaflets. AML, anterior mitral leaflet; LV, left ventricle; Ao, aorta.
From the above discussion, it is clear that percutaneous treatments for valvular heart disease are poised for major technical and clinical growth over the next decade. The percutaneous approach may be a treatment option for patients with critical valve disease and for whom surgical intervention now offers in relation to bypass surgery. Issues ventricular dysfunction; or perhaps a true alternative to surgical valve correction (akin to what percutaneous coronary intervention now offers in relation to bypass surgery). Issues regarding optimal device design, indications, safety, and efficacy still need to be worked out, however, before the position of these exciting new catheter-based therapies can be established relative to conventional medical and surgical treatments.

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Management of patients with carotid, renal, or peripheral arterial disease is complex. It requires not only excellent technical skills but also a full understanding of the therapeutic options including the risk of surgery or medical therapy alone. A full understanding of the natural history of the disease process and prognosis are also important to balance the risk and benefit associated with any procedure. Lastly, all procedures are prone to complications. Thus, an understanding of the incidence, risk factors and management of complications should be part of the knowledge base of endovascular specialists.

In this chapter, we hope to provide a comprehensive guide to peripheral interventions. Clinical presentation, differential diagnosis, diagnostic modalities, as well as known complications of each procedure and ways to prevent or mitigate them are presented. In addition to this chapter, supplemental clinical and technical tips are provided in Chapter 19 on angiography of the aorta and peripheral arteries and in Chapter 46 for integration of clinical, diagnostic, and therapeutic aspects in real-life case profiles, organized in the same head-to-foot sequence of regional techniques.

## GENERAL CONSIDERATIONS

Arteriosclerosis, whether located within the coronary or non-coronary arteries, shares a similar pathophysiologic basis, starting with fatty streak and progressing to larger plaques with positive and negative remodeling leading to variable luminal compromise. Gradually, over many years plaque progression with noncompensatory remodeling leads to narrowing of the arterial lumen causing ischemia. In the peripheral arteries, occasionally, plaques may rupture leading to thrombosis and even embolization. Understanding this pathophysiologic process provides the basis for medical management of peripheral vascular disease (PVD). Given similar pathophysiologic mechanisms, coronary artery disease (CAD) and PVD share similar risk factors. These include family history of vascular disease, tobacco smoking, diabetes mellitus, hypertension, hyperlipidemia, advanced age, and inactivity. Unfortunately, despite such similarity, PVD is frequently underdiagnosed and undertreated. More importantly, unlike CAD, risk factors such as hyperlipidemia in patients with PVD frequently are not treated as aggressively. There is no doubt that PVD is the CAD risk equivalent and should be treated as vigorously with aggressive lipid lowering, blood pressure control, smoking cessation, diet, exercise, and antiplatelet therapy.

## CAROTID ARTERIES

Approximately 800,000 individuals in the United States experience a stroke each year, with a 30-day mortality of 10%. Another 500,000 or more individuals suffer a transient ischemic attack (TIA) annually. The risk is higher in women, with approximately 55,000 more women than men having a stroke each year. Furthermore, blacks have an almost two-fold higher risk of first-stroke than whites.

The majority of strokes (~90%) are ischemic in nature; of these, only 15% to 20% are attributed to carotid artery stenosis. Importantly, the severity of carotid artery stenosis is strongly predictive of stroke risk, with a 5-year risk of 7.8% in asymptomatic patients with less than 50% stenosis versus 18.5% in patients with 75% to 94% stenosis. Furthermore, the presence of carotid artery disease is a significant marker of cardiovascular risk, highlighting the importance of risk factor modification and preventive strategies in this high-risk patient population.

Carotid endarterectomy (CEA) has long been considered the gold standard for carotid artery intervention. In the last 50 years since CEA was initially reported, significant technical advancements have improved morbidity, mortality, cost, and patient comfort. It was only after 40 years of widespread application of CEA, however, that definitive proof of its benefit was obtained. The landmark North American Symptomatic
Carotid Endarterectomy Trial (NASCET) and Asymptomatic Carotid Atherosclerosis Study (ACAS) investigations thus demonstrated that surgical endarterectomy, when performed for carotid bifurcation disease by experienced vascular surgeons on appropriately selected patients, effectively reduced the likelihood of ipsilateral stroke compared with standard medical therapy in both symptomatic and asymptomatic patients respectively.18,19 Indeed, a meta-analysis of all randomized clinical trials of CEA versus medical therapy show a 30-day risk of death and stroke of 3% for asymptomatic carotid disease and 6% for symptomatic patients,20,21

Clinical trials have provided level I evidence for CEA for both symptomatic and asymptomatic patients with severe carotid disease.18,19 However, these studies have been limited by a number of factors. First, the patients selected for these trials were low to moderate risk. For example, presence of severe CAD or heart failure was an exclusion for many of these trials. Furthermore, medical therapy in that era was limited to aspirin and occasional lipid lowering agents. Therefore, contemporary data for CEA versus medical therapy are currently not available. Lastly, myocardial infarction (MI), a well-known complication of CEA, has not been included in the composite endpoints in any of these trials.22

Because of the limitations and the need for general anesthesia in many cases, a less invasive approach was developed. It was originally performed as balloon angioplasty alone, but later as a result of pioneering effort by Drs. Roubin, Iyer, Yadav, Vitek, and others, carotid stenting gained significant momentum.23-27 In most institutions, percutaneous treatment of carotid arteries remained reserved for those circumstances wherein the surgical risk was very high.24,28 In 2001, Roubin published a 5-year single-center follow-up of 528 consecutive patients undergoing carotid stenting, with a 98% success rate, 1.6% mortality, and a combined endpoint of death and stroke of 7.4% at 30-day follow-up.29 Of note, the rate of stroke decreased significantly over the 5-year study period, from 7.1% within the first year to 3.1% in the fifth year. This was felt to reflect improvements in technique, interventional devices, and pharmacotherapy. The seminal work of Roubin and colleagues demonstrated that the results of carotid stenting could be comparable with CEA and highlighted the need for randomized controlled studies to determine the optimal treatment strategy.

The first such randomized controlled trial was the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) trial.30 The angioplasty procedure included stent insertion in only 26% of cases, the remainder were performed with balloon angioplasty alone. Distal protection was not available. Despite these limitations, the immediate and long-term results of angioplasty and endarterectomy were equivalent. Subsequently, smaller studies confirmed the benefits of carotid stenting, although the potential for distal embolization and consequent stroke remained a limiting factor (Table 34.1). To address this concern, distal protection devices were developed to minimize or prevent distal embolization.

The first randomized trial comparing carotid stenting with emboli protection to CEA was the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial.31 The SAPPHIRE study randomized 307 patients from 29 American centers to either carotid artery stenting (CAS) with distal protection or CEA. Entry criteria included asymptomatic carotid stenosis (>80% by ultrasound) or symptomatic stenosis (>50%), plus at least one feature placing the patient at higher risk for surgical endarterectomy. These features included age older than 80 years, the presence of congestive heart failure, severe chronic obstructive pulmonary disease (COPD), previous endarterectomy with restenosis, previous radiation

<table>
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<th>Carotid Endarterectomy</th>
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<tr>
<td>Periprocedural myocardial infarction</td>
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<td>Longer recovery</td>
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*Arrow indicates incidence when comparing carotid endarterectomy to stenting.
therapy or radical neck surgery, or lesions distal or proximal to the usual cervical location. Patients were screened by a team including a vascular surgeon, an interventionalist, and a neurologist. Consensus that the patient was a good candidate for both procedures was required before randomization; those rejected as surgical candidates underwent stenting and were included in a separate stent registry, whereas those rejected as candidates for intervention underwent surgery and were included in a surgical registry. At 30 days, the major adverse clinical events (MACE) were reduced by more than 50% with CAS as compared to surgery (5.8% for CAS, 12.6% for CEA, \( P = 0.047 \)). Interestingly, 408 patients in the SAPPHIRE study were deemed inappropriate for CEA and were therefore enrolled in the stent arm. Only seven patients were deemed inappropriate for carotid artery stenting.31

More recently, five randomized trials have evaluated the role of CEA versus CAS (Table 34.2). Endarterectomy versus Stenting in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S), Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE), and International Carotid Stenting Study (ICSS) were conducted in Europe and enrolled patients with symptomatic carotid disease only.32-34 These trials collectively failed to show equivalency between CAS and CEA. Indeed, CAS was associated with significantly higher 30-day stroke risk. Because of these data the Center for Medicare Services (CMS) has limited the use of CAS for asymptomatic high-risk individuals only.35 However, despite being randomized, these trials have been widely criticized for including operators with minimal CAS experience and for their failure to use embolic protection devices.36 In 2010, the long awaited National Institute of Health sponsored Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) was finally published.37 Unlike the three European trials, CREST showed equivalent 30-day outcome between CEA and CAS for the composite endpoint of death, stroke, and MI. Furthermore, CEA was associated with higher periprocedural MI, and cranial nerve damage whereas CAS had higher incidence of minor stroke.37 Collectively, the data from randomized clinical trials to date clearly demonstrate that a personalized approach to CAS and CEA would most likely result in the best outcome. Therefore, clinical and anatomic features including operator experience should guide the best revascularization strategy in patients with severe carotid disease (Table 34.3).

### Concomitant Carotid and Coronary Artery Disease

Around 7% to 10% of patients with severe CAD (left main trunk or three-vessel disease) have concomitant severe carotid disease.38 While most experts agree that symptomatic carotid disease should be treated prior or in conjunction with coronary bypass graft (CABG) surgery, little consensus exists for asymptomatic carotid disease.39-41 The risk of perioperative stroke in low-risk patients with asymptomatic severe (>80% stenosis) carotid disease undergoing CABG surgery is around 2% to 3%.42 However, most published reports of combined CEA and CABG or staged CEA followed by CABG surgery reveal a 9% to 12% 30-day risk of death, stroke, or MI.43 Based on the current available data we have recommended medical therapy for low-risk asymptomatic unilateral carotid disease in patients requiring CABG surgery (Figure 34.1). For all other cases including asymptomatic carotid disease stenting appears to be superior to the combined or staged CEA.49

### Treatment Considerations and Technique

#### Preprocedure Evaluation

A thorough history should be undertaken to determine symptom status. A full neurologic examination should then be performed by an individual certified in the NIH stroke scale.44 A baseline carotid duplex, and ideally a computed tomography (CT) or magnetic resonance imaging (MRI) of the head, should be obtained. Once a severe stenosis is identified, clinical and anatomical features need to be considered and a decision regarding the best approach should be made in conjunction with the patient and family. We prefer premedication with aspirin and clopidogrel (at least 300 mg prior to intervention with sufficient time to achieve efficacy), and prehydration to minimize hypotension.

#### Angiographic Evaluation

An arch aortography is performed under digital subtraction in the left anterior oblique (LAO) 30° to 40°. In this image the patient's head should be turned toward the right and tilted upward. Arch aortography is important in identifying the aortic arch (whether it is type I, II, or III), which will impact endovascular approach and the selection of appropriate catheters in order to engage the carotid arteries (Figure 34.2).45 Additionally, the takeoff of carotid and vertebral arteries should be examined. Other factors such as degree of calcification, presence of ostial common carotid disease, and involvement of the external carotid artery may affect the procedural approach and success (Figure 34.3). Subsequently, using appropriate diagnostic catheters such as 5F angled glide or JR4 for type I arch and Vitek, Simmons, or JB2 for more challenging anatomy, selective two-vessel (or four-vessel if indicated) cerebral angiography is performed. When performing selective angiography, the patient's head should be secured to the table using carotid head gear. Images in the ipsilateral 30°–40° and lateral projections should be considered. Formal measurements must be made of the target lesion using NASCET criteria where distal reference is used beyond the carotid bulb. Intracranial cerebral angiography should be performed at baseline to rule out intracerebral arterial abnormalities and to establish the baseline arterial anatomy (Figure 34.4). Of particular importance are the lesion morphology and the presence of collateral flow, patency of the...
Table 34.2  Outcomes (30 Days) of Selected Contemporary Randomized Trials of Carotid Endarterectomy Versus Stenting

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>Year</th>
<th>EPD (%)</th>
<th>Symptomatic (%)</th>
<th>Death</th>
<th>Stroke</th>
<th>Myocardial Infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAPHIRE</td>
<td>334</td>
<td>2004</td>
<td>96</td>
<td>29</td>
<td>2.5</td>
<td>1.2</td>
<td>6.1</td>
</tr>
<tr>
<td>EVA-3S</td>
<td>527</td>
<td>2008</td>
<td>92</td>
<td>100</td>
<td>0.1</td>
<td>0.1</td>
<td>0.8</td>
</tr>
<tr>
<td>SPACE</td>
<td>1200</td>
<td>2008</td>
<td>27</td>
<td>100</td>
<td>0.9</td>
<td>0.7</td>
<td>NR</td>
</tr>
<tr>
<td>ICSS</td>
<td>1713</td>
<td>2010</td>
<td>72</td>
<td>100</td>
<td>0.8</td>
<td>2.3</td>
<td>0.4</td>
</tr>
<tr>
<td>CREST</td>
<td>2502</td>
<td>2010</td>
<td>96</td>
<td>53</td>
<td>0.3</td>
<td>0.7</td>
<td>2.3</td>
</tr>
</tbody>
</table>

*EPD, embolic protection device; CEA, carotid endarterectomy; CAS, carotid artery stenting; NR, not reported; EVA-3S, Endarterectomy Versus Stenting in Patients with Symptomatic Severe Carotid Stenosis; SPACE, Stent-Protected Angioplasty Versus Carotid Endarterectomy; ICSS, International Carotid Stenting Study; SAPHIRE, Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy; CREST, Carotid Revascularization Endarterectomy Versus Stenting Trial.

circle of Willis, and the dominance of the intracerebral arterial supply (Figure 34.5)."}

Carotid Angioplasty and Stenting Procedure

A list of available equipment for carotid angioplasty and stenting is provided in Tables 34.4 and 34.5. The femoral approach is typically used, although the radial approach in selected cases is possible and may be preferred. Almost all devices are 6F compatible, allowing the use of an 80-cm-long nonkinkable sheath (i.e., Cook Shuttle, Destination, Pinnacle, or ArrowFlex sheaths). Unlike a 90-cm sheath, the 80-cm sheaths are compatible with standard bailout equipments that are typically 100 cm long. We typically use a telescoping system for carotid artery intervention. A 5F long diagnostic catheter is placed inside a sheath once the sheath has already been advanced to the mid descending aorta. The carotid artery of interest is engaged using the diagnostic catheter. Subsequently, the glide wire is advanced into the external carotid artery. Occasionally the wire is left in distal common carotid artery under close watch not to accidently touch the lesion with sheath manipulation. The sheath is advanced up to the ostium of the innominate or left carotid artery. The 5F diagnostic catheter is then advanced to the distal common carotid artery holding the wire and sheath in place. The sheath is then advanced over the diagnostic catheter (or slip cath) in the common carotid artery. The process may require several iterations of advancing catheters and removing slack from the system to achieve final positioning. Once a desired location is reached, the glide wire and catheter are slowly removed to prevent air trapping. One should never cross the carotid lesion with a 0.035 inch wire or catheters.

Certain safety precautions are necessary for CAS procedures: 1) catheters should always be bled back to avoid any air or cholesterol embolization. 2) anticoagulation and antiplatelet therapy should commence prior to advancing any catheters into the carotid system. 3) less time in the carotid system is better. Although one should be cautious and deliberate in the performance of these procedures, the number of complications increases with additional intraarterial time. 4) catheter advancement should always be over a wire, and larger catheters should be transitioned in a stepwise, coaxial fashion over smaller catheters. 5) onlyatraumatic guidewires should be advanced into the internal carotid artery to minimize the risk of spasm or dissection. 6) predilatation is recommended to confirm the ability to adequately dilate the stenosis. 7) the use of self-expanding (SE) stents is preferred for the carotid bifurcation and other compressible sites. 8) Balloon-expandable (BE) stents should be used only for aorto-ostial carotid lesions and distal (e.g., intracranial) internal carotid artery lesions. Eighth, when encountering resistance during advancement of balloons or stent delivery systems, removal and redilation with lower profile devices is appropriate. If an SE stent will not easily cross a predilated lesion, it should not be forced. Ninth, careful periprocedural hemodynamic monitoring is essential. Manipulation within the area of the carotid sinus can cause both acute and prolonged hypotension and bradycardia, requiring fluid resuscitation, atropine or α-adrenergic agents. Pacing is rarely needed but should be readily available. 10) Postprocedure hypertension must also be avoided, so as to minimize the chances of hyperperfusion syndrome, a potentially devastating entity that is occasionally seen following revascularization, particularly in elderly patients with previous near-occlusion and underperfused cerebral circulation. Tenth, postdilation should be performed to relatively low or nominal pressure. It is not necessary to eliminate completely the stenosis to achieve an excellent result. Indeed, attempts to reduce the stenosis to 0% relative to the reference segment may lead to distal embolization, dissection, or resistant hypotension relating to carotid body stimulation or compression.
**Table 34.3** Clinical and Anatomical Characteristics That May Favor Carotid Endarterectomy or Stenting

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Endarterectomy</th>
<th>Stenting</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥70</td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>Age &lt;70</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure (class III/IV)</td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>Ejection fraction &lt;35%</td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>Planned open heart surgery</td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>Recent myocardial infarction (&lt;4–6 weeks)</td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>Unstable angina</td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>Severe pulmonary disease</td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>Contralateral cranial nerve injury</td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>Symptomatic carotid disease</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Intolerance to antiplatelet therapy</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Inability to tolerate conscious sedation</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Low carotid volume operator/center</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td><strong>Anatomical</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-cervical lesion (≥C2)</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Restenosis after previous endarterectomy</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Ostial/below clavicle lesions</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Contralateral carotid occlusion</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Post neck radiation</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Prior radical neck surgery</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Severe tandem lesions</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Spinal immobility of the neck</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Type III aortic arch</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Heavily calcified lesion</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Significant thrombus burden</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Redundant internal carotid artery</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Significant common carotid artery disease</td>
<td>++</td>
<td></td>
</tr>
</tbody>
</table>

**Stent Selection**

If not all, the majority of stents used for carotid disease are nitinol SE stents; however, in rare cases we have used covered stents. Whether open or closed-cell design will have an important clinical significance is not well known. Newer hybrid stents, where the middle of stent is closed cell but ends are open are being developed. In general, the closed-cell design stents are more rigid (Table 34.5).
Concomitant Severe Carotid and Coronary Artery Disease

**Figure 34.1** Potential algorithm to treat severe combined carotid and coronary artery disease. High risk includes severe bilateral carotid disease, unilateral occlusion, bilateral occlusion, stroke or transient ischemic attack within the past 6 months, or evidence of prior neurologic event on imaging studies. CAS, carotid artery stenting; CEA, carotid endarterectomy; CABG, coronary artery bypass graft surgery; PCI, percutaneous coronary intervention.

**Figure 34.2** Aortic arch and the takeoff of great vessels are important aspects of carotid and cerebral intervention. Shown here are the three arch types. Note, in addition to arch type, careful attention should be given to the presence of severe ostial common carotid and innominate disease.
Chapter 34 Peripheral Intervention

PeriRheral Intervention

Figure 34.3 Note the presence of severe internal carotid artery disease (black arrow). Branches of external carotid artery are outlined. (1) Superior thyroid artery. (2) Lingual artery. (3) Facial artery. (4) Ascending pharyngeal artery. (5) Occipital artery. (6) Internal maxillary artery. (7) Superficial temporal artery. (Adapted from Krishnaswamy et al. Catheter Cardiovasc Interv 2010;75(4):530–539.)

Distal Protection

The combination of carotid stenting with distal protection has revolutionized carotid intervention (Table 34.4). The first randomized trial demonstrating outstanding results of carotid stenting with distal protection was the SAPPHIRE trial and this was quickly followed by several registries like ARCHer and SECuRITY. In general, the available cerebral protection devices function either by filtering atheromatous debris out of the flowing blood distal to the lesion or by occluding antegrade flow proximal or distal to the lesion to allow removal of atheromatous debris. Each design has relative merits and potential disadvantages. The filtering devices allow for continuous visualization for precise stent placement and allow cerebral perfusion as antegrade blood flow is unobstructed. The current filter pore size ranges from 80 to 150 microns, raising the question of what diameter of atheromatous debris is required to cause neurologic sequelae. The occluding devices, by design, limit visualization and, in the absence of adequate collateral circulation, may result in prolonged cerebral ischemia. Retrograde embolization to the aortic arch may occur if aggressive injection is performed. However, occluding devices offer the theoretical advantage of protecting against a wider range of particulate sizes. The optimal protection device or combination of protection device and stent remains unclear and is a source of intense clinical investigation. However, early data indicate that proximal protection may have some advantage over distal embolic devices.

Complications

The most feared complication of carotid stenting is stroke at the time of procedure. This complication most frequently happens from distal embolization prior to placement of the embolic protection devices or potential overload of the filters. Manipulation of the catheters and wires to place the sheath in the common carotid artery should be done in deliberate but delicate manner. Proper selection of patient and equipment is critical to prevent such complications. If the filter is filled and there is slow flow in the carotid, aspiration of the proximal column of blood is necessary prior to filter retrieval. Cerebral angiogram has to be carefully assessed for vessel cutoff. Depending on the size and location of the cutoff, wiring of
the lesions or other techniques can be used to minimize the size of infarction. Sometimes t-PA inhibitors can be useful in this situation. Intracranial hemorrhage is another complication that can be devastating. One cause of this is cerebral hyperperfusion, which may be prevented by careful blood pressure monitoring in most cases. Wire-related hemorrhage should be preventable by proper techniques.

Aside from access site related complications, the most common carotid stenting complications are bradycardia and hypotension. The primary operator should be extremely careful during the procedure as cerebral hypoperfusion due to bradycardia and hypotension may result in seizure activity and sudden movement by the patient. Securing the devices during predilatation, stenting, and postdilatation is therefore necessary.

### Table 34.4 Currently Available Distal and Proximal Cerebral Protection Devices

<table>
<thead>
<tr>
<th>Distal Protection</th>
<th>Diameter</th>
<th>Pore Size (μm)</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guardwire</td>
<td>Balloon occlusion</td>
<td>—</td>
<td>Medtronic</td>
</tr>
<tr>
<td>FiberNet</td>
<td>3.5–5, 5–6, 6–7</td>
<td>40</td>
<td>Medtronic</td>
</tr>
<tr>
<td>Accunet OTW</td>
<td>4.5, 5.5, 6.5, 7.5</td>
<td>120</td>
<td>Abbott Labs</td>
</tr>
<tr>
<td>Accunet RX</td>
<td>3.5–4.8, 4–7</td>
<td>140</td>
<td>Abbott Labs</td>
</tr>
<tr>
<td>NAV6 Emboshield</td>
<td>2.5–4.8, 4–7</td>
<td>140</td>
<td>Abbott Labs</td>
</tr>
<tr>
<td>Angioguard XP</td>
<td>4, 5, 6, 7, 8</td>
<td>100</td>
<td>Cordis</td>
</tr>
<tr>
<td>Angioguard Rx</td>
<td>4.5, 5.5, 6.5</td>
<td>100</td>
<td>Boston Sci</td>
</tr>
<tr>
<td>FilterWire EZ</td>
<td>3, 4, 5, 6, 7</td>
<td>50–200</td>
<td>Covidien</td>
</tr>
<tr>
<td>Spider</td>
<td>5, 7</td>
<td>100</td>
<td>Gore</td>
</tr>
<tr>
<td>Proximal Protection</td>
<td>Reversal of flow</td>
<td>—</td>
<td>Gore</td>
</tr>
<tr>
<td>Gore Flow Reversal</td>
<td>Flow clamping</td>
<td>—</td>
<td>Medtronic</td>
</tr>
</tbody>
</table>
Currently Available Self-Expanding Carotid Stents

<table>
<thead>
<tr>
<th>Stent</th>
<th>Metal Composition</th>
<th>Design</th>
<th>Tapered</th>
<th>Manufacturers</th>
</tr>
</thead>
<tbody>
<tr>
<td>AccuLink⁺</td>
<td>Nitinol</td>
<td>Open-cell</td>
<td>Yes</td>
<td>Abbott Laboratories</td>
</tr>
<tr>
<td>X-Act⁺</td>
<td>Nitinol</td>
<td>Closed-cell</td>
<td>Yes</td>
<td>Abbott Laboratories</td>
</tr>
<tr>
<td>Cristallo Ideale</td>
<td>Nitinol</td>
<td>Hybrid</td>
<td>Yes</td>
<td>Medtronic</td>
</tr>
<tr>
<td>Zilver</td>
<td>Nitinol</td>
<td>Open-cell</td>
<td>No</td>
<td>Cook</td>
</tr>
<tr>
<td>Protégé⁺</td>
<td>Nitinol</td>
<td>Open-cell</td>
<td>No</td>
<td>Cordis</td>
</tr>
<tr>
<td>Precise⁺</td>
<td>Nitinol</td>
<td>Open-cell</td>
<td>No</td>
<td>Medtronic</td>
</tr>
<tr>
<td>Exponent⁺</td>
<td>Nitinol</td>
<td>Open-cell</td>
<td>No</td>
<td>Medtronic</td>
</tr>
<tr>
<td>WALLSTENT⁺</td>
<td>Cobalt chromium</td>
<td>Closed-cell</td>
<td>No</td>
<td>Boston Scientific</td>
</tr>
</tbody>
</table>

*⁺FDA-approved carotid stents.

Important. In general, bradycardia is transient and improves on its own. Occasionally, atropine or α-adrenergic drugs might be required for the management of bradycardia and hypotension.

**VERTEBRAL AND BASILAR ARTERIES**

While vertebral artery stenosis is commonly encountered in patients undergoing arch or subclavian angiography, it rarely requires treatment. Intervention should be reserved for individuals with indisputable symptoms of vertebral basilar insufficiency (Table 34.6). Occasionally, patients with occluded carotid arteries are dependent on vertebral blood flow. In these rare cases vertebral artery intervention may be necessary (Figure 34.6). While any type of stroke could be devastating, posterior circulation or brain stem infarcts are extremely dangerous and could result in immediate death. Therefore, any decision regarding such interventions should

**Table 34.6 Symptoms Associated with Vertebrobasilar Insufficiency**

<table>
<thead>
<tr>
<th></th>
<th>Sign and Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual disturbance</td>
<td>Diplopia</td>
</tr>
<tr>
<td>Language/speech</td>
<td>Global aphasia, dysarthria</td>
</tr>
<tr>
<td>disturbance</td>
<td></td>
</tr>
<tr>
<td>Altered state of</td>
<td>Confusion, syncope</td>
</tr>
<tr>
<td>consciousness</td>
<td></td>
</tr>
<tr>
<td>Vestibular dysfunction</td>
<td>Dizziness, vertigo</td>
</tr>
</tbody>
</table>

**Figure 34.6** Selective right vertebral artery angiography. Both right and left extra-cranial vertebral arteries are occluded. Both right and left middle and anterior cerebral arteries fill via the posterior and anterior communicating branches. This patient has a complete Circle of Willis, which is present in approximately 25% of individuals. (MCA, middle cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery; PICA, posterior inferior cerebral artery; ICA, internal carotid artery; PCOM, posterior communicating artery.)
be made in consultation with neurology. Additionally, a thorough noninvasive assessment including MRI/MRA to evaluate the pattern of intracerebral blood flow and collateral circulation is paramount.

The basilar artery alone is responsible for perfusion to a number of critical areas in the brainstem. Accordingly, basilar artery angioplasty is reserved for those rare cases with acute occlusion or critical stenosis and symptoms related to posterior circulation. Intervention to this vessel may lead to occlusion of pontine branches or embolization to posterior circulation. Given the high risk involved in vertebral-basilar instrumentation, a multidisciplinary approach that includes a neurologist and a neuroradiologist is essential.

Treatment Considerations and Technique

Vertebral and basilar artery intervention should only be performed via a 0.014 inch system. The use of embolic protection devices is controversial and may lead to complications such as spasm or even plaque dislodgement.61 In general, most experts agree that embolic protection is not required for all cases and should be considered on a case by case basis. A long 5F or 6F sheath is typically placed in the subclavian artery. Subsequently, the vertebral artery is wired and a small coronary balloon is advanced to the area of interest. Always lean toward undersizing in order to avoid dissection.

Stenting is the best option for this location. Coronary stents are adequate in most situations and even drug-eluting stents can be used. Adequate coverage of the ostium is necessary to ensure long-term patency. Spasm is frequently encountered and may require nitroglycerine. Once a satisfactory result is obtained, a cerebral angiogram should be performed looking for abrupt vessel closure. A complete neurologic exam should be performed and patients should be monitored for at least 24 hours.

VESSELS OF THE AORTIC ARCH

Subclavian, Common Carotid, and Innominate Arteries

Atherosclerosis is commonly the cause of stenosis in the subclavian and great vessels. However, other conditions such as giant cell arteritis, Takayasu arteritis, and fibromuscular dysplasia (FMD) should be considered (see also Chapter 19). Disease of the subclavian and innominate arteries are frequently asymptomatic. However, occasionally patients may present with subclavian steal or upper limb ischemia (Figure 34.7). Less frequently, patients with prior coronary bypass surgery with LIMA may experience angina due to severe subclavian disease. In patients with bilateral subclavian disease where accurate blood pressure
measurement is important, intervention to one side may also be appropriate (Table 34.7).

In general angioplasty and stenting of the great vessels are the preferred primary approach; however, when there is total occlusion with extensive ostial calcification, surgery (carotid-subclavian, aortosubclavian, or axilloaxillary bypass or endarterectomy) may be the best option. Stent fracture in patients with severe calcification and ostial disease can occur and it is usually not associated with significant clinical manifestations, but it may increase the likelihood of restenosis. In general, intervention to the great vessels has a success rate of greater than 90% with a low complication rate. Primary stenting may further improve these results; however, it may not be possible in heavily calcified total or subtotal occlusions. No randomized comparison between surgery and stenting for great vessels is available; however, observational studies directly comparing surgery to an endovascular approach showed a stroke risk of 3%, mortality of 2%, and an overall complication rate of 13% with surgery; the stent series had 0% stroke, 0% death, and 6% overall complications rates. The recurrence rate was 12% for the surgical series and 3% for the stent series, although follow-up was shorter in the latter. In addition to the inherent biases related to observational data, the majority of patients in these studies had stenotic lesions rather than total occlusion.

### Treatment Considerations and Technique

#### Preprocedure

Similar to carotid and vertebral disease as described above, a full history and physical exam is the critical component of great vessel intervention. Understanding the patient's symptoms and whether they relate to great vessel stenosis or occlusion is important to prevent inappropriate intervention. The presence of bruits on physical exam is important, but their lack does not negate the likelihood of great vessel disease. In our clinic the first test to confirm great vessel stenosis or occlusion is a noninvasive duplex ultrasound evaluation, with determination of the direction of flow in the vertebral arteries (antegrade or retrograde, the latter indicating the presence of a steal phenomenon) and documentation of associated carotid disease. If there is a clinical suggestion of vasculitis, an erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) should be measured. Frequently, computed tomography angiography (CTA) of the arch and great vessels is performed to help with the interventional approach. Once a decision regarding intervention has been made, premedication with aspirin is standard, with optional addition of clopidogrel. There are currently no data regarding duration of clopidogrel therapy in this setting but in general, we treat all individuals with dual antiplatelet therapy for at least 1 month followed by life-long aspirin.

The choice of access site is dependent on location of the lesion, involvement of the ostium, and visualization of great vessels. Frequently, a 5F radial access and a 6F femoral approach are needed. The radial access will help with dye injection and stent positioning. This will allow precise stent placement without jailing the vertebral or internal mammary artery. The first step is to perform an arch aortogram in the LAO projection at 30°–40°. This will provide a “roadmap” prior to gaining selective access into the subclavian or innominate artery. For subclavian intervention, we typically use a telescoping technique with a 5F diagnostic catheter inside a 6F sheath. Using a coronary or a 0.035 inch stiff angle guidewire the lesion is crossed and the wire is advanced as far distally as possible. Depending on the arch type, a JR4, Cobra, Simmons, or a Vetek catheter may be necessary. The diagnostic catheter and the sheath are then advanced over the wire. A 0.014 inch or 0.035 inch balloon and stent can be used for subclavian interventions depending on the location of lesions. SE stents are reserved for distal locations. Balloon-expanding stents are better for lesions extending from the ostium to the origin of the vertebral artery. Inflation of the balloon for about a minute will reverse the flow in the vertebral artery and this technique can be used to minimize embolization to the brain. Emboli prevention devices are typically not used in subclavian interventions.

For innominate and common carotid artery interventions, we typically use an 8F guide catheter, usually an ALL. We have used boiling water to reshape this catheter to straighten the last curve. In our lab these interventions are almost always performed with carotid distal embolic protection. We use a 0.014 inch wire to gain access into the internal or external carotid artery. Subsequently, a filter embolic protection is passed into the distal internal carotid artery over a second 0.014 inch wire. Using both 0.014 inch
wires (0.014 inch × 2 = 0.028 inch) balloons and stents are advanced into the area of interest. Once the stent has been postdilated the embolic protection device is retrieved. The position of the distal filter should be checked frequently when advancing stents and balloons.

Before stenting the great vessels, we always recommend predilation using a 4 to 6 mm balloon. This will help to ensure that the stent will fully expand but also may help with stent size selection. Some operators suggest crossing the lesion with the sheath and then unsheathing the stent in order to prevent stent dislodgment and embolization. However, with the newer stents, this may not be necessary, and it is actually less traumatic to cross the lesion with the stent than with the guide or sheath. We recommend BE stainless steel or cobalt-chromium stent for these vessels. We rarely, if ever, place an SE stent in the ostium of the great vessels, given the lack of radial strength and difficulty with precise stent placement.

For lesions located beyond the internal mammary artery, SE stents should probably be used to avoid dissection and possibly late stent compression by extravascular structures. Covered stents have been used for intervention to the great vessels; however, BE covered stents (i.e., iCAST, Atrium Medical) are recommended. Care should be taken to avoid compromise of the origin of the right common carotid artery, when stenting the brachiocephalic (innominate) artery. Stents should be postdilated to match the size of the subclavian artery (generally between 5 and 8 mm). Overdilation should be avoided to minimize the risk of dissection that might extend into the vertebral or internal mammary artery or rupture with intrathoracic bleeding. If such dissections do occur, they can often be salvaged by placement of a stent within the origin of the affected branch vessel, although distal extension of the dissection within the branch vessel may render attempts at salvage futile. Following postdilation, pressure gradients may be repeated to demonstrate complete elimination of the gradient.

In general, a postprocedure duplex ultrasound is obtained. Resolution of symptoms is the best marker to monitor; bilateral arm blood pressure measurements are also usually recommended and are a simple bedside test to assess patency. Restenosis within subclavian arteries occurs in 10% to 20% of patients and may be treated by stenting (if not stented initially) or balloon angioplasty (for in-stent restenosis). Stent compression or fracture may occur. If clinically relevant, these can be treated by balloon reexpansion, oral rapamycin-supported balloon angioplasty, angioplasty with a drug-eluting balloon, restenting, and even placement of a SE stent within the old BE stent; however, data regarding these approaches are limited.

Complications

Complications associated with great vessel intervention are generally minor and infrequent, but may include problems at the access site, as well as inadvertent “jailing,” dissection, or embolization of the vertebral or left internal mammary artery, which may require balloon angioplasty. In our experience, while every attempt should be made to avoid vertebral artery compromise, its inadvertent jailing has minimal clinical sequelae and patients usually tolerate this well as long as the contralateral vertebral artery is patent. If flow is compromised, a 2 to 4 mm balloon should be used to dilate the ostium of the vertebral artery. Angiographic “perfection” in this setting is not necessary.

RENAL ARTERIES

Renal artery stenosis (RAS) is a common manifestation of generalized atherosclerosis; however, its treatment has been extremely controversial. In general, RAS can lead to resistant hypertension via the renin-angiotensin-aldosterone system (RAAS) or lead to ischemic nephropathy. While theoretically RAS should be treated to prevent renal ischemia, randomized trials to date have not shown a significant benefit from renal artery intervention to prevent progression of renal failure. However, the trials conducted to date have been criticized for including patients with stenosis of less than 70%, and for including individuals not at risk of renal ischemia or resistant hypertension (Table 34.8). The interventional community is anxiously awaiting the results of the CORAL trial. However, early data indicate the same limitations with this trial as those of others, including interventions for lesions of less than 70% severity.

The current goal standard for renal artery intervention is endovascular therapy with balloon angioplasty and stenting; however, on rare occasions surgery may be required. While atherosclerosis is most commonly responsible for RAS, an important other entity, FMD should always be considered, especially in young females with no atherosclerotic risk factors.

Fibromuscular Dysplasia

FMD is a nonatherosclerotic, noninflammatory disorder of unknown etiology that constitutes the second most common cause of RAS. It typically affects women from 15 to 50 years of age and is more common in first-degree relatives and in the presence of the ACE-I allele. FMD can also involve carotid and peripheral arteries, although renal artery involvement is seen in 60% of cases of FMD, with frequent bilateral involvement. Progressive renal stenosis is seen in 37% of cases and loss of renal mass in 63%. The most common form of FMD is medial fibroplasia, with intimal and adventitial fibroplasia as additional forms. FMD has a distinctive angiographic appearance, with a beaded, aneurysmal pattern (Figure 34.8). Medical management of hypertension is frequently successful; however, due to high rates of procedural success, elimination of hypertension, and low recurrence rate (10%), percutaneous intervention with balloon angioplasty is usually recommended. FMD localized within the main renal...
Table 34.8 Randomized Trials of Renal Artery Stenting for Renal Artery Revascularization Versus Medical Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Year</th>
<th>Indication</th>
<th>Angioplasty Alone (%)</th>
<th>Blood Pressure Outcome</th>
<th>Renal Function Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMMA</td>
<td>59</td>
<td>1998</td>
<td>HTN with unilateral RAS</td>
<td>91</td>
<td>NS</td>
<td>—</td>
</tr>
<tr>
<td>SNRASC</td>
<td>55</td>
<td>1998</td>
<td>Resistant HTN</td>
<td>80</td>
<td>—</td>
<td>NS</td>
</tr>
<tr>
<td>DRASTIC</td>
<td>106</td>
<td>2000</td>
<td>Resistant HTN</td>
<td>96</td>
<td>NS</td>
<td>—</td>
</tr>
<tr>
<td>ASTRAL</td>
<td>803</td>
<td>2009</td>
<td>Resistant HTN unexplained CRI</td>
<td>7.0</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>STAR</td>
<td>138</td>
<td>2009</td>
<td>CRI</td>
<td>1.6</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>NITER</td>
<td>52</td>
<td>2009</td>
<td>Resistant HTN with CRI</td>
<td>0</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

*EMMA, Essai Multicentrique Medicaments Versus Angioplastie; ASTRAL, Revascularization Versus Medical Therapy for Renal Artery Stenosis; STAR, Atherosclerotic Ostial Stenosis of the Renal Artery; HTN, hypertension; RAS, renal artery stenosis; CRI, chronic renal insufficiency; NS, none significant.

artery or its primary branches can be treated quite effectively with balloon angioplasty alone, with stenting reserved for failure or complications of balloon angioplasty (Figure 34.8). FMD that involves multiple branch vessels and/or aneurysmal disease is usually better treated surgically, potentially using the technique of “bench” (i.e., extracorporeal) reconstruction of the branch vessels.

Atherosclerotic Renal Artery Stenosis

A number of observational studies have shown benefit with renal artery intervention to treat atherosclerotic renal artery stenosis. However, a meta-analysis of the six trials conducted to date failed to show preservation or reversal of renal function (Table 34.8). The only clear advantage was the use of less antihypertensive medications for blood pressure control. For this reason, the current guidelines have given a class IIa indication for renal artery intervention for resistant hypertension or for preservation of renal function. Resistant hypertension is defined as a blood pressure of over 150 mmHg while on maximum dose of three antihypertensive medications including a diuretic. There are other conditions where renal artery intervention may also have a role, including recurrent flash pulmonary edema or congestive heart failure. A number of factors may predict blood pressure response after renal artery intervention. These include (a) rapid acceleration of hypertension over the prior weeks or months; (b) presence of “malignant” hypertension (e.g., end organ effect); (c) hypertension in association with flash pulmonary edema; (d) contemporaneous rise in serum creatinine; and (e) development of azotemia in response to angiotensin-converting enzymes (ACE) inhibitors administered for control of hypertension. Predictors of successful salvage or preservation of renal function are similar and include (a) recent rapid rise in creatinine, unexplained by other factors; (b) azotemia resulting from ACE inhibitors; (c) absence of diabetes or other cause of intrinsic kidney disease; and (d) the presence of global renal ischemia, wherein the entire functioning renal mass is subtended by bilateral

Figure 34.8 Fibromuscular dysplasia (FMD) involving the right renal artery in a female with resistant hypertension (A). The same patient after serial dilatation with 4.0 mm and 5.0 mm balloons (B). In general, we avoid renal artery stenting in patients with FMD. All patients with FMD undergo intravascular ultrasound assessment and pressure gradient is obtained using fractional flow reserve wire.
critically narrowed renal arteries or a vessel supplying a solitary kidney. Conversely, predictors of poor functional renal recovery following renal artery stenting include (1) renal atrophy demonstrated by kidney length less than 7.5 cm on ultrasound; (2) high (>0.8) renal resistance index measured from the peak systolic velocity ($V_{\text{max}}$) and the end-diastolic velocity ($V_{\text{min}}$) using the formula $\text{RRI} = 1 - (V_{\text{min}}/V_{\text{max}})$; (3) proteinuria greater than 1 g/day; (4) hyperuricemia; and finally, (5) creatinine clearance less than 40 mL/minute. None of these, however, constitutes an absolute contraindication, as individual patient responses are unpredictable.

It is important to note that the clinical spectrum of RAS is very wide, and not every patient with RAS needs to be stented. On one extreme is the patient with unilateral RAS, normal renal function, and mild or moderate hypertension well controlled medically, who would derive little immediate benefit and should probably be followed longitudinally, with serial reevaluation of renal function, kidney size, and control of blood pressure. At the other extreme is the patient with longstanding severe baseline renal insufficiency secondary to nephrosclerosis (e.g., diabetic nephropathy) with superimposed RAS or ultrasound findings suggestive of atrophy, in which case intervention is unlikely to procure any benefit. Determining the optimum timing for intervention within this spectrum is complex, often requiring close interaction between a nephrologist and an interventionalist. Although the approach of delayed intervention allows instigation of comprehensive antihypertensive therapy and risk factor modification, there is mounting evidence that earlier RAS intervention yields greater preservation of renal function, better control of renovascular hypertension, and reduced cardiovascular morbidity. Data from an NIH-sponsored clinical trial (CORAL) examining cardiovascular mortality after randomization between medical therapy and stenting for RAS will soon become available.

Finally, RAS should always be excluded in patients who present with flash pulmonary edema or unstable angina (Table 34.9). Flash pulmonary edema is particularly prevalent in patients with bilateral RAS or unilateral RAS supplying a solitary functional kidney and is generally refractory to medical therapy. Among these patients, renal revascularization has been shown to effectively alleviate pulmonary edema and unstable angina.

One of the main criticisms of all randomized trials that have compared renal artery intervention to medical therapy has been interventions to lesions with moderate severity. Recent data indicate that intravascular ultrasound (IVUS) and fractional flow reserve may not only help identify severe lesions but can also predict blood pressure response to treatment. A recent study by Lesser et al. showed that a peak hyperemic gradient of 21 mmHg predicts blood pressure response when renal artery stenting was performed.

### Treatment Considerations and Technique

Renal artery intervention can be performed via the femoral, brachial, or radial approach. In our practice, we use data from previous imaging studies to determine the best access site. For downward takeoffs usually a brachial or radial approach is preferred. However, most other angulations can be treated via the femoral approach. In general, in our practice we prefer the radial approach over the brachial approach.

#### Diagnostic Angiography

These techniques are described in Chapter 19. Nonselective arteriography is recommended prior to selective cannulation to identify the location of the renal ostia and to minimize the need for catheter manipulation in a diseased aorta. However, when renal artery stenting is performed to preserve kidney function in patients with renal insufficiency, every measure should be taken to decrease contrast use. In these cases we typically do not perform abdominal aortography. Instead, we use the “no-touch” technique to wire the renal artery and then take one picture in shallow LAO projection (Figure 34.9). A 3-cc contrast mixed with 3 to 4 cc of saline will be enough to outline the renal arteries and parenchymal flow. This injection is usually enough to also identify accessory renal arteries, which are present in roughly 25% of patients. We typically supplement this approach with IVUS to better assess lesion severity and to have a better understanding of lumen size and plaque burden. Diagnostic renal angiography can be performed using a variety of catheters. Catheter selection should depend on the angle of renal artery takeoff. Most renal arteries can be cannulated using an IMA, Judkins right, hockey stick, renal double curve, or SOS Omni. We highly recommend hemodynamic assessment of a renal artery lesion if severity is ever a question. This should only be performed via the fractional flow reserve (FFR) 0.014 inch wire. Traditional advancement of a diagnostic catheter through the lesion to assess hemodynamic significance should be avoided due to associated trauma, risk of embolization, and false gradients created by

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**Table 34.9** Possible Indications for Percutaneous Renal Artery Revascularization

<table>
<thead>
<tr>
<th>Indication</th>
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<tbody>
<tr>
<td>Recurrent flash pulmonary edema</td>
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<tr>
<td>Severe bilateral renal artery stenosis</td>
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<tr>
<td>Resistant hypertension (on maximal doses of three medications with one being a diuretic)</td>
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<tr>
<td>Resistant hypertension associated with fibromuscular dysplasia</td>
</tr>
<tr>
<td>Acute renal failure after angiotensin-converting enzyme (ACE) inhibitor use</td>
</tr>
<tr>
<td>Rapidly rising creatinine with preserved kidney size</td>
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</table>
The “no-touch” technique is the preferred method of obtaining renal angiography. With this technique, a 0.035 inch wire is placed above the renal artery in the aorta. This prevents scraping of the aortic wall with the catheter. Subsequently, using a 0.014 inch wire the renal artery is engaged.

We also recommend against placing 0.035 inch guide wires in the renal arteries and typically perform all renal intervention over a FFR wire or a 0.014 inch guide wire. Although the data in general are sparse, a significant pressure gradient can be considered to be greater than 10 mmHg mean and/or 20 mmHg peak-to-peak. A resting FFR value of 0.9 is also considered significant. Additional information can be obtained from hyperemia using dopamine or papaverine. In a study by Lesser et al. a hyperemic systolic gradient of > 21 mmHg was the strongest predictor of blood pressure response to renal artery stenting.84

Renal Artery Intervention

Once the severity of RAS is confirmed and a decision is made to intervene, angioplasty and stenting can be performed. It is not necessary to perform angioplasty prior to every stenting; however, if there is any doubt as to whether the lesion is expandable or not, angioplasty should be undertaken. Currently three stents are FDA approved for renal artery intervention; these include the Boston Scientific’s Express SD, Cook’s Formula, and Abbott Vascular’s RX Herculink Elite.

We frequently use IVUS to identify the location of the ostial renal artery (Figure 34.10). Fluoroscopic picture of the IVUS catheter is taken when the ostium is visualized on IVUS imaging. The position of the IVUS catheter is then used to place a stent in order to cover the ostium. Additionally IVUS is used not only to select appropriate stent size but also to evaluate stent apposition and edge dissection. Given the availability of FFR and IVUS, we believe these techniques should routinely be used to supplement renal artery intervention.

Complications

Complications associated with renal artery intervention are infrequent, but they could be catastrophic. Death has been reported and renal and aortic dissection can occur. Furthermore, embolization and perforation are other known complications. Some of these complications can be prevented by proper technique and potential use of IVUS for stent selection and procedural guidance. Atheroembolization has been reported, and in general, it is associated with aggressive guide manipulation. Distal protection devices have been studied in renal arteries; however, currently there is no conclusive evidence that their use is associated with better outcomes in all patients.85

Mesenteric Arteries

Indications for Treatment and Results

Mesenteric artery stenosis is an incidental finding frequently seen on imaging studies performed for other indications.
Fortunately, this finding rarely results in symptoms. The celiac, superior mesenteric, and inferior mesenteric arteries supply blood to the abdominal viscera. A redundant network of blood vessels usually compensates when one or sometimes even two vessels are severely diseased or occluded. These collaterals allow communication between the inferior and superior mesenteric arteries either via the meandering mesenteric artery that courses deep in the colonic mesentery or via the arc of Riolan (Figure 34.11). The celiac and superior mesenteric territories are connected by the pancreaticoduodenal arteries; the inferior mesenteric territory may be collateralized by the sigmoidal and hemorrhoidal arteries from the external iliac artery (Figure 34.12). As with coronary atherosclerosis, an imbalance of the arterial supply and demand results in development of symptoms. Intestinal arterial demand is greatest following a large meal. Classically, postprandial symptoms of abdominal pain, gas, diarrhea, food avoidance, and ultimately weight loss indicate severe global compromise of mesenteric blood supply (such as occlusion of two out of three mesenteric vessels and a critical stenosis in the third). With less profound ischemia, symptoms can be vague, including nonspecific postprandial discomfort, fullness or bloating, prompting multiple investigations. Although vague, symptoms progress insidiously, resulting in “food fear” and ultimately profound weight loss; the median weight loss in one series was 28 lb (range 3 to 100 lb). The angiographic diagnosis can be ambiguous as the mesenteric vessels originate and project anteriorly from the aorta and are inadequately visualized during conventional anteroposterior (AP) angiography. Therefore, extremely angulated (lateral views) are required to define aorto-ostial and proximal lesions in these vessels.

In severe cases surgical endarterectomy or bypass were previously performed, but this operation is associated with significant morbidity and mortality. In the last decade, balloon angioplasty and now stenting have become the first-line therapy. Endovascular treatment is also associated with morbidity and mortality and should be performed in consultation with a gastroenterologist when appropriate.

Mesenteric Artery Intervention

The mesenteric arteries have an anterior takeoff from the aorta; therefore, oblique and frequently lateral projections may be required. To obtain the best images, the arms should be placed above the head.

In almost all cases, mesenteric artery angiography and intervention should be performed via the brachial or radial artery. The majority of disease in the mesenteric arteries is aorto-ostial; therefore, cannulation with a guide or sheath should be performed extremely carefully to prevent atheroembolization or even ostial dissection. We prefer multipurpose diagnostic or guide catheters from the arm. Left coronary bypass, RES, or hockey stick guide can be used from the femoral access. Sheaths can be used but many lack appropriate curve to directly engage the mesenteric vessels. If a sheath is used, a telescoping technique is recommended. This is usually performed by using a long diagnostic multipurpose catheter inside a 6F sheath. Using the diagnostic catheter and a guide wire the mesenteric artery is cannulated

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**Figure 34.11** Selective angiography of the inferior mesenteric artery (*black arrow*) (A). Note the totally occluded superior mesenteric artery (SMA) and the celiac trunk (*white arrow*). Collateral flow from the arc of Riolan feeds the SMA (*large arrows*). Selective angiography of the SMA after stenting (B). Note the pancreaticoduodenal arteries (*large white arrow*) supplying collaterals to the celiac trunk (*white open arrow*) filling the hepatic (*white arrows*) and the splenic (*black arrows*) arteries.
Chapter 34 Peripheral Intervention

and the sheath is slowly advanced to the ostium of the vessel of interest over the guidewire and 5F diagnostic catheter. Unfortunately, this technique may not provide enough support for balloon and stenting. If celiac and superior mesenteric arteries are diseased we typically intervene on the superior mesenteric artery alone. Use of IVUS is recommended when stenting the mesenteric arteries to allow better stent sizing and to assess stent apposition. Mesenteric artery intervention can lead to catastrophic complications including bowel ischemia, infarction, peritonitis, sepsis, and even death. Similar to all vascular interventions this territory should be treated with “respect” and only intervened upon when there is little doubt about the cause of symptoms.

BE stents are typically used for mesenteric artery stenting; however, BE covered stents have also been used. For aorto-ostial lesions, BE stents are preferred given their radial strength and the ability for precise placement. Due to the curve of the superior mesenteric artery, for disease that is more distal SE stent may be preferred.

At the completion of the study multiple oblique images should be obtained. All patients should be observed for 24 hours. Any sign of fever, abdominal pain, nausea, vomiting, or bloody stool should be evaluated immediately for bowel ischemia.

LOWER EXTREMIT Y

Lower extremity peripheral arterial disease (PAD) is defined as any atherosclerotic condition that affects the aortoiliac vessels, common femoral artery, superficial femoral artery (SFA), popliteal, and the tibial vessels. An estimated 8 to 12 million Americans carry a diagnosis of PAD, but large numbers of patients are undiagnosed and only about 50% are symptomatic. In 2007, among Medicare recipients, 6.8% were treated for lower extremity PAD, with prevalence increasing with age. Among Medicare recipients older than 85, 12% required treatment for PAD. Furthermore, Medicare expenditures for PAD exceeded $4 billion in 2007. The prognosis for patients with PAD is extremely poor and similar to many malignancies. Within 10 years of diagnosis, more than 50% of afflicted patients have succumbed to this disorder and nearly 20% have had a limb amputated. The relative risk of death due to coronary heart disease is 6.6 (95% CI 2.9 to 14.9).

Clinical Presentation

The classic presentation is that of pain, tightness, aching, soreness, hardness, or heaviness that occur in the calf, buttock, hip, or arch of the foot during ambulation and resolves with rest (intermittent claudication). In more severe cases (critical limb ischemia) patients present with rest pain, ulcer, or even gangrene (Table 34.10). Critical limb ischemia, usually a chronic progressive process, should be differentiated from acute limb ischemia, a medical emergency. Acute limb ischemia typically occurs suddenly and is associated with the classic 5 “Ps” (Table 34.11). These include sudden pain, pulselessness, pallor, paresthesias, and paralysis. Acute limb ischemia typically requires an endovascular or an open surgical intervention and has been described as the ST elevation MI equivalent of the legs.
Intermittent claudication, critical limb ischemia, and acute limb ischemia are the presentation frequently encountered in patients with PAD; however, the majority of the patients with PAD are asymptomatic. Interestingly, asymptomatic patients have the same morbidity and mortality as those with intermittent claudication. Furthermore, asymptomatic patients are more likely to have lower exercise capacity.

**Diagnosis**

History and physical exam are the foundation for correct diagnosis and subsequent timely treatment of PAD. Attention to the timing of symptoms, location, duration, and risk factors related to atherosclerosis are critical. Any history of back surgery, trauma, arthritis, or neuropathy should be ascertained. Furthermore, the severity of symptoms including its impact on the patient’s quality of life and ability to perform physical activities should be assessed.
activity should be obtained. This will guide the level of treatment including whether or not an endovascular or surgical intervention is necessary. Subsequently, a full physical exam that includes a close inspection of skin for breakdowns, pulses, bruits, and temperature should be performed. Once PAD is suspected, confirmatory noninvasive tests should be obtained. We generally start with a simple segmental pulse volume recording (PVR) with exercise, if patients can tolerate this. Segmental PVRs are useful since they may help identify the exact location of a diseased segment within the lower extremities. Occasionally, additional anatomic data are required, and in these cases, a duplex ultrasound is generally obtained. In a few cases, abdominal CTA with runoffs is necessary to fully understand the anatomy of lower extremities.

**Indication for Intervention**

The current indication for lower extremity intervention is critical limb ischemia or lifestyle-limiting claudication. Additionally, all patients with symptomatic PAD should be offered a supervised exercise program and aggressive risk factor modification.

**AORTOILIAC OBSTRUCTIVE DISEASE**

Obstructive disease involving the distal abdominal aorta and the iliac vessels may present as buttock or hip claudication, erectile dysfunction in men, lower extremity claudication, or even critical limb ischemia. Leriche first described a series of patients with erectile dysfunction and symptoms of lower extremity claudication in his classic 1923 publication. Surgical revascularization began with endarterectomy in the 1940s, and bypass surgery in the 1950s. In 1979, Gruntzig and Kumpf described their experience with balloon angioplasty of iliac lesions, which yielded a 2-year patency rate of 87%. Long-term smoking appears to be the most significant risk factor, and females are more frequently affected than males. Given the size of the aorta and the iliac vessels, endovascular therapy, when feasible, should be the first line of therapy for these individuals. The current indication for aortoiliac revascularization is listed in Table 34.12.

Surgical revascularization for aortoiliac disease includes aortofemoral or aortoiliac bypass which has a long-term patency of 90% at 1 year, 75% to 80% at 5 years, and 60% to 70% at 10 years, but carries a mortality between 2% and 3%. More importantly, it is associated with significant morbidity and at a minimum requires cardiac clearance. Despite these limitations, surgical revascularization remains the best option for selected groups of patients where endovascular treatment would not be ideal. In general, endovascular repair of the abdominal aorta requires a relatively normal landing zone below the renal arteries for stent deployment. In cases where the renal arteries or suprarenal aorta is involved, endovascular repair would not be recommended. Occasionally a hybrid technique might be the ideal approach. The current guidelines also recommend surgery for TASC D lesions (TransAtlantic Inter-Society Consensus D lesions); however, many operators including our group would consider endovascular repair, and if this fails, then the patients are referred to surgery (Figure 34.12).

There are relatively few studies examining the outcome of PTA in isolated aortic segments, owing to the relatively uncommon occurrence of this entity (compared with combined aortoiliac disease). The results of balloon angioplasty alone for iliac stenoses, particularly focal lesions, is excellent, with acute technical and clinical success >90% across a large number of reports. Patency rates for 1, 3, and 5 years range from approximately 75% to 95%, 60% to 90%, and 55% to 85%, respectively. The wide disparity of these results is a reflection of multiple factors, including variations in selection criteria, discrepancies in measurements of outcome, and the evolution of technique over time. Factors associated with good results include a short, focal lesion; large vessel size; common iliac (as opposed to external iliac); single lesion (as opposed to multiple serial lesions); male gender; lesser Rutherford category (claudication as opposed to critical limb ischemia); and presence of good runoff. The results in patients with diffuse disease, smaller vessels, diabetes mellitus, female gender, critical limb ischemia, and poor runoff are less favorable.

**Stents for Aortoiliac Disease**

In 1993, the FDA approved the use of Palmaz stents (P-308 series, 30 mm long and 8 mm in diameter) for iliac arteries. Specific indications were for failed PTA (defined as a residual mean gradient of ≥5 mm, residual stenosis of >30%, or presence of a flow-limiting dissection). The SE WallStent prosthesis was approved for similar indications in 1996. The favorable acute results, relative ease of use, and paucity of complications encountered during aortoiliac stenting, however, has led to expanded use of these devices to reduce
recoil and improve on the immediate hemodynamic and angiographic result of PTA. Using stents, acute technical success is in the range of 90% to 100%, with average 1-year patency of 90% and average 3-year patency of 75%. Because of these superior acute and long-term results, a strategy of primary stent deployment for aortoiliac vessels has been adopted by many, although others reserve stenting only for suboptimal angioplasty results.

Tetteroo and colleagues published a randomized trial of balloon angioplasty compared with primary stenting, showing no difference in the primary endpoint when balloon angioplasty patients were allowed to cross over to stenting for a residual stenosis of 50% or a residual mean gradient ≥10 mm. However, if analyzed on a per protocol basis, stenting was far superior with 43% of patients requiring provisional stenting. Clinical and hemodynamic success rates were approximately 77% and 85%, respectively, at 24 months, comparable with many surgical series of aortobifemoral bypass. Even more compelling is the meta-analysis performed by Bosch et al. on 14 recent studies (all published after 1990) involving more than 2,100 patients undergoing aortoiliac PTA. This meta-analysis showed a superior immediate success rate for stents than for PTA alone (96% versus 91%) with a subsequent 4-year primary patency rate for stenotic lesions of 77% for stenting versus 65% for PTA alone. For occlusions, 4-year patency rates were 61% for stents and 54% for PTA.

**Treatment Considerations and Technique**

The two most important aspects of aortoiliac artery endovascular intervention are degree of disease (occlusion versus stenosis) and location. In general, if the stenotic lesion involves the distal common iliac and proximal external iliac artery, but distal external and common femoral artery are patent, a retrograde approach via the ipsilateral common femoral artery is appropriate. The ipsilateral retrograde approach also works well for stenotic lesions involving the ostium or proximal common iliac artery; however, in these situations a 5F access in the contralateral common femoral artery can be very helpful (Figure 34.13). This will allow placement of an IMA or an angle glide catheter right above the aortoiliac bifurcation. Injection via this catheter will then allow accurate placement of the stent at the common iliac artery ostium. This approach also provides direct access to the aorta in case of inadvertent jailing of the contralateral iliac or plaque shifting. Our general approach for occlusive lesions in the distal aorta, bifurcation, and iliac systems is the antegrade approach along with retrograde access. This is typically achieved via the left brachial approach or via contralateral cross-over technique (Figure 34.14). We reserve the left brachial approach for occlusive lesions involving the distal aorta, aortoiliac bifurcation, and proximal common iliac artery. When the brachial approach is used, an ipsilateral 5F common femoral sheath is also placed. This will allow externalization of the wire once the occlusive lesion has been crossed. When attempting recanalization of totally occluded lesions, it is extremely important to ensure true final luminal position (Figure 34.15). This can be achieved by injecting dye.

We use a straight or an angled glide wire supported by a 4F or 5F glide catheter when traversing stenotic or occlusive lesions. Although we always try to remain intraluminal when crossing these lesions, this may be difficult. The subintimal approach is appropriate, but this should be performed very carefully, and luminal entry should be gained as soon as the lesion has been traversed. Reentry into true lumen should always be above the common femoral artery. This will prevent

**Figure 34.13** Treatment of complex aortoiliac diseased segment (A). Balloon angioplasty (B) followed by stenting and final angiographic result (C).
jailing of the profunda femoris or the requirement for common femoral artery stenting.

Both SE and BE stents have been used when performing aortoiliac interventions. We prefer BE stents for aorta, aortoiliac bifurcation, and ostial and proximal common iliac arteries. SE stents are typically used from distal common and external iliac arteries. BE stents have higher radial strength and allow more precise placement; therefore, they are the preferred stents for bifurcation lesions in our laboratory. Covered stents have also been used to treat aortoiliac lesions. In a randomized trial comparing covered stents to SE balloon stents, both devices were safe and equal for TASC B lesions; however, covered stents were superior for TASC C and D lesions.

On occasion, we use other modalities to guide endovascular repair of the aortoiliac system. IVUS and pressure assessment can facilitate endovascular repair. By convention, a 5 mmHg mean resting pressure gradient is taken as indicative of a significant residual stenosis. If the resting gradient is borderline, a persistent mean pressure gradient of >15 mmHg after administration of a vasodilator (200 to 300 μg of nitroglycerin) is considered significant. IVUS is also very helpful in defining the anatomy and in guiding stent diameter.

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In summary, percutaneous therapy has now become the first line of therapy for aortoiliac obstructive disease. With the exception of patients with very extensive disease, PTA with stent deployment is associated with a highly successful acute and long-term outcome. If this strategy fails, subsequent surgical intervention remains feasible. While the current guidelines continue to recommend surgical revascularization for TASC C and D lesions, most experienced operators prefer endovascular therapy over open surgery, even for complex totally occlusive aortoiliac lesions.  

Complications

Complications are relatively infrequent with aortoiliac angioplasty (<6% based on multiple series). Most common are access site complications, including local or retroperitoneal bleeding, pseudoaneurysm, and arteriovenous (AV) fistula (see Chapter 4). Thrombotic occlusion at the site of angioplasty is extremely rare, as is rupture (which can have devastating consequences). Arterial rupture must be recognized promptly and controlled by inflation of a balloon within the lesion (balloon tamponade), reversal of anticoagulation, and volume resuscitation. Surgery may be required, but stent grafts are increasingly being used to treat this complication. Other complications include distal embolization, which was encountered in alarming frequency in early studies of recanalized total iliac occlusion. More recent studies indicate an incidence of <5%. Systemic complications, such as contrast or atheroembolic induced renal failure, MI, stroke, and death, all occur with an incidence of <0.5%. Complications requiring surgical repair are also relatively infrequent, in the range of 2%. An aortic occlusive balloon (CODA, Cook Medical) with a 10F to 14F sheath should always be available in the laboratory and all personnel should be aware of its location.

COMMON FEMORAL ARTERY

The common femoral artery, the so called “left main” of the leg has previously been considered the exclusive purview of the vascular surgeon, whose approach through a local incision (often under local anesthesia) allows endarterectomy and patch angioplasty with good results. Due to concerns regarding stent fracture and compression, elastic recoil, or compromise of the profunda femoral artery, most experts continue to avoid endovascular therapy for this artery. However, recent series from Europe and other centers have shown good results in highly selected patients. Surgery also has been associated with complications such as wound infection, poor healing, restenosis, and large cosmetically unfavorable scar. We believe in a personalized approach to the common femoral artery regarding the best treatment approach (endovascular, surgical, or hybrid). In general, younger patients and those with heavy calcification should be considered for surgery. For older patients with significant cardiac disease, obese patients, and individuals that are at increased risk of wound infection, an endovascular approach may be better. However, all efforts should be to minimize the use of stents in this location. Our current approach is atherectomy followed by gentle low-pressure balloon angioplasty. In the future, drug-coated balloons and possibly bioabsorbable stents may provide additional tools to treat the common femoral artery.

Treatment Considerations and Technique

The contralateral femoral or brachial artery approach is preferred. We use a 0.035 inch wire when treating proximal and mid common femoral artery; however, for distal disease when both the profunda and SFA are involved, we recommend two 0.014 inch wires, protecting both vessels. Occasionally when distal runoff is poor, a filter wire can be placed in the SFA. Currently four atherectomy devices are available (Laser, Diamondback, Silverhawk, and Pathway). For noncalcified lesions, Laser atherectomy can be attempted but debulking with laser is typically not adequate. For calcified lesions, we prefer either rotational or directional atherectomy. When using atherectomy, we have a low threshold for placing a distal embolic protection device. Restenosis, generally accepted to be >50%, is the biggest limitation of common femoral artery angioplasty. Nonetheless, patients often may experience persistent relief of critical symptoms, even in the face of moderately severe restenosis.

PROFUNDA FEMORAL ARTERY

The deep femoral artery is the main source of collaterals to the lower extremity. In the face of occlusion of the SFA or a femoral bypass graft, the profunda alone becomes responsible for maintaining viability of the lower extremity. Surgery for disease involving the ostia of the SFA and profunda involves endarterectomy and patch angioplasty. Balloon angioplasty has been reserved for situations in which severe ischemia is present (Rutherford category 4, 5, or 6) and surgery is absolutely contraindicated, or when critical lesions involve the mid or distal portions of the descending branch of the profunda that are less accessible to the surgeon. Technically satisfactory results of profunda PTA have been described and suggest that this is a relatively safe procedure. However, because of the potential for producing limb-threatening ischemia or limb loss if the vessel occludes, treatment of this site should generally be reserved for patients with rest pain or critical limb ischemia in whom no good surgical options are available.

SUPERFICIAL FEMORAL AND POPLITEAL ARTERIES

This vessel, the longest nonbranching artery in the body, continues to present a challenge for both endovascular and surgical approaches. Despite a mean vessel diameter between...
5 and 6 mm, restenosis is nearly twice that of coronary interventions. Furthermore, due to the presence of significant collaterals from profunda femoris to the popliteal and lower leg, most patients do not become symptomatic until the artery has totally occluded. Unfortunately, once the occlusion occurs, it is typically long and over 20 cm making endovascular intervention more challenging. Occasionally patients modify their activity level to prevent claudication; therefore, they frequently present with critical limb or rarely acute limb ischemia. In general there is direct correlation between lesion length and presence of occlusion and long-term patency.

Moreover, the SFA undergoes significant mechanical stress such as torsion, compression, expansion, and rotation, and these forces can create fractures and restenosis. Because of these limitations, revascularization for SFA has been reserved for lifestyle-limiting claudication only after risk factor modification, a supervised exercise program, and use of cilostazol (Pletal) if not contraindicated.

Like any other interventions, a number of factors should be considered before attempting to recanalize the SFA. These include lesion length, presence of stenosis versus occlusion, landing zones, distal runoff, patient compliance and comorbidities. In general, patients with mild, nondisabling claudication should be placed on conservative treatment with an exercise program to augment collateral flow rather than undergo interventional therapy for SFA disease. Less than one-fourth of these patients will progress to the point of developing more disabling symptoms or a threatened limb, which mandates therapy. For patients with rest pain or those with Rutherford class V and VI, a more aggressive approach is necessary.

Considerable controversy remains as to the relative role of percutaneous therapy versus surgery. The results of balloon angioplasty in the SFA have improved over time. Murray and colleagues noted that the technical success improved from 70% to 91% between 1980 and 1989, with excellent acute and long-term efficacy even for lesions >10 cm long. Similarly, the success rate in crossing occluded segments of the SFA and popliteal arteries have improved dramatically as a consequence of technical advances. Foremost among these is the use of hydrophilic guidewires. Among eight large series of patients undergoing PTA of femoral-popliteal stenoses and occlusions, most of whom were claudicants, the acute technical success ranged between 82% and 96%. Primary patency rates at 1, 3, and 5 years averaged 60%, 50%, and 45%. Several factors influence long-term outcome following SFA-POP angioplasty. Patients with intermittent claudication (versus tissue loss), a more severe lesion at baseline, and lower posttreatment residual stenosis tend to have a better outcome at 1 year, whereas those with diabetes, threatened limb loss, or diffuse atherosclerotic vascular disease with zero to one vessel runoff have a worse outcome. The analysis of Hunink and colleagues examined the relative benefit and cost effectiveness of PTA versus bypass surgery for 5-year outcomes in approximately 4,800 PTA and 4,500 bypass procedures performed since 1995. Their conclusion was that, for patients with disabling claudication owing to femoral-popliteal stenosis or occlusion, PTA is the preferred initial treatment, whereas for patients with chronic critical ischemia owing to femoral-popliteal occlusion, bypass surgery is the preferred treatment (if feasible). The excellent acute results that can be obtained from percutaneous techniques in the current era, and the fact that subsequent surgical bypass is still possible if needed, has led some to support a strategy of initial endovascular therapy, including for the treatment of critical limb ischemia.

**Adjunct Therapies**

For stenoses of the SFA and popliteal arteries, the standard approach is that of balloon angioplasty. Various technologies, including stents, and directional, rotational, and laser atherectomy have been investigated as means of improving long-term patency and reducing restenosis in the SFA (Figure 34.16). In contrast with the documented benefits achieved by use of endovascular stents for iliac arteries, experience thus far in the SFA has been less favorable. Results with nitinol SE stents are conflicting. In some studies, the restenosis rate has been prohibitively high; yet in other studies, complex SFA disease treated with stenting has yielded exceptional long-term results. Preliminary results with drug-eluting stents in the SFA and/or popliteal circulation have not been as favorable as in the coronary circulation. However, more recently, Cook’s Silzer PTX drug-eluting stent has shown some promise in short to moderate length lesions. The data show better patency as assessed by duplex ultrasound at 2 years when compared to balloon angioplasty and provisional stenting. Furthermore, drug-coated balloons are currently being routinely used in Europe, and two trials have recently started in the United States. Fracture-resistant stents, such as the IDEV Supera stent, have also shown promise but more data is necessary. Neither directional nor rotational atherectomy has been demonstrated to have an advantage for SFA and popliteal revascularization, save for those rare patients in whom the extent of calcific deposits renders the lesion refractory to alternative techniques (Figure 34.17). Laser angioplasty has been used effectively in SFA and popliteal revascularization, and the recent FDA approval of larger catheters may enhance debulking with this device. An ongoing randomized clinical trial (EXCITE Trial) is currently evaluating the role of laser atherectomy for in-stent restenosis.

For occluded femoral-popliteal arteries, whether or not to use thrombolytic therapy in advance of PTA is controversial. Lytic therapy can be successful in some patients with chronic total occlusion, because the occlusion in lower extremity arteries is often characterized by a lengthy, gelatin-like thrombus superimposed on a high-grade atherosclerotic lesion. Lytic therapy thus can convert a long occlusion to one that is either shorter or nonocclusive, which may respond better to PTA (Figure 34.18). Despite the theoretical benefit, most interventionalists opt for direct revascularization with...
PTA, followed by use of SE stents for extensive recoil or flow-limiting dissections.

Some promising strategies lie on the horizon for treating the vexing problem of SFA restenosis: it is hoped that drug-eluting stents, covered stents, or local drug delivery might reduce the incidence of restenosis. For cases where the vessel is not amenable to revascularization, various strategies to increase blood flow by triggering growth of new collaterals,
Chapter 34 Peripheral Intervention

A 69-year-old male status post balloon angioplasty and stenting of the distal SFA and P1 segment of the popliteal artery presents with recurrent claudication. Angiography reveals a totally occluded stent (A, white arrows). Severe narrowing in the mid segment of the stent (black arrows) (B and C) after pulse spray lytic therapy and Posis mechanical thrombectomy. Good results after balloon angioplasty alone (D).

Figure 34.18

Treatment Considerations and Technique

Access

The most important aspect of SFA intervention is access. Before approaching a case all noninvasive and invasive tests including prior angiograms should be reviewed. This will guide the best access site selection. The most common approach for SFA disease is contralateral crossover technique. However, brachial, ipsilateral antegrade, popliteal, and pedal access may also be needed (Figure 34.19). Familiarity with the local anatomy at the level of the common femoral artery is essential (see Chapter 19). The use of a kink-resistant sheath is critical to maintaining access around the bifurcation of the aorta, especially in the case of the acutely angulated bifurcation. Any number of curved (Cobra, IMA) or retroflexed (Omni, SOS, Simmons) catheters may be used to obtain access to the contralateral common iliac artery. The advantages to this approach include the ability to image the common femoral and its bifurcation and the ability to treat iliac and infrainguinal disease in the same sitting.

We typically use a 6F sheath and place the tip at the level of the common femoral artery. Most stents are 6F sheath compatible; however, the Cook Zilver SE stent is a 0.018 inch system that can be used through a 5F sheath. We then use a stiff angle glide catheter and a 4F or 5F angled or straight glide catheter as support. In general, all stenoses are crossed through the lumen; however, total occlusions typically require a subintimal pass. A number of chronic total occlusion devices have become available. These include the Crosser device (BARD), Frontrunner (Cordis), and even laser atherectomy; however, to date little data exist regarding the efficacy of these devices. In our experience, each device has a niche application and having a basic knowledge about each device is important.

Occasionally, reentry to true lumen can be very difficult when a subintimal technique has been selected. Many experts use 0.014 inch or 0.018 inch stiff chronic total occlusion wires. This approach works around 30% to 40% of the time. Alternatively, an Outback or a Pioneer reentry device can be used. The Outback device uses fluoroscopy to direct a needle toward the true lumen (Figure 34.20). The Pioneer device uses IVUS to detect the lumen. Subsequently, similar to the Outback device a needle is pushed toward the true lumen and reentry is obtained.

INFRAPOLITEAL ARTERIES

Dotter and Judkins in their original description of peripheral angioplasty in 1964, included two cases of angioplasty of infrapopliteal vessels. Since their original report, the
Various access sites are required when performing infrainguinal intervention. Retrograde common femoral artery (A). Antegrade ipsilateral common femoral artery (B). Pedal access with retrograde wire (arrows) at the level of popliteal artery above the knee (P2 segment) (C).

Development of techniques and delineation of indications for intervention below the knee have evolved. Today endovascular therapy for below knee disease is increasing in most centers across the United States and the world. Pedal, tibial, popliteal, and antegrade access have allowed more options to treat patients with below the knee disease. Furthermore, low-profile long balloons, soft floppy 0.014 inch and 0.018 inch wires, and now drug-coated balloons and stents have truly revolutionized therapy for below knee disease. While isolated below knee disease is generally not responsible for claudication symptoms, many patients (approximately over 70%) with critical limb ischemia have below knee disease. Of these, 30% to 40% have isolated below knee disease only.

In a large series reported by Dorros et al., success was achieved in 406 out of 417 patients (96%); the success rate in stenoses (98%) was superior to that in occlusions (76%). In-hospital complications were extremely low. The vast majority of patients with critical limb ischemia (95%) improved following revascularization. Such improvement does not necessarily imply ongoing patency. Restoration of flow through only one of the three major vessels to the foot may be sufficient to heal a distal ischemic lesion. Once healed, most patients will do well even in the face of documented reocclusion or restenosis. However, recent data indicate that improving blood flow to the area that is responsible for tissue loss is most likely the best option for patients with Rutherford class V and VI.

For patients with claudication, infrapopliteal disease usually coexists with more proximal disease, revascularization of
which alone is often sufficient to achieve symptomatic relief. However, if all three below knee vessels are compromised, it is not unreasonable to consider canulating of at least one vessel. This may not only help long-term patency of the SFA interventions but also may provide a more complete symptom relief.

Many of the patients treated with infrapopliteal angioplasty to date have been those who were too high risk or otherwise not candidates for bypass surgery.147 The BASIL trial is the first randomized clinical trial to compare angioplasty with open surgical revascularization in patients with critical limb ischemia.148 In this trial, both surgery and angioplasty resulted in similar amputation-free survival; however, in the short term, surgery was more expensive. In general, surgery was associated with higher incidence of bleeding and wound infection, while angioplasty was associated with a higher revascularization rate.148 Given the advances in drug-eluting balloon technology and low-profile devices in conjunction with advanced operator experience, we anticipate that the number of below knee endovascular interventions will continue to rise in the near future.

Techniques

Over 90% of below knee interventions in our laboratory are done via the antegrade ipsilateral common femoral artery approach. Similar to iliac and SFA disease, appropriate preparation including a full review of prior noninvasive and invasive tests is critical. The diagnostic portion of the angiogram will need to focus on the foot and distal pedal vessels. We highly recommend selective injection via catheter placed at the level of the knee. This will allow identification of pedal and tibial vessels in case retrograde pedal or tibial access is necessary. Digital subtraction is preferred. Not infrequently, anatomic variants will be present, such as the anterior tibial arising above the knee joint. In addition, it is not unusual to mistake one of the small side branches or collaterals for the main arterial trunk. Adequate anticoagulation is critical, and administration of vasodilator therapy (nitroglycerin or papaverine) may be useful. Initial attempts to cross stenoses or occlusions should use small, coronary-type guidewires (0.014 inch or 0.018 inch), although 0.035 inch hydrophilic type wires can also be used to cross complex occlusions located within the popliteal artery. Confirmation of a luminal position in the distal vessel should be obtained prior to dilating, by removing the wire from the catheter and injecting a small amount of diluted contrast through the guide or the support catheter into the distal vessel.

When performing infrapopliteal PTA, care should be taken to not compromise future potential surgical options. For example, overdilation and disruption of a previously uncompromised distal vessel may prohibit subsequent bypass to that site.

Rotational atherectomy, FoxHollow atherectomy, cryoplasty, or excimer laser angioplasty (Figure 34.16) can be useful as adjunctive therapy. Specifically, lesions that have unfavorable morphology, such as total occlusions, heavy calcification, and ostial disease, may benefit from these niche devices.149,150 Previous studies with rotational atherectomy have shown it to be useful acutely, although data on long-term follow-up do not suggest a benefit over balloon angioplasty alone. The use of stents—including drug-eluting stents—has been advocated and evaluated in a number of small studies; however, their use in the United States is considered off-label.151-153 To summarize, the percutaneous therapy of infrapopliteal vessels is still in evolution, and indications are expanding. It is not unreasonable, especially for patients with threatened limbs who are high-risk surgical candidates, for experienced operators to attempt percutaneous revascularization of offending infrapopliteal lesions before committing the patient to surgery. Although the restenosis/reocclusion rates are high, long-term limb salvage can nonetheless be successfully achieved. For the rare patients who have severe intermittent claudication on the basis of infrapopliteal disease alone, PTA may be a reasonable option. Finally, when SFA or popliteal disease occurs in conjunction with infrapopliteal lesions, revascularization below the knee may be reasonable to increase the outflow following recanalization of the proximal vessel.

Stenosis in a lower extremity bypass graft can threaten the patency of the graft and shorten its life.154 The etiology of bypass graft stenoses is variable. Stenoses that occur within the first few weeks or months of graft placement usually indicate a technical problem that is best treated by repeat surgery and graft revision. If there is anastomotic problem, percutaneous therapy is typically very effective. Graft failure within a later time frame (several months to years) can be due to intimal hyperplasia, atherosclerosis, or progressive fibrosis of a poor venous conduit. Several other factors may contribute to graft failure, including the presence of poor inflow or outflow, low cardiac output, a hypercoagulable state, compromise of the graft owing to patients crossing their legs, or external compression of the graft by sclerosis and fibrosis (for example, from a scarred groin).155 Prosthetic conduits are more likely to present with abrupt occlusion, whereas native venous conduits tend to present with a progressive downhill course. Of course, even in the case of the latter, abrupt thrombosis and acute limb ischemia can occur.

Frank or impending graft failure is often not heralded by increasing clinical symptoms. Accordingly, a strategy of regular graft surveillance using duplex ultrasonography is recommended to preserve and extend the life of the graft. For impending graft failure, either detected by duplex ultrasonography or increasing symptoms, immediate arteriography is recommended, followed by either surgical or percutaneous revascularization. As stated in the American Heart Association task force guidelines in 1994, focal lesions of the distal
anastomosis of a femoral-popliteal or femoral-tibial graft are amenable to PTA. Other lesions that may be amenable include focal stenoses of proximal graft anastomoses or short-segment lesions (3 cm or less) occurring within the bypass graft. Surgical revision is recommended for long lesions (especially >10 cm) and stenoses associated with anastomotic aneurysms.

Patients presenting with acute or subacute graft thromboses (<14 days) are best treated with catheter-directed thrombolysis. An alternative is balloon embolectomy, although the latter strategy may be associated with a higher morbidity and mortality over the ensuing year. The one exception to this is the recently placed graft that fails almost immediately, which should return immediately to the operating room for surgical thrombectomy and revision. For patients with long-standing grafts that fail, determination of the factors responsible may require reestablishing enough flow to visualize the graft angiographically. In cases of early graft failure, examination of angiographic studies may provide clues previously overlooked, such as stenosis of an inflow vessel, poor or inadequate distal runoff, or the presence of a venous side branch that was not sutured.

Techniques

For patients presenting with impending graft failure based on a duplex study, access should be obtained to optimize the therapeutic alternatives. Lytic therapy should be considered for thrombosed grafts. For anastomotic lesions, balloon angioplasty is typically effective. If the lesion is resistant to balloon dilation alone, directional or laser atherectomy may prove useful for salvaging the graft. Likewise, although stents have been advocated by some for use in failing vein grafts, their utility has not been studied in any formal trials to date. Drug-eluting stents may prove to have an important role in this situation. In general, we highly recommend the use of embolic protection when performing atherectomy or even cutting balloon angioplasty in old bypass grafts.

Chronic DVT has also been a target of intervention in patients with venous claudication or in those with venous ulcers. Unfortunately, currently tools to treat chronic venous disease are limited in the United States.

Techniques

For acute (within 2 to 4 weeks) lower extremity DVT, we typically recommend pulse spray lytic therapy followed by mechanical thrombectomy using one of the available devices such as Angiojet rheolytic catheters. A retrograde, via the contralateral common femoral vein, or an antegrade approach via the popliteal vein is a potential option. In general, we prefer the popliteal approach. We rarely, if ever, place a prophylactic inferior vena cava (IVC) filter in these patients. For subacute DVT, lytic therapy infusion over 24 to 72 hours may be required. These individuals require close monitoring in the intensive care unit. When placing patients on a lytic infusion, low-dose heparin (600 to 800 unit/hour) should also be administered simultaneously. These individuals should be monitored for signs of intracranial bleed. Furthermore, blood counts and fibrinogen levels should be monitored.

TRAINING AND CREDENTIALING

Percutaneous intervention for treatment of PVD has been adopted by multiple specialties, including interventional cardiology, vascular surgery, interventional radiology, and others. Such widespread application necessitates development of standardized guidelines for training and credentialing to ensure that patients will receive optimal care. Accepted guidelines regarding the minimal requirements necessary to care for patients with PAD and perform peripheral vascular procedures have been described in the multidisciplinary Clinical Competence Statement on vascular medicine and catheter-based peripheral vascular interventions. More specific recommendations apply to carotid interventions and have recently been ratified by the cardiology, vascular surgery, and vascular medicine communities, with a view to establishing a common set of criteria for training and credentialing to facilitate safe and orderly dissemination of this new therapy into clinical practice.

Cardiologists, whether still in fellowship or established in practice, who wish to care for patients with PAD and perform peripheral interventions must prepare properly to provide their patients optimal care. Until the cognitive, clinical, and procedural skills are incorporated routinely into formal cardiology fellowship programs, additional training is necessary. In particular, carotid revascularization involves interventional skills, equipment, and clinical management skills that differ significantly from those used in other vascular distributions. Moreover, it involves treatment of a uniquely sensitive organ system, wherein minor errors or complications can have catastrophic effects. Given the high-

VENOUS DISEASE AND INTERVENTION

An estimated 100 persons per 100,000 each year are newly diagnosed with venous thromboembolism in the United States. Of these, about two-thirds have acute deep venous thrombosis (DVT) while one-third have pulmonary embolism (PE). In addition to significant mortality, both conditions are associated with a number of morbidities that may be prevented when prompt endovascular intervention is performed. Over 30% to 40% of patients with DVT may suffer from post thrombotic syndrome (PTS) after lower extremity DVT. Similarly with rising prevalence of malignancy the incidence of upper extremity DVT has also been on the rise. While typically more benign, it has been associated with superior vena cava syndrome and upper extremity discomfort.
risk nature of carotid revascularization and the availability of alternative treatment modalities, decisions regarding optimal therapy require a comprehensive knowledge base of the disease and its ramifications to properly assess the risk–benefit ratio of each therapeutic option. Experienced operators have been shown to have improved outcomes in carotid stenting.

As a result of these considerations, a joint committee, including the societies of each specialty involved, has proposed minimal training requirements that cover proficiency in the cognitive, technical, and clinical skills necessary to safely perform carotid stenting. The cognitive requirements include comprehensive understanding of the risk factors, epidemiology, pathology, pathophysiology, natural history, clinical presentation, and therapeutic alternatives for patients with carotid artery disease to allow appropriate decision making regarding indications, limitations, and complications of the procedure.

REFERENCES


The catheter-based treatment of congenital heart disease has been the traditional domain of pediatric interventional cardiologists. But the successes of both pediatric cardiac medicine and pediatric cardiac surgery over the past 40 years have resulted in a rapidly growing population of adults with corrected and palliated congenital cardiac lesions that few adult cardiologists have experience in managing. While most adult interventional cardiologists have limited training in the evaluation and transcatheter repair of these congenital lesions, pediatric interventional cardiologists who are expert in congenital heart disease, generally have little training in the commonly superimposed “adult” cardiology issues (such as pregnancy, hypertension, obesity, and coronary artery disease). This chapter focuses on a series of interventions for congenital heart disease that apply to both the pediatric and the adult population, noting procedural modifications that are required to accommodate a baby or an adult patient. Since knowledge of the physiologic and hemodynamic consequences of these lesions is at least as critical as knowing the steps of the procedures, a brief review of the underlying pathophysiology is also included in each section.

THE CONGENITAL CATHETERIZATION LABORATORY

Catheterization laboratories (cath labs) that perform procedures on patients with congenital heart disease differ from those treating mostly coronary disease. Most congenital procedures are best done in a biplane cath lab, as finding septal defects and complex surgically constructed pathways requires three-dimensional imaging. Case times are usually far longer than those of coronary cases, and the spectrum of equipment required for congenital cases is quite different. Because of the wide variety of congenital lesions and patient sizes, as well as the uncertainty as to when a particular catheter or device might be needed, a large number of items must be stocked. The laboratory administration thus must be willing to accept having some equipment expire unused rather than risk not having the critical catheter or wire available when it is needed.

In contrast to the early days of congenital catheterization, it is currently uncommon to perform purely diagnostic procedures. Echocardiography (transthoracic in children, transesophageal in adults), and now cardiac magnetic resonance imaging (MRI) are powerful noninvasive imaging modalities that allow the definition of the anatomy and assessment of both simple and complex physiology (including shunts, valvar dysfunction, and obstructions within the circulatory pathways). Instead, cardiac catheterization has become the preferred and minimally invasive way to perform repairs and palliations of straightforward congenital heart defects whose correction was previously limited to the operating room.

CONGENITAL OBSTRUCTIVE LESIONS

Obstructive Lesions of the Right Ventricular Outflow Tract

Obstruction to pulmonary blood flow is one of the most common and important abnormalities associated with congenital heart disease, and congenital interventions frequently involve relief of this problem. Congenital obstruction of the right ventricular outflow tract can occur in the muscular right ventricular outflow tract (subvalvar obstruction), at the valvar level, in the main pulmonary artery (MPA) (supravalvar obstruction), or at the level of the branch pulmonary arteries.
Although the level of obstruction can usually be determined noninvasively, each lesion has a unique hemodynamic pattern and angiographic appearance (see below). They have in common, however, increased afterload on the right ventricle (RV) myocardium, resulting in right ventricular hypertrophy and reduced diastolic compliance of the ventricle as a receiving chamber with a corresponding increase in right atrial filling pressures. The clinical symptoms associated with these lesions depend both on the degree of obstruction and the age of the patient.

**Subvalvar Pulmonary Stenosis**

Subvalvar obstruction is usually muscular in nature and is not generally amenable to catheter intervention (Figure 35.1A). Residual or recurrent “infundibular” obstruction is most commonly found in patients who have undergone repair of tetralogy of Fallot. Double-chambered right ventricle (DCRV) also features hypertrophy of the infundibular muscle, causing it to closely appose the free wall of the RV in systole and narrow the outflow tract below the pulmonary valve. In children, this lesion may be associated with small membranous ventricular septal defects (VSDs) or membranous subaortic obstruction. Over time, the membranous ventricular septal defect may close spontaneously as the infundibular obstruction progresses, so that DCRV may present in the adult as an apparently isolated subvalvar obstruction.

Pulmonary valve annular hypoplasia may also present in the setting of significant right ventricular outflow obstruction and can be found in patients as residua of surgically corrected congenital heart disease (CHD). This lesion is not generally amenable to transcatheter intervention owing to the fibrous ring of the hypoplastic annulus that resists balloon dilation.

**Supravalvar Pulmonary Stenosis**

Except when scarring from previous surgical interventions produces narrowing of the MPA (i.e., following arterial reconstruction in neonatal transposition of the great arteries, or tetralogy of Fallot), supravalvar obstruction generally occurs at the sinotubular junction and is congenital. Sinotubular junction stenosis can be confused echocardiographically with valvar disease, because the normal leaflets are limited in their forward motion by the distal ridge of muscular tissue (Figure 35.1B), appear to dome, and exhibit turbulent flow at the leaflet tips on Doppler, just as is seen in valvar pulmonary stenosis (PS). Balloon dilation of supravalvar obstructions is largely unsuccessful owing to the muscular/elastic nature of the arterial wall in the MPA, and has been associated with MPA rupture. Stents have been placed successfully to relieve obstruction in the supravalvar region, but risk stenting open the pulmonary valve and causing severe insufficiency, most often a poor trade-off for moderate PS.

**Valvar Pulmonary Stenosis**

Valvar PS is a common congenital lesion. Similar in nature to congenital aortic stenosis (AS), it is typically caused by commissural fusion that precludes the leaflets separating fully (Figure 35.1C). The result is a diminished valve orifice/valve area resulting in increased RV afterload.

The natural history studies of isolated valvar PS in children indicate that a pressure gradient >50 mmHg is associated with poor long-term outcomes, including RV myocardial dysfunction, ventricular arrhythmia, and sudden death, whereas pressure gradients <30 mmHg are not associated with symptoms, changes in lifestyle, or life expectancy. As treatment shifted from surgical to catheter-based therapy in the 1980s, the indications for intervention have changed. Currently, any patient with a peak-to-peak valvar gradient ≥40 mmHg should be considered for balloon valvuloplasty.

**Neonatal Critical Pulmonary Stenosis**

Neonates with critical valvar PS, or with valvar pulmonary atresia, present with cyanosis. Desaturated blood returning to the right atrium (RA) can either enter the severely hypertrophied, sometimes diminutive RV chamber or flow right to left across the patent foramen ovale (PFO), as it did throughout fetal life. This shunt adds desaturated blood to the pulmonary venous return on the left side of the heart, accounting for the systemic hypoxemia. If the atrial level shunt is large enough, and resulting antegrade pulmonary flow is small enough, the patient will be dependent on the coexistence of a patent ductus arteriosus (PDA) to provide pulmonary blood flow. When the PDA begins to close (12 to 48 hours), the child becomes progressively hypoxemic, requiring prostaglandin E1 (PGE1) to reopen and to maintain ductal patency until an appropriate intervention can be performed.

Even after successful balloon intervention in the neonate (see below), the hypertrophied RV continues to present a diastolic impediment to forward flow, fostering a continued right to left shunt at the PFO, and ongoing systemic desaturation. When PGE1 is discontinued, and the PDA begins to close, pulmonary blood flow will be reduced, and systemic oxygen saturations will fall. As long as the infant maintains oxygen saturations greater than 70% and does not develop a systemic metabolic acidosis, PGE1 does not need to be restarted. Over a course of days to weeks, after elimination of the right ventricular afterload, the right ventricular myocardium thins and becomes more compliant. It becomes easier to fill the RV, right-to-left shunting diminishes, and the patient’s oxygen saturation normalizes. Rarely, ongoing RV noncompliance, often in combination with right ventricular and tricuspid valve (TV) hypoplasia, can result in persistent desaturation in the absence of significant residual PS, and may require closure of the PFO/atrial septal defect (ASD) to eliminate the right-to-left shunt.

**Pulmonary Stenosis after the Neonatal Period**

In most children, PS presents as an asymptomatic heart murmur. Gradients are followed noninvasively with Doppler echocardiography. It is important to note that the peak instantaneous echo gradient usually overestimates the peak-to-peak gradient measured in the cath lab (Figure 35.2) when considering the timing of the intervention in a child. Severe
Figure 35.1

A. Top. Subvalvar pulmonary stenosis (PS). Severe muscular dynamic narrowing of the RV outflow tract (white arrows), well below the level of the valve leaflets (black arrows). Bottom. Systolic pressure remains unchanged (pullback 1) as diastolic pressure falls indicating transition into the ventricle. On further withdrawal of the catheter (pullback 2), there is a large systolic gradient with no change in diastole, consistent with an intraventricular obstruction. MPA, main pulmonary artery; RV, right ventricle.

B. Top. Supravalvar PS. The thickened pulmonary valve leaflets (white arrows) abut the supravalvar muscular ridge at the sinotubular junction (black arrows), not allowing full leaflet excursion. Bottom. There is a jump in the systolic pressure on pullback, but no fall in the diastolic pressure, indicating that the catheter remains in the PA, distal to the valve. A second pullback reveals no further systolic gradient coming back into the ventricle.

C. Top. Valvar PS. Doming valve leaflets (black arrows) are fused and cannot open fully. Jet of contrast through valve orifice is well profiled. Bottom. Systolic pressure gradient occurs at same site/time where diastolic pressure falls, indicating transition through the valve from artery to ventricle.
obstruction is associated with surprisingly few symptoms in
young children. Rarely, children with severe PS may maintain
patency of the PFO allowing right-to-left shunt at times of
peak exercise (exercise-induced cyanosis). In patients who
are cyanotic at rest, it is important to recognize that neither
the echo nor catheter estimates of valve gradient accurately
reflect the degree of obstruction, since only part of the cardiac
output is traversing the valve.

Adolescent/Adult Patients

Valvar PS rarely presents de novo in the adolescent and adult
population. The harsh systolic murmur invariably brings
these patients to attention early in childhood. However, the
lack of symptoms, and lesser gradients, in the pediatric age
group, may delay early intervention. Mild degrees of obstruc-
tion are tolerated without issues for many decades but can
occasionally be associated with new onset symptoms of
exercise intolerance, breathlessness, and fatigue in the older
adult. Classic signs of right heart failure—peripheral edema,
jugular venous distension, and ascites—are rare. But the
excessive right ventricular afterload limits RV systolic perfo-
rance, thereby diminishing left ventricle (LV) preload and
cardiac output during exertion. Adult PS patients tend to be
more symptomatic than children with similar gradients, but
we have seen patients in their eighth and ninth decades of life
with very high gradients (>100 mmHg) and few symptoms.

Valvar PS in the adult may also be acquired as part of
carcinoid heart disease. These valves become thickened and
dense and more closely resemble dysplastic neonatal valves,
whose resistance to flow is not related to valve leaflet fusion,
but rather to the force required to push open the thickened
leaflet. As is the case in the newborn disease, these thickened
valves are generally not responsive to balloon valvuloplasty.

Pulmonary Valve Stenosis with
Significant Regurgitation

When pulmonary valve stenosis or obstruction within a sur-
gically placed RV to pulmonary artery (PA) conduit coexists
with significant pulmonary regurgitation, the result is both
a volume overload and afterload increase on the RV. In this
setting, relief of the obstruction alone, may not alleviate the
most severe hemodynamic derangement, the regurgitant flow,
and may actually make it worse. Until recently, surgical inter-
vention with valve replacement was the only alternative avail-
able to the patient.

Over the past decade however, beginning with the work
of Bonhoeffer's group in Europe, the development and sub-
sequent clinical use of an implantable pulmonary valve has
changed not only the interventional management of patients
with residual postsurgical pulmonary valve disease, but also
is reshaping many of the surgical paradigms for earlier man-
agement. With an excellent intervention available for replace-
ment of the pulmonary valve inside of a surgical conduit, or
inside the annular ring of a preexisting replacement tissue
valve, surgeons are moving away from mechanical valves,
and from complex RV outflow tract reconstructions, when a
valved conduit can be more simply placed from the RV to the
MPA. This is now done with the knowledge that the conduit
placement may represent the last surgical intervention for
some patients.

Since so many complex congenital malformations,
including pulmonary valve atresia, tetralogy of Fallot, double-
outlet RV, and some of the aortic valve malformations, require
intervention for, or reuse of the native pulmonary valve, the
need for later valve replacement is growing. This is particu-
larly true in light of the growing recognition of the deleteri-
ous long-term effect of pulmonary valve insufficiency on the
RV myocardium. The Melody Valve (Medtronic) is approved
in the United States, and the Edwards-Sapien Valve, approved
for aortic valve replacement’ is in clinical trials. Today, patients
with tetralogy of Fallot who have had valved conduits or pro-
thetic valves placed, and patients who underwent the Ross
procedure, where the pulmonary valve is autotransplanted
to replace the diseased aortic valve and a valved conduit is
used between the RV and the lungs, represent the two largest
patient populations who are receiving these valves.

Careful evaluation of the underlying coronary anatomy
is critical in determining the appropriateness of the interven-
tion. When the conduit is placed on the anterior surface of the
heart, coronary branches may pass directly beneath it, and may
be potentially compressed by placement of the stented valve and distension of the conduit. Evaluation and pretreatment of the valve landing site is critical for optimal valve longevity. Because the conduits sit directly beneath the sternum, there is often an element of compression of the conduit which is dynamic, and can lead to stent fracture (Figures 35.3 and 35.4). Prestenting the landing site of the new valve, potentially with several stents layered inside each other, has significantly improved the survival of the implant, minimizing stent fracture, which affected 23% of the initially reported series.8,9

Branch Pulmonary Artery Stenosis

Branch PA stenosis or hypoplasia may be acquired (e.g., either at sites of prior surgery, or from extrinsic compression) or may be congenital (i.e., tetralogy of Fallot). Numerous systemic congenital syndromes are also associated with branch PA stenosis/hypoplasia (Williams syndrome, congenital rubella, Alagille syndrome, and others). Branch PA stenosis is typically a hemodynamic burden that must be dealt with in children, but can be seen in adults as residue of earlier

Figure 35.3 In this patient with tetralogy of Fallot and pulmonary atresia, the conduit passed over a large anterior RV coronary branch that arose from the proximal left coronary artery. Selective coronary angiograms with simultaneous inflation of an angioplasty balloon (B) in the conduit demonstrate occlusion of this RV branch. Angiography from a right anterior oblique projection shows (A) early occlusion of the anomalous coronary (arrow), with persistent distal contrast, and (B) subsequent resumption of flow as the balloon was deflated (arrow). (C and D) Subsequent angiography in a lateral projection demonstrates complete occlusion of the coronary branch with balloon inflation to higher pressure. In C, the arrow indicates the proximal stump of the occluded vessel, which then fills (multiple arrows) as the balloon is deflated in D. (Reproduced with permission from McElhinney DB, et al. Circulation 2010;122:507–516.)
congenital heart surgery or rarely as an isolated congenital lesion. Anatomy ranges from single stenotic areas, to multiple stenoses, to diffuse hypoplasia of the vessel. In contrast with other right-sided obstructive lesions, the branch PA stenosis not only increases RV afterload, but also results in mal-distribution of the pulmonary blood flow with hypoperfusion of selected lung segments or of an entire lung, and overcirculation to others because of the parallel pathways available to the pulmonary blood flow. Indications for angioplasty include elevated right ventricular systolic pressure, hypertension in unaffected portions of the vascular bed, marked decrease in flow to an affected portion, and/or symptoms. In children, growth of the distal vessels depends on the blood flow to those segments. Segmental hypoperfusion in childhood is associated with poor growth of the affected PA, and is itself an indication for intervention.

Figure 35.4 Angiograms demonstrating (A) preimplantation conduit obstruction and PR and (B) relief of obstruction and a competent valve after TPV. This patient with tetralogy of Fallot and pulmonary atresia had a primary indication of PR assigned on the basis of preimplantation echocardiography, which showed severe PR and a mean echocardiographic RVOT gradient of 18 mmHg, although the directly measured RVOT gradient was 60 mmHg at the time of catheterization. At the 2-year follow-up, there was no stent fracture, no PR, and a mean Doppler RVOT gradient of 11 mmHg. (C) Preimplantation mean Doppler RVOT gradient and echocardiographic PR grade are depicted in each patient according to the site-determined primary implantation indication: RVOT obstruction (solid red circles), PR (solid blue triangles), or mixed PR and obstruction (open purple circles). Patients of all NYHA classes are depicted; thus, some patients with moderate PR and a gradient >40 mmHg are in the mixed indication category (NYHA class II or higher), and others are in the RVOT obstruction category (NYHA class I). (Reproduced with permission from McElhinney DB, et al. Circulation 2010;122:507-516.)
Quantitative lung perfusion scans, and more recently MRI/MRA, have been extremely useful in the ongoing assessment of these patients. Flow to each individual lobe can be quantified, yielding information about relative severity of individual stenotic lesions. This can help direct therapy prior to arrival in the cath lab and avoid unnecessary catheter/wire manipulation during what are often lengthy procedures.

**Percutaneous Balloon Pulmonary Valvuloplasty**

Percutaneous pulmonary valvuloplasty in children was first reported by Semb et al.\(^\text{11}\) in 1979. However, the static balloon technique, reported by Kan et al.\(^\text{12}\) in 1982, was the first to be applied widely. Results have demonstrated the safety and effectiveness\(^\text{13-16}\) of this technique and have established it as the treatment of choice for children and adults with isolated pulmonary valve stenosis.

**Pediatric Technique**

Echocardiographic evaluation is critical to successful outcome prior to intervention. It defines both the degree of obstruction as well as the valve morphology, allows extremely accurate measurement of the pulmonary valve annulus, and can rule out any associated defects. Balloon dilation catheters are now available on catheter shafts as small as 3F, allowing pulmonary balloon valvuloplasty even in premature infants under 2 kg.

After administration of appropriate anesthesia, femoral venous access is obtained and a balloon-tipped angiography or end-hole catheter is used to perform the right heart catheterization. In the absence of associated defects, the PA saturation is used to estimate predilation cardiac index (Fick calculation). In most cases, femoral arterial access is not required, as complications from arterial access probably far outweigh the complications of the valvuloplasty especially in small children under 5 kg. The need for heparin administration (50 to 100 U/kg), in a purely right-sided catheter procedure is unclear. An end-hole catheter is advanced across the valve to a branch PA and a pressure pullback is performed (Figure 35.1C). The peak-to-peak, and mean gradients across the pulmonary outflow are measured. Right ventricular angiography is then performed using both lateral and cranial-angled AP projections to localize the valve and confirm the echocardiographic annulus size by measuring the valve diameter at the level of the valve hinge points. A balloon diameter 1.2 to 1.4 times that of the annulus is selected, since the use of oversized balloons in pulmonary valvuloplasty has been shown to produce optimal results in children. In larger patients, with an annulus size >20 mm, modifications in technique are required (see Section “Adult Patients”). A balloon length of 2 to 3 cm, depending on patient size, is adequate in most children and avoids some of the potential complications of right ventricular outflow tract trauma and injury to the TV.

A balloon end-hole catheter can be floated to the distal right or left PA (angled, torquable catheters may also be used), and a stiff exchange-length guidewire is placed in the branch PA, taking care not to injure the small distal branches of the PA. The sheath and catheter are removed, and the desired valvuloplasty balloon is introduced over the guidewire. Although some have advocated the introduction of a “naked” balloon through the groin, we prefer the use of a short venous sheath large enough to accommodate the appropriately sized balloon. Once the balloon catheter is centered on the pulmonary valve, the position can be adjusted quickly using a series of very-low-pressure partial inflations to look for the valve “waist.” When in the appropriate position, the balloon is inflated rapidly, with mild traction to prevent forward motion, until the waist disappears most often with a “popping” sensation. The balloon is then immediately deflated. The pop of the valve corresponds to the tearing of the stenotic valve commissures. We like to record the fluoroscopic images of this inflation, so that the result can be immediately reviewed, especially if there is any question of the effectiveness of the dilation.

After successful opening of the valve, the balloon will usually jump forward with forward flow, which must be distinguished from the forward “squirt” of a balloon that has been positioned too far into the PA, since the latter indicates that the valve has not been effectively dilated. In patients with dysplastic or thickened pulmonary valves, there will be no pop as the balloon is inflated to full pressure, but only a gradual resolution of the waist with increasing balloon pressure and a return of the waist as balloon pressures fall. As mentioned, these valves are rarely amenable to balloon valvuloplasty.

If a suboptimal result is obtained, repositioning and immediate reinflation may help. A monorail-type angiographic catheter can be advanced over the wire to assess the residual gradient, without removing the guidewire. Alternatively, a larger-lumen end-hole catheter (i.e., a guide catheter) with a Y adapter (Tuohy-Borst valve) can be advanced over the wire to perform a pullback, measuring pressure from the side port of the Tuohy-Borst as the catheter is withdrawn across the valve. In this way, residual pressure gradients can be measured and accurately localized to either the valvar or infundibular level (see Section “Complications”). Residual valvar gradients of more than 20 to 30 mmHg are unusual and suggest suboptimal balloon size or position and warrant repeat dilation with advancement of a potentially larger dilation catheter over the guidewire that is still in place in the PA.

**Age-Related Modifications of the Procedure**

In neonates, access for the procedure can be obtained at the umbilical vein, provided the ductus venosus in the liver has not closed. This route is readily accessible and avoids injury/obstruction of the femoral vein. In older patients, internal jugular and subclavian approaches are also acceptable for the procedure. Percutaneous transhepatic access has also been used.

With severe PS, with a closed PDA, the catheter across the tiny valve lumen may completely or virtually completely obstruct flow. In this setting, we prefer to perform the RV angiogram prior to crossing the valve to minimize the potential for hemodynamic compromise. Once the valve is crossed,
the catheter is removed quickly, leaving only the guidewire (to minimize obstruction to flow). In neonates, it is almost never possible to pass a balloon-tipped catheter through the valve, making our catheter of choice a torqueable 4F or 5F end-hole catheter with a multipurpose or Berenstein curve. This catheter is manipulated through the TV and flipped up into the RV outflow tract, and either a 0.014-inch torque-control guidewire or a small hydrophilic guidewire can be used to probe for the valve orifice. Once the valve is crossed, the wire is positioned either in a branch PA or through the ductus arteriosus into the descending aorta where it could be snared from the descending aorta to stabilize the position further, if needed.\textsuperscript{17} Most often, in this setting, we will first use a smaller balloon on a smaller catheter shaft to predilate the valve, followed by an oversized balloon to finish the procedure.

Valvar pulmonary atresia also presents with cyanosis in the neonate. In these babies, patency of the ductus arteriosus is required to provide pulmonary blood flow. In some cases, the size of the pulmonary valve annulus, the RV chamber volume, and the TV annulus may be sufficient to allow handling of the normal pulmonary blood flow. In these patients, several techniques have been used to perforate the atretic valve, including stiff guidewires, transseptal needles, or radiofrequency ablation—the most common choice today.\textsuperscript{18-20} Once the valve is perforated and a wire advanced into one of the branches or down the descending aorta (through the PDA), balloon dilation proceeds as if for critical neonatal PS. In some cases, ductal stenting can also be performed to maintain adequate pulmonary flow, as the RV becomes more compliant over time.

Adolescent/Adult Technique

Percutaneous balloon valvuloplasty in adults is similar to what is described above for younger children. The principle difference is that the valve annulus is larger, and owing to the need for balloon diameter oversizing to 120% to 140% of the valve annulus, balloons of 25 mm or larger are often required. There are three solutions to this size issue:

1. Custom balloons are available in sizes greater than 30 mm. With a balloon of this size, no real differences are required in the technique, but the balloons have longer inflation times, longer deflation times, lower burst pressures, and require larger sheath sizes.
2. Double-balloon technique. A second venous access is obtained and a balloon-tipped end-hole catheter is passed to the distal PA. A second stiff exchange-length guidewire is placed across the valve. The perimeter of the combined balloons is selected to be 20% to 40% larger than the measured annulus,\textsuperscript{21} and the balloons are inflated simultaneously. The double-balloon technique allows the use of two smaller sheaths but requires additional venous access and additional personnel; it is also more technically challenging, requiring accurate positioning of two balloons during simultaneous inflation.
3. In these cases, we prefer the use of an Inoue balloon for adolescent/adult pulmonary valvuloplasty.\textsuperscript{22} After hemodynamic evaluation and RV angiography, a 14F sheath is exchanged over a wire and a 0.032-inch stiff exchange guidewire is positioned in the branch PA. An Inoue balloon is selected with a diameter 1.2 times the valve annulus. The balloon is stretched/slenderized, and passed over the wire to the RA. At that point, the balloon is softened by retraction of the metal support rod, and the distal portion of the balloon is inflated slightly to help float the catheter through the valve. If there is difficulty in manipulating the Inoue balloon through the RV to the PA, a long 14F Mullins sheath can be passed over a wire into the PA, and the Inoue can be advanced through the long sheath (the sheath may need to be cut shorter to accommodate the Inoue length). Once positioned in the main PA, the valvuloplasty is performed exactly as a mitral valvuloplasty. A Y adapter can be attached directly to the back of the Inoue, and pressure can be measured from the sideport during pullback, over the wire. Advantages of the Inoue technique include the ability to upgrade the balloon size without having to change out the catheter, and minimizing the risk of TV or branch PA injury with the short length and positional accuracy of the balloon. Principle disadvantages are the large sheath size required and the higher cost of the Inoue compared with other balloon dilation catheters.

Complications

Acute Subvalvar (Infundibular) Obstruction

With severe valvar PS, particularly in older children and adults, concentric right ventricular hypertrophy is present universally. When the afterload at the valve is acutely removed, a hypercontractile RV outflow tract may create a dynamic subvalvar muscular obstruction, which has been termed the “suicide right ventricle.” The total gradient across the outflow tract may actually be higher after dilation than it was prior to the balloon dilation. It is critical to recognize the difference between residual valvar obstruction and resulting subvalvar reactive obstruction, so as not to perform unnecessary additional valve dilations. A careful pullback pressure recording performed over a wire (as outlined earlier) is the best way to determine the level of residual obstruction. With an intact atrial septum, if the subvalvar obstruction is severe enough, cardiac output may fall acutely. In patients with the potential for right to left shunt at the atrial level, hypoxemia will ensue. Acute treatment of these patients is much like that with left-sided hypertrophic obstructive cardiomyopathy. Volume loading should be combined with beta and/or calcium channel blockers to reduce myocardial contractility. Over the course of several weeks to months, as the hypertrophy of the outflow tract muscle recedes with reduction of the RV afterload, subvalvar obstruction will resolve.\textsuperscript{23}

Other complications are rare and include TV injury, as a result of wire tension on the TV leaflet during inflation or in pulling the partially deflated balloon back through the TV.
Pulmonary insufficiency can be seen after successful dilation, but is usually well tolerated acutely. Long-standing valvar regurgitation, however, may lead to RV dilation and dysfunction in adults. In children, long balloons may rarely injure/rupture the curved RV outflow tract as the balloon straightens, and a long balloon advanced or propelled too far into one of the branch PAs may cause injury at that site. Finally, the wire tracking through the TV can pinch or damage the atrioventricular node, resulting in high-degree atrioventricular block. In our experience, however, more than 94% of pulmonary valve procedures in all age groups were uncomplicated, with most complications clustered in the smaller infants.

Over more than two decades, pulmonary balloon valvuloplasty has been shown to be an extremely safe and effective therapy, in all age groups. Acute and long-term gradient reductions are comparable to surgical interventions, whereas complications, including pulmonary regurgitation, are less prevalent than after surgery. Balloon valvuloplasty is a curative procedure for most patients and should be considered the procedure of choice for valvar PS with a transvalvar gradient of >40 mmHg at any age, in symptomatic adults with gradients >30 mmHg, and in neonates with critical PS.

**Balloon Angioplasty for Branch Pulmonary Artery Stenosis**

Balloon angioplasty for hemodynamically important branch PA lesions can be accomplished with small peripheral vascular balloon catheters. Specially designed high-pressure balloon catheters or bladed cutting balloons may be used for more resistant lesions. Placement of intravascular stents has become the treatment of choice in older children and adults who have completed or nearly completed their growth. Particularly in the proximal, more muscular branches of the pulmonary tree, stents more reliably improve vessel size, overcoming the recoil of these elastic vessels, and reduce the need for oversized balloons. With increased experience demonstrating that later stent reexpansion is possible/safe, stents are now being used in even the youngest patients in critical situations.

**Technique**

Branch PAs may be dilated from any venous access, depending on the catheter course required. Often, access to the left PA can best be achieved from the femoral approach, while a superior approach may be the easiest to get to the right PA. Following a Glenn shunt, the only access to the branch PAs would be from above. In the case of an aortic to PA shunt, the PAs would need to be accessed from the femoral artery. After heparinization, and the placement of a small arterial catheter for blood pressure monitoring, right heart hemodynamics are measured, and the magnitude and location of gradients in the PAs are determined. In patients with symptoms of severe right ventricular failure, creation of an ASD (to maintain cardiac output) prior to dilation may decrease morbidity and mortality, by maintaining cardiac output (LV preload) even with the balloon inflated in the lungs. Pulmonary angiograms should include selective biplane injections in each lung and in affected lobes or segments. Selective catheterization of the lung segments is best accomplished using a torqueable end-hole catheter and a floppy-tipped torque wire. Steerable/deflectable catheters, used frequently by electrophysiologists for ablation procedures, are also available but may be too short in larger patients. Once satisfactory wire position is attained, an angiographic monorail catheter is the tool of choice to image and to assess the severity of the stenosis. Alternatively, a larger-lumen angiographic catheter may be passed over the wire, with a Y adaptor at its end, to allow angiography and pressure measurement from the sideport. Either technique allows pressure measurements, angiograms, and dilations to be performed without losing wire position. Lower-volume, selective injections in the affected lobes almost always yield superior images compared to injections in the central PA. Prior to dilation, a stiffer exchange-length wire should be passed to the largest vessel distal to the stenosis to support balloon positioning. Use of the largest vessel also minimizes the risk of rupture/vessel injury of small distal vessels with balloon inflation.

The ideal balloon has a low profile, a short distal tip, and a high maximal inflation pressure. The balloon diameter is chosen to be two to four times the diameter of the lesion but not more than two times the diameter of the normal vessel on either side. The balloon is inflated until the waist disappears or until maximum inflation pressure is reached. Inflation times range from 10 to 60 seconds, depending on the response of the waist and how well the cardiac output is maintained. Unlike dilation of the semilunar valves, in which all output from the ventricle is eliminated during inflation, perfusion of the other lung/lobes will maintain cardiac output and will allow longer inflation times. Like with coronary angioplasty, successful dilation generally results in tearing of the intima and media.

Following dilation, the balloon catheter is exchanged again over the guidewire for a monorail catheter, and the lesion is reassessed hemodynamically and angiographically. Successful dilation is often accompanied by an increase in pressure distal to the angioplasty site, and results in both a decrease in proximal pressures and a decrease in the gradient across the area. Angiograms are repeated to measure the diameter of the stenosis and to look carefully for tears and aneurysms that may preclude further balloon dilation. For this reason, distal lesions are generally dilated prior to proximal lesions, and more severe stenoses are dilated prior to milder ones.

**Results**

The criteria for successful dilation have been arbitrarily defined as an increase in diameter of >50%, an increase in flow in the affected segment of >20%, and/or a decrease of >20% in the systolic right ventricular-to-aortic pressure ratio. Using these criteria, the early success rate using low-pressure...
balloons was approximately 60%. The use of cutting balloons and high-pressure balloons with inflation pressures greater than 20 atmospheres increased success rates to 75%. The success rate for postoperative stenoses is higher than for congenital stenoses, which tend to be much more resistant to dilation. There is an incidence of subsequent restenosis following balloon angioplasty of approximately 15%. Complications have included death in approximately 1% of patients secondary to PA rupture or reperfusion pulmonary edema. Aneurysms occur in 3% of dilations and are most common in small vessels distal to the stenosis. Although the success rate using low-pressure balloons has changed little over the years, the complication rate has decreased owing primarily to improved technique. The use of high-pressure balloons does not seem to have significantly altered the complication rate. Balloon angioplasty at surgical sites should be used with caution in patients less than 4 to 6 weeks after surgery to minimize the risk of vessel rupture.

**Use of Bladed Cutting Balloons**

Later experience with bladed cutting balloon catheters has shown improved outcomes for the treatment of what were previously considered undilatable lesions. Small studies, under compassionate use protocols, have shown significant improvement in vessel size using oversized cutting balloons that cut through intimal and medial layers. After cutting-balloon inflation, subsequent use of high-pressure balloons and/or intravascular stents has further improved outcome with success rates reported in up to 92% of vessels.

**Use of Intravascular Stents**

Intravascular stents were first used for elastic/resistant branch PAs in 1989 and are now the most commonly used in CHD. Although balloon angioplasty remains the treatment of choice in peripheral lesions and in infants/small children (growth issues), stent implantation in the PA bed has become first-line therapy for proximal obstructions, lesions owing to surgical distortion, external compression, inadequate results of balloon angioplasty, and obstructive intimal flaps following balloon angioplasty. Infants who undergo surgical repairs such as the arterial switch for transposition of the great arteries, repair of tetralogy of Fallot with branch PA plasty, and palliations such as shunts or PA banding may have acute postoperative obstructions that create hemodynamic instability or place the obstructed lung at risk for long-term hypoperfusion. Stent usage in the immediate postoperative period, as an alternative to repeat surgical intervention, can be lifesaving and is more reliable than balloon angioplasty alone. Since early stent use in the branch PAs, technology has improved both in the stents themselves and in the delivery balloons. The use of stents has improved the success rate of branch PA interventions to >90%.

Most experience with stent implantation in branch PAs is with the balloon expandable Palmaz and Genesis stents (Johnson & Johnson, New Brunswick, NJ), though newer stent designs may have significant advantages including trackability, conformability to vessel course, reduction in balloon and vessel damage owing to smoother device edges, diminished stent shortening with expansion, and improved visibility with alternative materials. Innovations in balloon design include a marked reduction in catheter shaft diameter and slip-scratch-resistant balloon surfaces (to reduce the incidence of the stent slipping off or puncturing the balloon). The BIB (balloon-in-balloon) balloon dilation catheter system (Nu-Med, Hopkinton, NY) is being used for many indications and helps minimize the risks of stent malposition.

Heparinization and prophylactic antibiotic use is recommended in these typically long procedures. Predilation with a balloon is optional but is not necessary for most branch PA lesions. Stent and balloon sizes are selected for the individual lesion. The stent is crimped onto the balloon and can be delivered using one of two techniques. With a standard approach, an oversized long sheath or guiding catheter is passed over a stiff exchange-length guidewire (with a short floppy tip), such that the sheath tip is distal to the lesion to be stented. The balloon/stent combination is then advanced over the guidewire through the sheath to the implantation site. Alternatively, the front-loading technique involves passing the balloon catheter fully through the sheath outside the body, crimping the stent onto the balloon, and pulling it back into the front of the sheath before introducing this assembly over the wire. Combined techniques are also used in which the long sheath is advanced over the wire to the inferior vena cava (IVC), the stent then mounted on the balloon, and advanced over the wire to the tip of the sheath prior to advancing the entire system over the wire to the target lesion. The stent is deployed as described in Chapter 31. Antiplatelet therapy is the norm, for a period of 3 to 6 months to prevent in-stent thrombosis. For patients with normal pulsatile flow in the PAs, aspirin alone should be sufficient. For patients with nonpulsatile flow (bidirectional Glenn shunt or Fontan), dual antiplatelet therapy or warfarin is warranted, though there is little data available on which to base such a decision. There is a very low rate of restenosis in the branch PAs except for the relative stenosis that develops as the patient grows.

**Stents in Extracardiac Conduits**

Stents may also be used to extend the life of surgical conduits inserted between the heart and the branch PAs. With rapid growth of the infant, such conduits may kink and develop intraluminal obstruction. Balloon angioplasty alone in this setting has been largely unsuccessful because the conduit will reassume its kinked course on balloon deflation. In several patients, we have been able to hold off conduit replacement for several years using this approach, removing the stent with the explanted conduit at later surgery. This may allow for placement of an adult-sized conduit at the next surgery, and future placement of transcatheter valve implants (see above). For patients with obstructions in full-sized conduits, a pulmonary valve implant would be the current procedure of choice.
Anatomy/Physiology

Similar to obstructions of the right ventricular outflow tract, congenital obstruction of the left ventricular outflow tract can occur at the subvalvar level, at the valvar level, at the supra-valvar level, or in the aortic arch itself (coarctation of the aorta). The increased afterload on the LV myocardium results in concentric left ventricular hypertrophy and reduced diastolic compliance of the ventricle as a receiving chamber with a corresponding increase in left atrial and pulmonary venous pressures. The severity of patient symptoms is proportional to the elevation of left ventricular filling pressures. Patients may present with dyspnea on exertion when symptoms are mild and/or with orthopnea, syncope, or sudden death with ventricular dysfunction. Most children tolerate large degrees of left ventricular outflow tract obstruction without symptoms, presenting with a murmur alone, but symptoms become more common in the older child and adult.

Transcatheter Therapy for Left-Sided Obstruction

Subaortic stenosis encompasses a spectrum of disorders ranging from simple membranous obstructions of the subaortic area, to fibromuscular tunnel obstructions, to the more familiar hypertrophic cardiomyopathy. Like subvalvar lesions of the right side, subaortic obstructions are primarily a surgical issue. Membranous obstructions of the left ventricular outflow were treated with balloon angioplasty early in the interventional era, with limited success and with routine recurrence of obstruction.

Fibromuscular tunnel obstructions are generally not amenable to catheter intervention. Stents have been used in a few patients with critical postoperative obstructions, with very limited success, high morbidity, and a significant incidence of stent failure.

For the more common hypertrophic cardiomyopathy with muscular subaortic obstruction, alcohol ablation of septal tissue in adults has been widely adopted as an alternative to surgical muscle resection. There is no significant experience with this technique in children and adolescents, because septal hypertrophy is rarely clinically apparent before puberty and continues to develop during adolescence and young adulthood. Dual-chamber pacing has been reported to alleviate the degree of obstruction in younger patients, but with comparative studies is less effective in adults than either surgery or alcohol ablation.

Supravalvar AS typically occurs at the sinotubular junction, as a congenital lesion. This is the pathognomonic lesion for Williams syndrome, a genetic deletion syndrome associated with developmental delay, abnormalities of calcium metabolism, and a diffuse arteriopathy. This lesion should also be treated surgically because the elastic properties of the tissue at that site make balloon angioplasty ineffective, and the use of a stent in this position risks entrapping aortic valve leaflets with resulting aortic regurgitation.

Valvar Aortic Stenosis

Balloon aortic valvuloplasty for congenital AS in a child was first reported in 1983. It has been performed subsequently in large numbers of patients with both congenital and acquired valvar stenoses. In acquired calcific valve stenosis, acute relief of gradient is possible. However, the rapid rate of restenosis, the risk of cerebral embolization, the risk of disrupting the valve leaflets and causing severe valvar insufficiency, along with unpredictable and suboptimal degrees of obstruction relief has left balloon valvuloplasty for calcified valves as an emergency option only, when surgical valve replacement is not an option. The recent successes of transcatheter aortic valve replacement are changing the paradigms for treatment of older adults with severe aortic valve disease.

In children, adolescents, and young adults with congenital valvar AS, however, balloon valvuloplasty remains an excellent alternative to surgical valvotomy or to valve replacement, since the pathology involves more commissural fusion and less leaflet rigidity seen in adult patients with senescent and densely calcified aortic valves.

Neonatal Critical Aortic Stenosis

Physiologically, critical AS is a different entity from severe AS in older children, since the valve may be virtually atretic and the left ventricular cavity may be moderately to severely hypoplastic. Unlike hypoplasia of the right ventricle in critical PS (in which right atrial blood may cross the PFO to maintain LV preload and cardiac output), the size of the left ventricle has a direct impact on survival. LV hypoplasia, reduced LV compliance, and reduced emptying in the face of extraordinary afterload lead to increased left atrial and pulmonary venous pressures. While the PFO (or ASD) may act as a pop-off valve for the left atrium (LA), reducing pulmonary venous pressures and congestion, any blood that shunts from the LA to the RA, reduces LV preload, and as a result further reduces left ventricular output. Low cardiac output and pulmonary venous congestion may be incompatible with postnatal life. If LV hypoplasia is a concern, the alternative is to assign these patients to a stage I palliation for hypoplastic left heart syndrome. A retrospective analysis of a group of patients with critical AS undergoing surgical valvotomy or balloon dilation at Boston Children’s Hospital led to a scoring system (based on echocardiographic measurement of left-sided structures) that can be used to triage such patients.

The neonate with critical AS may be asymptomatic immediately after birth because of the normal remnants of the fetal circulation. Left atrial return crosses the PFO to the RA, rather than entering the LV. The volume-loaded RV ejects blood into the MPA, where flow is distributed between the lungs and the systemic circulation via the ductus arteriosus, based on the relative resistance of each pathway. If a normal...
blood volume reaches the aorta, there are no clinical problems. However, as pulmonary resistance falls and as the ductus arteriosus starts to close, RV blood preferentially flows to the lungs. A corresponding fall in systemic blood flow results in diminished tissue oxygen delivery, anaerobic respiration at the cellular level, and profound metabolic acidosis. Reestablishing and maximizing systemic flow is the key to resuscitating the acidotic newborn. Prostaglandin is required to reopen the ductus, and elevation of pulmonary vascular resistance is desirable (minimize FiO₂, allow pCO₂ to rise).

When most of the systemic flow arises from the ductus arteriosus, rather than the LV, the measured valvar pressure gradient across the stenotic valve is not a meaningful number, as the flow across the valve can approach zero. Prior to ductal closure, critical AS is manifested by right-to-left systolic flow at the ductus arteriosus with equal systemic arterial desaturation in all four limbs.

**Pediatric Technique**

Using routine sedation, a femoral vein and artery are entered percutaneously and the patient is heparinized. The venous catheter is used to measure right heart pressures and cardiac output (when no shunts are present) before and after dilation. In older patients, aortic valves can be dilated from the femoral vein using a transseptal approach, but this risks entrapping/stenting open/injuring the mitral valve, and the retrograde approach from the femoral artery remains the most common technique. The typical method for crossing the stenotic aortic valve from the aorta is to advance the soft end of a straight wire out of a steerable catheter (multipurpose or Judkins Right curve) and use it to probe for the valve orifice. We often use a hydrophilic guidewire, as the reduced friction of its surface allows for more rapid in and out movements, but probing must be done gently to avoid perforating a cusp or damaging the coronary arteries. When the LV is entered, a transvalvar gradient is measured by simultaneously recording pressure from the catheter and from the femoral sheath (one French size larger than the catheter). An aortogram may be done to define the anatomic landmarks if the time for crossing becomes prolonged. We do not routinely do a baseline aortic angiogram, as the amount of aortic regurgitation should have been documented by echo as part of the precatheterization evaluation. A pigtail catheter is exchanged over a wire, a left ventriculogram may be performed and the aortic annulus can be measured at the hinge points of the valve.

In contrast to the pulmonary valvuloplasty, the balloon diameter is chosen to be only 75% to 90% of the annulus diameter. Animal and clinical studies demonstrate that aortic valvuloplasty with a balloon/annulus ratio greater than 1.0 is more likely to be associated with aortic regurgitation. A double-balloon technique was used in the past to allow for the use of smaller sheaths, when the annulus was larger, and there was concern for femoral artery injury in small children. However with balloons on shafts as small as 3F and 4F today, there is little indication for such an approach. The pigtail catheter is exchanged for the balloon dilation catheter, which is centered across the valve, inflated and deflated rapidly, and pulled back to the descending aorta. The gradient and the cardiac output are remeasured following dilation, and an aortogram is performed to look for aortic regurgitation. If the residual gradient is >55 mmHg and an aortogram shows no or only mild regurgitation, a larger balloon may be used. It is far better, however, to leave a residual gradient than to cause significant aortic insufficiency in the small child, as surgical bailout options are limited (Ross procedure).

It can often be difficult to keep the balloon positioned in the valve during inflation, against the force of left ventricular ejection. A stiff catheter shaft, long balloon, and extra stiff exchange wire will help stabilize the position, or the balloon can be advanced so that it lies along the top of the aortic arch rather than under the underside of the arch. An increasingly common technique, suggested by Cribier, involves the use of a transvenous pacing catheter positioned in the RV to rapidly pace the ventricle during balloon inflation to reduce ventricular ejection and provide a more stable balloon position. This technique is a critical component of the transcatheter aortic valve implantation procedure.

**Technique for Critical Neonatal Aortic Stenosis**

Before the catheterization begins, the baby’s hemodynamic status must be optimized. We perform this catheter procedure with the baby intubated and paralyzed and receiving a prostaglandin infusion. The FiO₂ is turned down to 21%, and pCO₂ is allowed to rise to the mid-40s to increase pulmonary vascular resistance and maximize systemic flow across the PDA. Body temperature is carefully monitored.

The umbilical artery can usually be used in the first week of life. Catheter manipulation is more difficult from the umbilical artery owing to the inferoposterior loop in its course before it enters the descending aorta, but its use avoids damage to the femoral artery in these very small infants. Surgical cutdown at the carotid artery for catheter access has also been employed. This approach simplifies crossing the valve because of the straight path to the valve from the neck. As with older patients, a transeptal approach can be used from either the femoral or umbilical vein, with no puncture required since all neonates have a PFO. But this approach is rarely used since it carries a much higher risk of mitral valve injury than in the older population.

**Results/Complications**

Balloon valvuloplasty for congenital AS has been an effective palliation in the pediatric population with excellent gradient reduction and increase in valve area. But the procedure is complicated by the development of significant aortic regurgitation in 10% to 30% either immediately or within weeks of the procedure (inversely related to balloon/annulus ratio); femoral arterial complications in 30% to 40% (inversely related to the size of the patient), and restenosis. Survival with
freedom from reintervention was seen in only 50% of patients at 14.4 years in one cohort of 269 patients and in 60% at 12 years in a group of 74 patients. Transient left bundle branch block occurred in 15% and ventricular arrhythmias requiring cardioversion in 3%. In a 25-year review of balloon aortic valvuloplasty at Texas Children’s Hospital, death or transplant was significantly correlated with poor baseline LV systolic function, and the need for recurrent intervention was significantly higher in neonates than in older patients (34% versus 9%).

Patient selection based on echo criteria and improved catheter technology are improving outcomes in this difficult group. We currently recommend balloon dilation of congenitally stenotic aortic valves in patients with transvalvar gradients >55 mmHg and no more than mild aortic regurgitation and in neonates with critical AS who have adequate left heart size.

**COARCTATION OF THE AORTA**

The location of the obstruction in a patient with coarctation of the aorta (typically just distal to the takeoff of the left subclavian artery) creates not only an increase in left ventricular afterload, but also differential hypertension, with high pressures proximal to the obstruction and low to normal pressures distal (Figure 35.5A). High pressure in the ascending aorta and its branches predisposes these patients to many of the usual risks associated with hypertension. Intracranial aneurysms may be present in as many as 10% of patients with coarctation. As a result, the natural history of untreated coarctation includes risks of developing premature coronary artery disease and cerebral aneurysm rupture. However, unlike patients with essential systemic hypertension, pharmacologic normalization of cerebral and coronary pressures will proportionally reduce descending aortic pressure, and can produce iatrogenic claudication with exercise, abdominal cramping with splanchnic hypoperfusion, and significant renal dysfunction (prerenal azotemia). Intervention on the coarctation is thus required to achieve normotension in this population.

In neonatal critical coarctation of the aorta, the transverse and isthmic portions of the aortic arch may be hypoplastic and also in need of repair. The newborn will be asymptomatic initially as the carotids and subclavia are supplied adequately by the ascending aorta, while right to left shunting at the ductus arteriosus supplies flow to the lower part of the body (as discussed earlier). At this time, there may be differential cyanosis, with significantly lower arterial saturations in the legs.

**Figure 35.5**

A. Top. Pre stent implant. Arrow denotes coarctation site distal to left subclavian artery (*). The dilated internal mammary artery (IMA) acts as a collateral between ascending and descending aorta. Bottom. Pullback tracing from ascending to descending aorta. Large systolic gradient present, descending aorta with damped tracing. B. Post stent implant. Top. Status post stent angioplasty of coarctation site. IMA and left subclavian (*) remain marked. The stent margins are demonstrated by the arrows. Bottom. Pullback tracings from ascending to descending aorta. Post stent implantation, there remains no pressure gradient through the aorta. Systolic pressures in the ascending aorta have fallen, and the damped tracing of the descending aorta has normalized.
than in the arms. The pulse and blood pressure in the lower extremities may not be substantially different from those in the arms. With ductal closure, the critical obstruction of the aorta precludes adequate flow to the lower portion of the body. Pulses vanish in the lower extremities only, and a severe metabolic acidosis ensues. Prostaglandin is required to reestablish flow to the lower portion of the body.

As surgical aortic arch reconstructions have become routine at major pediatric heart centers as part of the stage I palliation of hypoplastic left heart syndrome, neonatal arch repair remains the standard of care, and many centers continue to send all pediatric coarctation patients for surgical interventions as a primary therapy, reserving transcatheter intervention for older (full-grown) patients, or for those with recurrent postoperative obstruction.

Percutaneous balloon angioplasty of coarctation was first described in 1982 as an alternative to surgery and has been used since in pediatric patients with both native (unoperated) coarctation as well as with recurrent (postoperative) coarctation. A study of experimental coarctation in lambs demonstrated that relief of obstruction occurs by tearing the intima and media, similar to other angioplasty procedures. Short- and long-term complications seen in that study, including perforation/rupture resulting in death, dissection, and late aneurysm formation, have all been described in patients.

Stent angioplasty for coarctation has become the procedure of choice in adolescents and adults in whom the stent can be expanded to a full, or nearly full adult aortic diameter, so as to avoid the need for later redilation of the stent.

Pediatric Balloon Angioplasty Technique

Under routine sedation, femoral venous and arterial access is obtained percutaneously. The patient is heparinized to an activated clotting time (ACT) > 200 seconds. Coarctation is almost always best approached from a retrograde femoral arterial approach, though transvenous, transseptal, and antegrade approaches have been reported (when residual aortic arch obstruction must be addressed following stage I surgical palliation of single ventricles, a venous approach is commonly used). Right and left heart hemodynamics are measured (including cardiac output), and pullbacks are performed with an end-hole catheter from the LV back through the aortic valve and through the area of the coarctation. Multiple levels of obstruction are possible—a bicuspid aortic valve is associated with coarctation of the aorta in > 70% of patients. Biplane aortography is best performed with right and left anterior oblique (RAO and LAO) projections. The diameters of the narrowest area of coarctation and of the normal proximal and distal aorta are measured.

For postoperative recurrent coarctation, the balloon is chosen to be 2.5 to 3.0 times the narrowest area but not greater than 1.5 times the normal proximal or distal aorta. For native obstructions, the balloon is commonly chosen to be equal to the diameter of the aorta at the isthmus. The balloon dilation catheter is centered across the coarctation, inflated until the waist disappears, and deflated. The balloon catheter is exchanged for a smaller pigtail catheter to allow simultaneous measurement of the ascending aortic pressure with the pigtail in comparison with the distal pressure from the side arm of the existing sheath. The dilated area should not be recrossed without a guidewire because of the danger of perforating a weakened portion of the arterial wall. A repeat aortogram should be performed following dilation to determine the angiographic effect of the inflation and to detect tears, ruptures, or dissections. If significant obstruction remains despite disappearance of the balloon waist during inflation, a larger balloon can be used. Although chest discomfort may be quite significant during balloon inflation, persistent pain after balloon deflation suggests aortic rupture or dissection.

Results

Of the first 64 angioplasties at Boston Children’s Hospital (unpublished data) in 62 patients ranging in age from 3 days to 67 years, 5 had native and 59 recurrent coarctation. In that series, procedures were considered successful if the gradient was reduced by > 50% and the diameter was increased by > 30%. Based on those criteria, 83% of procedures were successful. The balloon-to-lesion ratio was 3.0 for the successful group and 1.6 for the failures. The most consistent predictor of failure, in this and in others’ experience, is the patient with “mild” coarctation: lower pressure gradients and larger minimal coarctation diameters prior to intervention. Balloons substantially larger than the native aorta are necessary in this group, risking injury to the normal aorta. This group is probably best addressed with a stent angioplasty technique (described later). Transverse aortic arch hypoplasia is another consistent predictor of suboptimal outcome.

The most common complication in children is loss of the arterial pulse secondary to large catheter/artery size ratio. Iliac artery rupture and a retroperitoneal hemorrhage resulting in death have been reported in infants. The incidence of femoral artery injury has decreased with the availability of lower-profile balloons. During follow-up in the Boston series, three patients were found to have small asymptomatic aneurysms at the angioplasty site (two recurrent and one native coarctation). Aneurysm formation following dilation of both native and recurrent coarctation has been reported by several groups. There appears to be little difference in the incidence of aortic injury between the two groups in published data with an incidence of < 10% in either group.

Coarctation of the Aorta in the Adult

The technique as outlined above is also applicable to adult patients, and several series have reported excellent outcomes in adult patients with < 10% rupture, dissection, aneurysm formation, or restenosis rate. In the adult population, some
of the severe complications resulted from trying to normalize the diameter of a very small aortic segment. However, the implantation of a stent, at the coarctation site has become first-line therapy for adults with coarctation.

First reported in 1995,\textsuperscript{71,72} primary stent implantation is now the procedure of choice in most laboratories for either native or recurrent coarctation in the adolescent and adult patient (Figure 35.5B). Stent implantation has decided advantages over balloon angioplasty in terms of lower residual gradients and reduced rates of restenosis, and is markedly more effective than balloon angioplasty alone in the patient with mild coarctation. Implantation of a stent eliminates the elastic recoil of the aortic tissue and allows the use of substantially smaller balloons. This may result in a smaller number of aortic injuries, though acute dissections and aortic rupture have also been reported with stenting.\textsuperscript{77} As a result of these acute complications, the use of covered stents has become the procedure of choice outside of the United States where these devices are approved and available. Ongoing studies (COAST, COAST II, http://clinicaltrials.gov/ct2/show/NCT01278303) continue to collect data comparing the use of covered and bare-metal stents for both native and recurrent coarctation. Physicians who are participating in the covered stent trials are able to use the devices for emergency bail-out. Where unavailable, covered stents have been manufactured in the cath lab by some physicians,\textsuperscript{78} for use as a primary implant or for emergency use.

The choice of stent, when all are available, ultimately will be tailored to the needs of the patient. For stenting within the more proximal aortic arch, for example, bare-metal stents will remain the treatment of choice to minimize the risk of occluding carotid or subclavian arteries. In contrast, for patients with known aneurysm formation at the site of a native or previously repaired coarctation with residual obstruction, a covered stent is the clear choice over a bare-metal stent. For simple coarctation, the COAST trial results will give us better insight in the near future.

**Stent Angioplasty Procedure**

The procedure is generally performed from a femoral arterial access with deep sedation or general anesthesia. Radial access is also obtained by some operators to maintain continuous monitoring of the arterial pressure, even during balloon inflation. Hemodynamics and angiography are performed as above. Over a stiff guidewire, often placed into the subclavian artery (to provide a more stable pathway), a long sheath is advanced through the coarctation. The sheath size will generally need to be at least two French sizes larger than the sheath size needed for introducing the dilation catheter to allow for the thickness of the stent. For covered stents, the thickness is increased, and the sheath may need to be larger. We use a technique of “preclosing” the arterial site with a commercially available suture-based closure device. The knots are laid down at the arterial site, but not pulled tight until the end of the procedure. This reduces the bleeding risk, and the need for prolonged groin pressure and bedrest, especially in heavier patients. Once the long sheath is passed through the coarctation, the stent is crimped onto the balloon (unless preloaded), and passed through the sheath to the delivery site. Rapid right ventricular pacing is employed to minimize the forward pressure on the balloon. Once deployed, follow-up angiography and pressure measurements are performed, and postdilation can be performed with larger balloons if needed. The goal is to eliminate the obstruction, not necessarily to create a pristine aortic profile angiographically. It is acceptable to leave a mild waist, if there is no further gradient at the site. There is certainly more leeway to aggressively reinflate the stent when a covered stent is implanted, as the risk of dissection or tears is reduced.

Stent malposition may occur as the balloon/stent is pushed distally by the systolic force of the forward aortic flow, particularly with milder coarctation. In cases with bare-metal stents, the stent can be safely reexpanded lower in the aorta, avoiding coverage of side branches. However with the use of covered stents, redeployment in the abdominal aorta may be problematic. The use of BIB balloons and rapid ventricular pacing (see above) minimize these issues. Balloon puncture by the partially inflated stent is also possible as the stent needs to conform to the curved structure that is the distal aortic arch. This is also less of an issue using BIB balloons, and stiffer wires than it had been in the past. Stent fracture is an unusual but potentially late complication of the procedure.\textsuperscript{81} The loss of structural integrity and radial strength may lead to recurrent obstruction at the site, to thrombus formation or to injury of the aorta at the site of fracture.

Coarctation of the aorta is the fastest growing indication for stent implantation in patients with congenital heart disease. Longer-term follow-up of stent implantation for adult coarctation, as an alternative to balloon angioplasty alone, is required before definitive recommendations can be made.

**Congenital Mitral Stenosis**

Congenital mitral stenosis usually involves abnormalities of the chordae tendineae, with either shortened or abnormal chordal attachments, such as in the “parachute” mitral valve. Unlike patients with acquired rheumatic mitral valve stenosis, congenital mitral stenosis is generally not suited to balloon valvuloplasty. In young children, the morbidity and mortality rate make this a treatment of last resort.

**CONGENITAL LESIONS ASSOCIATED WITH SHUNTS**

Clinically important left-to-right as well as right-to-left shunts can result from congenital defects of the cardiac septa or anomalous venous connections to the heart. The degree of
shunting and the patient’s tolerance of that shunt depend on the defect size, the resistance of each of the alternate paths of flow, and to a large degree on ventricular compliance. Since left ventricular compliance diminishes as part of the normal aging process, many shunt lesions that have been well tolerated through childhood can become hemodynamically burdensome for patients later in life, similar to chronic aortic or mitral regurgitation.

Atrial Level Communications: Anomy of the Atrial Septum

The fetal circulation requires a right-to-left shunt at the atrial level (via the foramen ovale). The formation of the atrial septum, therefore, involves a complex embryologic process whereby two independent crescent-shaped tissue membranes (septum primum and septum secundum) form the elements of the septum and grow to overlap one another centrally. The compliant septum primum is situated to the left of the more rigid septum secundum and acts as a one-way flap valve—a patent foramen ovale (PFO) that allows ongoing right-to-left flow during fetal life. After birth, left atrial pressure rises, the flap valve of the foramen ovale closes, and the septum primum and secundum fuse to one another (in 75% to 80% of the population) to complete septation of the atrial chambers. The remaining 20% to 25%, however, have a persistent flap valve—a patent foramen ovale (PFO), with the potential for continuous or intermittent right-to-left flow.

Other failures in the normal development of the septum primum and septum secundum can result in true holes in the septal wall, known as atrial septal defects (ASDs). These defects are named for their normal embryologic counterparts and include septum primum ASDs at the crux of the heart, adjacent to the semilunar valves (an actual defect of the endocardial cushion); secundum ASDs located centrally in the fossa ovale (a defect of the septum primum); and sinus venosus ASDs, most commonly at the superior margin of the septum between superior vena cava and right pulmonary venous return (improper incorporation of the sinus venosus portion of the fetal heart into the RA). Shunting defects of the atrial septum are by far the most common congenital heart disease discovered de novo in adults.

Pathophysiology of Atrial Level Shunts

LA mean pressure exceeds RA mean pressure through much of the cardiac cycle due primarily to differences in left and right ventricular compliance (diastolic filling properties). When an ASD is present, there is left-to-right flow across the defect throughout the cardiac cycle. In diastole, the more compliant RV fills more easily than the stiffer LV and blood flows from the LA to the RV preferentially than to the LV. This increased RV volume traverses the lungs, overloading the LA, and is the driving force of left-to-right shunting when the atrioventricular valves are closed in systole. The RV will dilate to accommodate the increased volume, and is the best indicator of a hemodynamically important left-to-right shunt.

Because of the ability of the RV to maintain its systolic performance in a dilated state, children are virtually never symptomatic with ASDs. But physiologic parameters change with maturation. The LV walls begin to hypertrophy as afterload increases (part of the normal aging process), resulting in a stiffer chamber which is harder to fill. This leads to increasing left-to-right shunt across the ASD as patients age. It is for this reason that ASD patients typically only become symptomatic in the third to fifth decades of life. Symptoms are most often new-onset, progressive exercise intolerance which is the result of limited cardiac output (limited LV preload in the presence of the left-to-right shunt), and atrial arrhythmia secondary to volume overload and stretching of the right-sided chambers and the conduction system.

Rarely pulmonary vascular disease (Eisenmenger’s) can be associated with ASD. When the RV hypertrophies to compensate for its increased afterload, its compliance changes as well. If RV compliance is nearly equal, or exceeds LV compliance, right-to-left shunting can occur across the defect. Other factors such as TV disease, congenital right ventricular hypoplasia, or right ventricular myocardial infarction can also change physiologic conditions and augment the potential for right to left flow. With sufficient right to left flow, the patient may present with chronic hypoxemia, with positional hypoxemia, or with transient changes in saturation with exercise that presents as exertional breathlessness.

Even in patients with normal right-sided mechanics, following Valsalva/strain, there is a momentary augmentation of systemic venous return and a transient elevation of RA volume and pressure. With any defect of the atrial septum, including the one-way “valve” of the PFO, this can result in transient right to left flow across the defect, of varying magnitude. Right-to-left shunts have been associated with a number of other clinical symptoms including stroke, paradoxical thromboembolization to the systemic circulation, migraine headache (particularly with aura), decompression illness in divers, and with obstructive sleep apnea. Most of these relationships, and their specific mechanisms, remain poorly defined. The vast majority of patients with a PFO or with a small ASD is asymptomatic and may not require interventional therapy.

Transcatheter Closure of an Atrial Septal Defect

Only secundum-type ASD is currently amenable to transcatheter repair. Both the primum type and the sinus venosus type defects lack sufficient surrounding septal rims for a device to be stable, and the device may impede upon
surrounding venous and valvar structures. Closure of large ASDs, either by surgery or by a transcatheter approach, has been shown to significantly increase exercise capacity. Right ventricular volume usually returns to normal or near normal levels, but the RA may remain enlarged even after device closure. This may account for the early observation that closing an ASD in adults may not eliminate the increased long-term risk of developing atrial fibrillation seen with ASDs. Closure eliminates the risk of paradoxical embolization. Severe pulmonary hypertension, with persistent right-to-left shunt at the defect resulting in systemic desaturation, is a contraindication to defect closure.

In 1975, the first transcatheter ASD closure was performed by Mills and King in a 17-year-old female patient. Lock's original Clamshell device was the first device to be used in a widespread clinical trial, but was removed from use owing to a >80% incidence of device arm fracture. From the late 1980s through the mid-1990s, the button device and the ASDOS device were used extensively in Europe. In the mid-1990s, Das developed Angel Wings, the first self-centering device.

But in the last decade, transcatheter closure of ASD has become a routine clinical procedure. Currently, the Amplatzer Septal Occluder, the Amplatzer Cribriform Device, and the HELEX Septal Occluder are approved for use in the United States. A number of other devices are in use outside of the United States.

The HELEX is designed with a short connecting pin between the disks, and works by covering the defect on both sides (Figure 35.6A–C). There is no self-centering mechanism. As a result, the ideal device should be twice the measured diameter of the defect to minimize the risks of either residual shunting around the device edge or embolization. The Cribriform device (Figure 35.7A) is similar in design, and has been approved for closure of the multiply fenestrated atrial septum. It is similar in design to the HELEX device (Figure 35.7B) in that both have a small central connection between the occluders, and can cover a large area of septum with a small central connection obstructing several defects simultaneously (Figure 35.7C–D). In contrast, the Amplatzer Septal Occluder (Figure 35.8A–C) has a central “waist” which actually fills the defect, while the larger left and right atrial disks simply act to secure the device to the surrounding tissue rims. The center waist of the device is chosen to be equal, or minimally larger than the balloon stop-flow diameter of the defect (the balloon size at which all flow across the defect is stopped by echo imaging).

The techniques for implanting any of the double-disk occluders are similar, regardless of the specific device chosen. Femoral venous access is obtained. After a hemodynamic assessment including shunt calculation, a 6F or 7F multipurpose catheter with an A-2 curve is passed to the superior vena cava. The catheter is then withdrawn slowly, aiming the tip toward the patient’s left shoulder, until it “jumps” into the defect. A floppy tipped wire can then be advanced through the septum to the left upper pulmonary

Figure 35.6  A. HELEX Septal Occluder (WL Gore Medical, Flagstaff, AZ). B. Post-implant fluoroscopy (LA, left atrium; RA, right atrium). C. Postimplant intracardiac echocardiography (LA, left atrium; RA, right atrium).
**Figure 35.7**

A. Amplatzer Cribriform Occluder (AGA Medical, Golden Valley, MN).  
B. Amplatzer PFO Occluder.  
C. Postimplant fluoroscopy of PFO device, note different-sized disks.  
D. Postimplant transesophageal echo image of Cribriform device (equal-sized disks), showing device in good position in septum. LA, left atrium; RA, right atrium; Ao, aorta.

**Figure 35.8**

A. Amplatzer Septal Occluder (AGA Medical, Golden Valley, MN).  
B. Postimplant fluoroscopy.  
C. Postimplant intracardiac echo image, showing device entrapping the thin septum primum (white arrow).  
LA, left atrium; RA, right atrium; Ao, aorta.
vein, the most stable wire position. Alternatively, with the catheter placed in the IVC, angled toward the patient’s left shoulder, a J-wire can be passed through the defect to the left heart. This technique is particularly useful in cases where additional smaller fenestrations may surround the larger defect, and best assures that the largest defect is crossed. The wire is exchanged for a stiffer, more supportive exchange length wire. A sizing balloon is then passed over the wire to straddle the defect. With gentle inflation, the balloon will expand at each end, where it is unconstrained, and remain narrowed centrally at the site of the ASD. With echo imaging, the balloon is inflated slowly until all shunt flow is eliminated. The size of the balloon can be measured, and an appropriately sized device can be selected. After careful deairing of the delivery sheath, the device is collapsed into the sheath and advanced to the LA. The left atrial occluder is opened and pulled back against the septum, ensuring that no portion of the device prolapses back through the defect into the RA. The right atrial occluder is then opened. The device position is carefully evaluated with echo imaging, reassessing the entrapment of all septal rims, and the elimination of shunting by color flow mapping (Figure 35.8). Agitated saline injections can also be used to rule out significant residual right-to-left shunting. If the device position is suboptimal, the device can be recaptured and redeployed. Once in good position, the device stability can be tested with a push-pull test on the connecting catheter. The device is then released and the procedure is completed.

Transcatheter Closure of Patent Foramen Ovale

The techniques for PFO closure are generally the same as for ASD closure. For an inexperienced operator, the biggest challenge can be finding and crossing the defect. Using the techniques as outlined above, the catheter or wire will naturally be directed into the fossa ovale. Echo imaging can be quite helpful as an adjunct. A floppy-tipped guidewire can be visualized easily with echo, as it is delivered through a multipurpose catheter. Balloon sizing is less helpful in determining device size with the PFO, as the flap can be opened to very large sizes with sufficient balloon pressure. However, balloon occlusion and agitated saline injection can help identify the patient with an alternative source of right-to-left shunt prior to the implant, and may give important anatomic information about the length and compliance of the PFO tunnel.

Special Techniques

1. Additional fenestrations: In some patients there will be additional fenestrations of the septum primum. If these defects are clustered in the fossa ovale as is usually the case, a large single-occlusion device can be used. Occasionally, the distance between these defects is too great for closure with a single device, and additional devices can be placed during the same procedure. To ensure that the first device does not partially cover the distal defects and make subsequent crossing more difficult, we will often obtain an additional femoral venous access and cross both the main ASD/PFO as well as the most distal defect with separate catheters and wires. With the wire in place through the distal defect, the first ASD/PFO is closed using the usual technique. A second sheath is then advanced over the wire through the additional fenestration, and a second device is placed.

2. Long, rigid PFO tunnel: Rarely, if the septum primum is relatively inflexible and the overlap of septum primum and septum secundum is long (>1 cm), it may be difficult to withdraw the closure device far enough into the tunnel to successfully open the right atrial occluder. This may leave a partially opened RA occluder or extra traction on the LA occluder that may back it into the tunnel in a partially collapsed position. This is less of an issue when using the Amplatzer devices, as they are more rigid and tend to conform the anatomy to the native configuration of the device. With the HELEX devices and other less rigid devices, the device tends to adapt more to the anatomy of the tunnel. There are two techniques for dealing with this unusual situation:

a. Transseptal puncture technique: Instead of crossing the septum through the PFO, a standard Brockenbrough transseptal puncture can be performed under echo guidance. The septum primum is punctured just at the overlap site of the septum secundum (Figure 35.9). Once across the septum, the wires are exchanged to place the super stiff guidewire in the left upper pulmonary vein as above. Echo guidance is critical here, as it is imperative that the puncture be performed as close to the overlap as possible, and that the puncture position be checked from orthogonal angles prior to device placement.

b. Balloon detunnelization: Once the wire is through the PFO to the pulmonary vein, a sizing balloon can be advanced over the wire to the LA. The balloon when initially inflated will demonstrate a sizable distance between the indentation at the entrance to the PFO tunnel and the indentation at the exit on the LA side. With increasing balloon pressure, the indentations on the balloon move toward one another, as the balloon straightens. With sufficient force, some of the LA attachments of septum primum can be disrupted, leaving a more compliant tunnel. There are some risks of tearing the septum if sufficient force is employed.

3. Rarely, femoral venous access to the heart will be unavailable, owing to previous instrumentation, venous thrombosis, or an IVC filter that will not allow passage of the necessary catheters. In these cases, an alternative access
will be required. For those experienced with transhepatic access, this is the first choice, because the catheter course from the IVC to the fossa ovalis is maintained. For others, a right internal jugular (RIJ) approach or right subclavian approach is possible. However, because of the orientation of the PFO’s flap valve, the catheter from the SVC impacts the septum on the wrong angle to cross the defect. Recently, for such patients, we have used a deflectable electrophysiology sheath, introduced from the RIJ. These types of sheaths can be deflected to 270 degrees of curvature within the RA, orienting the approach to the septum to facilitate passage through the defect. A 5 French multipurpose catheter and a floppy tipped guidewire are advanced to the tip of the sheath, and the wire is advanced through the defect to the left upper pulmonary vein. This will provide sufficient support to advance the catheter to the LA. It can then be manipulated through the mitral valve into the LV apex. A stiff guidewire with a ventricular loop is then exchanged and left in the LV apex. The delivery catheter of the device can then be advanced over the wire in to the left heart. Measuring pressures from the sheath can guide the pullback to the LA, so that the mitral valve is not compromised by placement of the device. The device is then delivered in the usual fashion.

There are no devices approved specifically for PFO closure in the United States, nor are there any approved indications for PFO closure. Each case must be examined on its own individual merits and indications. Devices approved for ASD closure, such as the Amplatzer devices and the HELEX Septal Occluder, are used routinely in an “off-label” fashion for patients who require closure. Other non-device technologies such as transcatheter suture closure, radiofrequency energy application to effect closure and “glue” technologies have been explored, but have not undergone sufficient testing yet, as the market for the procedure has failed to develop, and funding is unavailable. The CLOSURE I study (NMT Medical), was the first completed, randomized prospective study comparing the efficacy of medical therapy and PFO closure in preventing recurrent stroke.103a

The study failed to demonstrate superiority of closure over “best medical therapy”, though the small number of patients enrolled, the entrance criteria, the short follow-up period, and post-procedural complications related to the device used in the trial (device thrombosis, residual shunting and atrial arrhythmia), all potentially blurred distinctions between the groups. The RESPECT Trial (AGA Medical/St. Jude Medical) was published subsequently.103b This somewhat larger series, was designed without a fixed follow-up period, in order to capture a predetermined number of recurrent cerebral embolic events. With fewer post-implant device related complications and better closure rates, the intent to treat analysis just missed proving a significant benefit to closure over medical therapy (p = 0.08) with 9 recurrent strokes in the closure arm and 16 in the medical arm of the study. However, the results were clouded somewhat by the fact that 3 of the 9 recurrent stroke patients assigned to the closure cohort never had the PFO closed. However, two additional pre-specified analyses did show a statistical benefit to closure. In the “per-protocol” analysis, assessing those patients in each arm who were treated exactly as planned in the protocol, there were 6 recurrent events in the patients who followed the protocol in the closure group and 16 who followed the specified protocol in the medical group (p = 0.03). In the “as-treated” analysis, there were 5 recurrent events in patients actually treated with closure and 16 in the patients treated with medical therapy (p = 0.007). Perhaps even more important than the study outcome, was a Hazard analysis which showed a statistical benefit to closure in patients with 1) a superficial stroke by imaging, 2) a substantial shunt by bubble contrast imaging, and 3) the presence of an atrial septal aneurysm. These three features can help us choose patients, going forward, who might best benefit from potential intervention, and can help us in designing future studies. The REDUCE Trial (WL Gore Medical) continues to enroll patients.

Results—Atrial Septal Defect/Patent Foramen Ovale Closure

In a wide array of reviews and collected cohorts, transcatheter closure of an ASD or a PFO is a safe and effective procedure. In two recent reviews,104,105 closure rates were in excess of 93%, with procedural failure primarily the result of poor patient and defect selection (i.e., too large). Minor procedural complications, including femoral venous
access complications, transient atrial arrhythmia during the procedure, and impingement of the device on surrounding valvar and venous structures occurred in about 5%. Serious procedural complications, such as pericardial effusions/perforations, valve injury, air embolization, device embolization and retrieval, and retroperitoneal bleeding occurred in approximately 1% of patients, less than in concurrent surgical series. Postimplant, the incidence of new onset atrial arrhythmia (5% to 8%) including simple premature atrial contractions, supraventricular tachycardia, and other atrial tachyarrhythmias, were not significantly different from that of surgical series. Following successful closure, the dilated RV normalized in dimensions in over 75% of patients, with a significant relationship between older age and failure to return to normal. Transcatheter closure is now the procedure of choice for secundum ASD repair, as it offers significant advantages in terms of pain, length of hospital stay, cosmesis, and recovery time with comparable closure rates in all but the largest defects.

PFO closure rates, whether for stroke prevention, migraines, and other symptoms, are comparable to that seen with ASD closure. In the CLOSURE I trial, complete closure rates at late follow-up were between 85% and 90%. In previously published series, and in the RESPECT Trial, closure rates with the Amplatzer PFO device were superior (>90%).\textsuperscript{106-143} The prospective data collection associated with the RESPECT trial will give the best information on the device's closure rate. The HELEX device, used for PFO closure, has little long-term data available. In our experience, using transcranial Doppler techniques to assess residual shunts, there has been no appreciable difference between the HELEX and the CardioSEAL/STARFlex devices.

Complications of the PFO procedure are similar to those of the ASD procedure, and like with the ASD closures, are largely device dependent. While these rates are quite low, they are magnified when the comparison is being made between device implantation and medical therapy, not open heart surgery (as it is for ASDs). This is especially true in an era when the benefit of the procedure has yet to be definitively demonstrated.

Several important issues remain with the currently approved devices for atrial septal repair. Based on reporting to the U.S. Food and Drug Administration's Medical Device Complication web site,\textsuperscript{107} the former CardioSEAL device (NMT Medical, Boston, MA) was afflicted with thrombus formation on the device in the first few months after implantation.\textsuperscript{108,109} Device erosion (cardiac perforation) is the most commonly reported serious long-term complication with the Amplatzer devices (AGA Medical, Golden Valley, MN) with rates as high as 1/500 patients.\textsuperscript{107,110} Additional safety studies are being undertaken by the manufacturer. Thrombus formation has been reported with the Amplatzer device as well.\textsuperscript{111,112} There is no indication that either thrombosis or erosion is a significant issue, to date, with the HELEX device, though it seems to have a higher rate of embolization and device malposition than its competitors.

There is no consensus yet on the appropriate degree of anticoagulation after device implantation. Aspirin alone has been used in many centers with a combination of aspirin, Plavix, and warfarin being used by others. We generally treat our patients with aspirin 325 mg daily for 6 months and Plavix 75 mg for 3 months.

The incidence of infective endocarditis of the device is also unknown. Most centers recommend antibiotic prophylaxis for dental work or other minor surgical procedures for a period of 6 to 12 months from the time of device implantation.

### Ventricular Septal Defects

Like atrial septal defects, congenital deficiencies in the ventricular septum are varied in anatomy. The most common VSDs occur in the membranous septum. Endocardial cushion defects affecting the ventricular septum and defects of the muscular portion of the septum are less common. Left-to-right shunts at the ventricular level result in pulmonary overcirculation, but with a concomitant left ventricular volume overload. With a large enough defect, the pressure head of LV contraction is transmitted to the PA in systole. This makes VSDs physiologically different from ASDs in which there is simply volume loading of the right side of the heart. The resistance to flow at the defect itself is the primary determinant of shunt volume in children. As a direct sequela of the magnitude of the LV volume load, patients with small defects may be symptom free, without significant LV enlargement by imaging. With larger defects, the patient will present with the classic symptoms of congestive heart failure (CHF) early in infancy. With a moderate-sized defect, the patient may be asymptomatic in childhood, despite a significantly dilated LV. These patients may present in adulthood with new symptoms of CHF as with aging normal changes in LV myocardium decrease chamber compliance. The volume load associated with the VSD will no longer be handled at low diastolic pressures, as when the patient was younger. LA pressures rise, and pulmonary venous congestion may ensue, particularly with exertion, when blood flow through the left heart increases further. Patients with unrestrictive defects, who do not undergo repair in the first 2 to 3 years of life, risk the development of irreversible pulmonary vascular disease (Eisenmenger syndrome).

### Transcatheter Closure of Ventricular Septal Defects

Transcatheter closure of inlet (endocardial cushion-type) VSDs is not yet possible based both on the embryologic and anatomic relationship of these defects to abnormalities of the atrophic-ventricular valves, and to the lack of surrounding support structures to stabilize such a device. Similarly, the design of devices to close membranous VSDs was quite challenging, as the aortic valve, the TV, and the conduction system all abut this portion of the septum. The Amplatzer Membranous VSD device has been used only in trials in the United States, but is available clinically outside the United States. It is an asymmetric device to account
for the surrounding cardiac structures. Study and clinical results demonstrate at least a 5% risk of new onset complete heart block due to impingement of the device on the atrioventricular node and the His-Purkinje fibers which run through that portion of the septum. This risk far exceeds that of the surgical experience in VSD repair.

More than the rhythm complications, these devices suffer from the principle issue of therapies that are designed for a congenital pediatric population: the potential clinical need (market) for such a device is quite limited. Patients with small, asymptomatic defects do not require closure. Since severe CHF occurs, with larger defects, in the first month of life, surgical repair of these defects is technically easier and probably safer than transcatheter repair. Older patients with larger defects, who have not been repaired, will most often have developed pulmonary vascular disease. Only the older patients, with adult onset symptoms are an ideal population for a transcatheter approach.

Although much less common than membranous VSDs, large muscular VSDs, which may occur anywhere in the muscular portion of the septum, present a difficult challenge for the surgeon. Apical and anterior defects may be impossible to visualize and repair through the TV. Right ventricular septal trabeculations make identification from the RV septal surface difficult. The original surgical approach was through a left ventriculotomy. However, long-term follow-up of these patients revealed a high rate of LV aneurysm formation and an equally disturbing number of patients with global LV dysfunction.

The need for successful transcatheter therapy has therefore been more acute in patients with muscular rather than with the membranous defects. At the same time, the anatomy is more favorable to a transcatheter approach as most have good surrounding tissue rims to support the device, without concerns of valvar or electrophysiologic compromise. Reports of successful transcatheter muscular VSD closures have appeared since the early 1990s.

The procedure remains technically challenging in small children, and a number of strategies have evolved to incorporate transcatheter management in infants with CHF due to a large muscular VSD. Initially, a staged approach was used. PA banding was performed in the infant (a closed heart procedure) to limit pulmonary flow and eliminate symptoms of CHF. With subsequent growth of the child, transcatheter defect closure would become technically easier and could be followed with surgical band removal (also a closed heart procedure). More recently, perventricular “hybrid” surgical approaches have been demonstrated, in which a surgical incision exposes the RV free wall. A needle can be used to puncture the RV free wall (under echocardiographic guidance), and a wire advanced through the needle to the defect and into the LV. A sheath is advanced over the wire into the LV, and the closure device is deployed in the usual fashion. The puncture site in the RV free wall can be closed with a purse-string suture.

Numerous devices have been used for closing muscular VSDs in the past. These were primarily devices designed for closure of ASDs that were used off-label in the ventricular septum. Amplatzer has since developed a device designed specifically for closure of muscular VSD (Figure 35.10). Similar in design to the ASD devices, the center waist of the Muscular VSD Occluder is longer to account for the increased thickness of the ventricular septum. The device is now approved for use in the United States.

**Technique of Muscular Ventricular Septal Defect Closure**

After a complete left and right heart hemodynamic assessment and an echocardiographic assessment of the defect and the surrounding anatomy (TEE or intracardiac echo imaging), an LV angiogram is performed to best profile the defect (Figure 35.10B). The defect is then crossed from the left ventricular septal surface, either with a torquable coronary catheter or with a balloon-tipped catheter (balloon wedge catheter) introduced retrograde via the femoral artery or antegrade via a transvenous transseptal approach. The defect is typically easier to cross from the LV side, as it is a smooth, less heavily trabeculated surface, and the catheter is crossing in the direction of the high-velocity flow.

A soft extension-length guidewire (i.e., Benson Wire) is passed through the defect to the RV and advanced to the PA. From a transvenous approach (femoral for anterior muscular defects and jugular for midmuscular and apical defects
produces the straightest course for device delivery), a balloon wedge catheter is advanced through the right heart to the PA and exchanged for a snare catheter, which is used to capture and exteriorize the wire. This creates a reliable “rail” over which the device delivery sheath can be passed. Using the balloon catheter to cross through the TV and capturing the wire in the PA minimizes the risk of having the wire become entangled in the TV, and disrupting chordal attachments. The largest dimension of the defect may then be confirmed with balloon sizing (the balloon introduced over wire to straddle the defect—see ASD closure earlier), but unlike an ASD, the dimensions as measured on echo do not stretch as they do with balloon sizing. The device is then chosen to exceed the defect size by 1.6 to 2.0 times when a double-umbrella device is used, or by 2 to 3 mm when an Amplatzer Muscular VSD Occluder is selected.

Next the appropriate size delivery system is advanced from the venous access, over the exteriorized wire to the RA, RV, and through the defect to the LV. Echocardiography and hand injections through the sheath will confirm its position. The wire is then removed from the arterial side and the device is delivered through the long sheath in the usual fashion. The LV occluder is opened and pulled back against the septum. Resistance will be felt as the device is pulled into the defect. Echo and angiographic injections will confirm LV septal position, and the RV septal occluder is then delivered. When angiographic and/or echo images confirm the position of the device on both sides of the septum, the device is released.

**Results—Ventricular Septal Defect Closure**

Twenty-three European centers collaborated to report their experience with transcatheter closure of congenital VSDs; 430 patients underwent attempted closure of a congenital VSD of which 119 were muscular defects, 250 were perimembranous, 45 were residual defects post surgery, and 16 patients had multiple defects. The procedure was technically successful in 95% of the cases. The procedures were done primarily with the Amplatzer group of devices. Failures were primarily related to complications, or device malposition requiring immediate surgical intervention.

Complications occurred in 12.7%, with serious complications in 6.5% and included device embolization (1.3%), creation of aortic regurgitation (3.4%), creation of tricuspid regurgitation (6.6%), minor rhythm disturbances (2.5%), complete heart block (4%) of whom a majority required pacemaker implantation. Only 0.8% of patients with defects in the muscular septum developed rhythm disturbances. There was one death. In the multivariate analysis, the only definitive risks for procedural complication were patient age ($P = 0.012$) and patient weight ($P = 0.0035$). A US registry had very similar results.

While transcatheter closure of the VSD is technically feasible, careful patient and defect selection remains the most important aspect of the procedure. For asymptomatic patients with small defects, the closure may not be clinically indicated. For patients with membranous-type defects sufficiently large to cause clinical symptoms, the surgical option remains an excellent alternative.

**POST-MYOCARDIAL INFARCTION VENTRICULAR SEPTAL RUPTURE**

One additional area of interest for adult interventionalists is postinfarction ventricular septal rupture. These defects are always muscular in location and occur in the distribution of the distal LAD, yielding mid and apical muscular VSDs, or in the RCA producing inferior (inlet) VSDs. In an era of aggressive angioplasty at the first signs of ischemia, this complication of myocardial infarction is far less common than in previous generations.

Untreated, large defects are nearly always fatal, as a large left-to-right shunt, pulmonary overcirculation, pulmonary hypertension, and left ventricular volume overload are superimposed on a severely compromised/ischemic pump. Acute surgical intervention with patch closure has been difficult, because the surgeon has little reliable tissue in the margins of the defect in which to place sutures. Exclusion strategies similar to those used for apical aneurysms are now being more commonly employed. Similarly, following early transcatheter closure of large defects, ongoing necrosis of surrounding tissue can lead to important residual shunts and device instability after early implantation. Small defects are interesting from a diagnostic perspective, but do not impose a significant hemodynamic burden. Interestingly, though, with ongoing tissue necrosis, the defect can become more hemodynamically important over the first few weeks.

It is current teaching that these defects, once identified as hemodynamically important, should be closed as soon as possible, whether by a surgical or transcatheter approach. Waiting for days to stabilize the patient medically is unreliable, as the shunt may only increase with time and the onset of multisystem organ failure over several days of poor cardiac output makes the patient less likely to recover from either intervention. In the best surgical series of 65 such patients treated aggressively after the infarct, there was a 30-day mortality of 23%, with marked improvement with concomitant grafting of the coronary arteries at the time of VSD repair. Similarly, Hiele et al. reported 29 consecutive patients presenting with a postinfarction ventricular septal rupture. There was an 88% 30-day mortality in those with cardiogenic shock and multisystem organ dysfunction versus a 38% 30-day mortality in those without. The Amplatzer Muscular VSD device was used in 18 postinfarction patients in a US registry between 2000 and 2003; 13 of 18 underwent closure between 14 and 95 days after the infarction. A device was deployed in 16 of 18 patients. The 30-day mortality was 28%, reflecting some element of self-selection as the patients had already survived the initial insult for at least two weeks.
The transcatheter device implantation technique is identical to the treatment of congenital muscular VSDs (as above). Transcatheter intervention is an excellent approach for patients with infarcts in the LAD distribution, while surgical intervention is probably more likely to succeed when the defect arises from an RCA infarct. Catheter repair of these posterior defects is complicated by the proximity to the atrioventricular valves and their support structures. A recent publication demonstrated the feasibility of a hybrid approach for the postinfarct ventricular septal rupture.122

Transcatheter Embolization of Extracardiac Shunts

Shunts outside the heart occur when a congenitally abnormal connection exists between an arterial source and a low-pressure venous or cardiac chamber. Left-to-right extracardiac shunts are associated with pulmonary overcirculation and a reduction in systemic perfusion, owing to the difference in resistance between the normal arteriolar bed and the low-resistance runoff site. The most common example is a persistently patent ductus arteriosus.

Right-to-left shunting can also occur through abnormal connections outside the heart. In patients with a Fontan or bidirectional Glenn, where systemic veins are surgically connected directly to the PAs, systemic venous pressure is elevated. Venous collaterals may develop from the high-pressure veins to low-pressure systemic veins, to low-pressure cardiac chambers, or to the pulmonary veins. The runoff acts as a steal from the pulmonary flow, and may cause systemic hypoxemia if large enough. Intrapulmonary shunts, such as congenital pulmonary arteriovenous malformations, also create a right-to-left shunt, where the unoxygenated pulmonary arterial blood drains to the lower pressure pulmonary veins.

PATENT DUCTUS ARTERIOSUS

The ductus arteriosus is a normal fetal arterial connection between the aorta and the PA, which in the presence of high pulmonary resistance (as in the fetus) allows right ventricular outflow to return via the aorta to the placenta.

With the baby’s first breath, pulmonary vascular resistance drops as the lungs aerate. Systemic resistance rises as the low resistance placental pathway is removed from the circulation. These physiologic changes induce an acute increase in pulmonary blood flow. Rapidly rising systemic oxygen levels trigger contraction of the smooth muscle layer in the ductal tissue, through a prostaglandin-mediated pathway. Within 48 to 72 hours of life, >95% of infants have a closed ductus arteriosus, completing the conversion of the fetal circulation to the normal postnatal circulation. In some infants, the ductus does not close or remains partially open and is termed a patent ductus arteriosus.

As the lungs mature over the first few weeks of life, pulmonary resistance continues to fall both absolutely and relative to systemic resistance. When a PDA is present, the aortic flow has an alternative, low-pressure runoff into the pulmonary circulation. With a large PDA, there is pulmonary overcirculation, systemic undercirculation, and the usual symptoms of CHF within weeks of birth. Surgical correction remains the treatment of choice for most newborns, especially the premature infants, with CHF secondary to a PDA. The Amplatzer Duct Occluder (see below), which can be delivered via the venous circulation through small sheaths with good occlusion results (see below), makes even smaller infants candidates for transcatheter repair.123

In most children, the PDA is small when present, a tiny fraction of its initial prenatal diameter. Resistance to flow through this small tube is high, and the resulting volume of the left-to-right shunt is small. The LV is not significantly volume loaded, and symptoms are uncommon. Most of these children are diagnosed when a cardiac murmur is identified, or when the PDA is discovered incidentally at echocardiogram. In this setting, the principle risk is that of endocarditis (endarteritis) at the ductus or at the site of the high-velocity jet’s impact on the PA wall. Closure of the PDA has been recommended routinely in children to eliminate both the volume load and the risk of infection, since the first successful litigation of a PDA by Gross in 1938.

In adults, however, a PDA is a relatively uncommon finding. Most frequently, the defect is discovered incidentally during an echocardiogram, following an episode of endarteritis or when a murmur is present. In the older adult, other symptoms may occur. With decreasing LV compliance, the additional LV volume load from left-to-right shunting is less tolerated, resulting in increased filling pressures and pulmonary venous congestion. Shortness of breath with exertion may develop in a patient who has tolerated the PDA for decades. Similarly, increased systemic vascular resistance, associated with adult-onset hypertension, may drive more blood across the defect into the pulmonary circulation, increasing the shunt and bringing on symptoms of exercise intolerance for the first time.

We have treated several adult patients with PDA who develop frank angina on exertion in the setting of very mild coronary artery disease. Electrocardiographic changes on stress tests, or hypoperfusion on a stress thallium examination, may be positive in the absence of significant coronary lesions by angiography, because the low-resistance runoff from the aorta produces a diastolic steal phenomenon.

Transcatheter Closure of Patent Ductus Arteriosus

While the initial nonsurgical repair of the PDA was described by Forstmann,124 over the past two decades, successes with transcatheter closure techniques have all but eliminated surgical repair of small PDAs. The first device to gain widespread popularity was developed by Dr. William Rashkind.125 Although never achieving FDA approval in the United States, this double-umbrella device was used throughout the world and in clinical trials in the United States until the early 1990s.
In 1992, with the Rashkind device unavailable for closure of PDA, Dr. John Moore’s group first described the technique of closing a PDA with a Gianturco coil (Figure 35.11A–C), a device that had been in use for other vascular occlusion procedures since 1972. While the Rashkind devices had been available only to physicians at selected study sites, the coil occlusion procedure brought PDA closure into the mainstream of pediatric interventional catheterization. Various techniques were developed to deliver the coils, including the original single-catheter, transarterial approach of Moore, a single-catheter transvenous approach, the snare-assisted technique, detachable coils, the Latson catheter technique, the use of 0.052-inch thickness coils, and the placement of coils within a nylon sack inside the PDA. In contrast with the Rashkind device, the coil was deliverable through catheters as small as 4F; making it a viable alternative to surgery even in small children.

More recently, the Amplatzer Duct Occluder (Figure 35.12A–C) has replaced coil embolization techniques in many laboratories for all but the smallest PDAs. More
recent Amplatzer devices have expanded the armamentarium for the interventionalist, including the Muscular VSD device for larger, shorter PDAs, particularly in the setting of elevated pulmonary arterial pressures (Figure 35.10A), vascular plugs for longer tubular PDAs (Figure 35.13A,B), and a modification of the Amplatzer Duct Occluder (Amplatzer Duct Occluder II (Figure 35.14)), which is not yet available in the United States.


**Technique of Patent Ductus Arteriosus Closure: Amplatzer Duct Occluder**

An aortic angiogram is performed with the holes of the pigtail just distal to the takeoff of the left subclavian artery. Both the minimum dimension of the PDA and the length of the ductus are measured. The Amplatzer Duct Occluder is selected based on these measurements, with the pulmonary end of the device selected to be approximately 2 mm larger than the minimum angiographic dimension. An end-hole catheter is manipulated to the MPA (we usually start with a multipurpose curve) and used as a guide to probe for the opening of the PDA with a floppy-tipped torque wire. In some circumstances, when the PDA cannot be located from the PA side of the defect, the PDA can be crossed from the aortic side with an exchange-length guidewire, the wire snared in the PA (from a femoral venous access), and can be exteriorized through the femoral vein. Alternatively, once snared in the PA, the snare-wire combination can be pulled back through the PDA into the descending aorta. The snare catheter can then be exchanged, over a wire, for the device delivery catheter. The sheath tip is positioned well down the descending aorta and carefully flushed to remove any air. The device is then loaded into the sheath. The large aortic retention disk is opened in the descending aorta and withdrawn into the ampulla of the PDA. The PA end of the device is then delivered. A repeat aortic angiogram can be performed prior to release to ensure proper position (Figure 35.12C). In many cases, there may be substantial residual shunt for the first few minutes after initial implantation. This will resolve over a period of 10 to 15 minutes.

**Results—Patent Ductus Arteriosus Closure**

Cuaso et al. reported on a 10-year experience with the Amplatzer Duct Occluder in 231 patients in the Philippines ranging in age from 3 months to 64 years with a minimal ductal dimension ranging from 1.3 to 10 mm (mean = 4.2 mm). Successful device implantation occurred in 229 out of 231 patients, with complete angiographic closure at the end of the procedure of 88%, and 100% of patients at 6-month follow-up. Mild LPA stenosis was observed in two patients, both of which were reduced over the course of 1 year, with patient growth. There were two device embolizations, related to unfavorable anatomy, and both patients had surgical retrieval of the device with ligation of the PDA. There was one femoral arterial complication.

In an earlier series from the late 1990s, Bilksis et al. reported a similar series of successful implantation in 205 out of 209 patients, with a >99% complete closure rate at 1 year. There were similar complications and complication rates.
Transcatheter closure of PDA is the treatment of choice for all asymptomatic children with small PDA. We continue to use coil embolization techniques for PDA with a minimum dimension of <2 mm and the well-established Amplatzer Duct Occluder for children with larger PDAs and for adult patients.

**TREATMENT OF OTHER EXTRACARDIAC SHUNTS**

**Systemic Arteriovenous Fistulas**
Fistulous connections between a systemic artery and a systemic vein may create a sizable left-to-right shunt, with symptoms of exercise intolerance or frank CHF. The vein provides a lower-resistance runoff for the blood in the involved arterial branch. Unlike other left-to-right shunt lesions, systemic arteriovenous fistulas create a volume load for both ventricles. These fistulas may be congenital, but may be acquired through trauma or complications from surgery or catheterization.

**Coronary Fistulas**
Coronary fistulas are hemodynamically similar to other systemic fistulas. Drainage is most commonly to the coronary sinus or directly to the RA, RV, or PA. In addition to the usual symptoms of exercise intolerance and shortness of breath secondary to the magnitude of the left-to-right shunt, these patients may present with a coronary steal, in which the low-resistance runoff to the fistula will reverse diastolic flow in the normal coronary artery branches. With diminished forward flow, ischemia may occur with exertion.

**Aortopulmonary (Bronchial) Collaterals**
Aortopulmonary collaterals may be congenital or may develop in children who undergo single ventricle repairs involving venous supply of pulmonary blood flow (Glenn shunt, Fontan operation). These vessels most often arise from the thoracic aorta, the internal mammary arteries, and other branches of the subclavia. The left-to-right shunt creates a volume load on the LV, similar to a PDA.

In patients who have undergone previous congenital surgical palliations, an old Blalock-Taussig or other surgical shunt that either recanalized or was never taken down at later surgical stages may present as an ongoing left-to-right shunt. When this connection is no longer needed, it also creates a left ventricular volume load.

**Pulmonary Fistulas**
These unusual defects connect pulmonary arterioles, proximal to the air-containing spaces, to pulmonary venules, resulting in the return of unoxygenated blood to the LA (Figure 35.15A–C). If a defect is large enough or if there are multiple defects present (most often in hereditary hemorrhagic telangiectasia or Osler-Weber-Rendu syndrome), patients may be quite cyanotic. These defects have been a source of paradoxical thromboembolization in some patients who were erroneously diagnosed with PFO.

**Venovenous Collaterals**
In patients with single ventricle repairs where the systemic veins bypass the right heart and connect directly to the PAs, a pressure difference exists between those veins that lead to the lungs and those that return to the heart. This differential will result in rerouting of blood flow away from the lungs to return via the lower-resistance pathway back to the atrium. In the patient dependent on venous flow to the lungs, these venous connections result in diminished pulmonary flow and cyanosis.

**Techniques of Device Embolization**
All types of extracardiac vascular anomalies can be treated with catheter-based embolization techniques. These techniques are largely the same, regardless of the vessel designated for closure or the device chosen for the task. Coils are often the simplest and least expensive technique in part because of the variety of delivery catheters that can be used. Special considerations must be taken for large fistulae, which are discussed below.

The vessel to be embolized is identified angiographically. Regional as well as selective injection in the vessel is essential, as some defects have multiple feeding sources (i.e., pulmonary fistula, Figure 35.15A–C), all of which must be occluded for a successful intervention; and some target vessels supply normal structures as well as the fistulous connection (i.e., coronary fistula), making the positioning of the occlusion device more critical. We prefer to use a multipurpose catheter with distal side holes for the selective injections. Once the vessel has been acceptably imaged, a site for placement of the embolic device should be selected. Optimal locations include native narrowings, turns in the vessel course, bifurcation points, or long, straight, tubular segments. The target vessel is measured at the desired embolization site. For coil embolization, a device diameter 1 to 2 mm larger than the site diameter is selected. The delivery catheter is an end-hole catheter of a shape that approximates the wire course for stability of the catheter position. The delivery catheter is exchanged over a wire and advanced past the desired site of implantation. The coil is then introduced to the catheter and pushed to the tip of the catheter (with a guidewire of a diameter approximating the catheter’s inner lumen dimension), just distal to the site of implantation. The first loop of coil is delivered just distal to the optimal site by advancing the guidewire as the delivery catheter is withdrawn slightly. The remainder of the coil can
be delivered in one of two ways: by fixing the delivery catheter and advancing the guidewire into the catheter to push out the coil; or by fixing the guidewire in place, and withdrawing the catheter over the wire, exposing the coil. A repeat angiogram is performed, and additional coils may be placed to complete the occlusion. Antibiotic prophylaxis is recommended for a period of 3 to 6 months to allow for complete endothelialization. MRI scanning will put significant stress on the original Gianturco coils (steel), can heat the coils significantly, and can create tremendous local reverberation artifacts. Newer, MRI-compatible coils have largely replaced the use of the steel devices. We recommend that the device be allowed to endothelialize completely before exposing the patient to the magnetic field (3–4 months).

The use of coils has limitations, particularly for larger vessels. Other technologies such as detachable balloons135 have been used in these settings in the past. A series of Amplatzer Vascular Plugs (Figure 35.13A–D) are the current standards for embolization, when coils are not appropriate. These devices range from the cylindrical VP1, to the multi-lobed VP2, to the more rectangular VP3. The VP4 is a dual-lobed device, designed to be delivered through a very small catheter, similar to a coil. All but the VP3 are available in the United States as of 2013. All are attached to a delivery cable with a screw mechanism, making it completely retrievable, until the operator wishes to release it. To a varying degree, the devices will conform to the size/shape of the target vessel.

Results/Complications

Embolization techniques are straightforward and are limited only by the operator's ability to achieve a stable catheter position in the vessel to be occluded. Once such a position is achieved, the procedure should be successful in 100% of cases. Complications include device embolization and potential obstruction of nearby side branches. Embolization occurs most frequently in arterial structures with high flow states when the device selected is not large enough, or when a selected coil is too large, does not coil appropriately in the target vessel, and pushes the delivery catheter back out of the target vessel. Embolized coils can usually be retrieved with a snare technique. Hemolysis has been seen with incomplete closure of high flow defects.
CARDIAC CATHETERIZATION IN ADULT PATIENTS WITH FONTAN PHYSIOLOGY

Perhaps the greatest accomplishment in congenital heart disease in the last generation has been the combined surgical/interventional management of patients with functional single ventricles. In these patients, the systemic venous return is surgically rerouted directly to the PAs, no longer returning to the heart, leaving only the pulmonary venous return filling the single ventricle and being pumped to the aorta. Since Fontan described this approach to bypass the right side of the heart over 40 years ago,136 the concept has been applied to all congenital lesions in which the heart cannot be fully septated.

Currently, the Fontan is performed between 2 and 4 years of age as the final step in a staged surgical approach. Acute management of these patients remains principally a pediatric issue. However, over the last decade, a growing number of patients are reaching adulthood with Fontan physiology, presenting difficulties for adult cath labs that are not comfortable in dealing with this physiology on a regular basis.

Fontan Physiology

In a two-ventricle circulation, pulmonary venous return is pumped by the LV to the systemic circulation with sufficient energy to traverse the systemic vascular bed (overcoming systemic vascular resistance). The blood then returns through the systemic veins to the RV, which adds enough additional energy to the blood to traverse the pulmonary vascular bed (overcoming pulmonary resistance). In a Fontan circulation, the one functional ventricle must generate enough energy to traverse both systemic and pulmonary vascular beds in series.

Since there is no additional energy added after crossing through the systemic vascular bed, flow to the lungs is a passive flow system, where the blood from the SVC and IVC flows “downhill” through the PA, pulmonary veins, LA, and then into the single ventricle. It is clear, therefore, that any derangements of pulmonary vasculature, including elevated pulmonary vascular resistance, competitive flow (aortopulmonary collaterals), atrioventricular valve stenosis or regurgitation, elevation of (left) ventricular end diastolic pressure, or even rhythm disturbances with loss of atrioventricular synchrony will impede forward flow in this circulation and create higher systemic venous pressures. When systemic venous pressures exceed 15 to 20 mmHg, venous stasis/pooling will occur. The result is diminished pulmonary flow, diminished left atrial return, and inadequate left ventricular preload, resulting in low cardiac output. Patients with a failing Fontan physiology typically present with classic right heart failure: fluid retention, peripheral edema, ascites, and low output.

In some children, a small Fontan “fenestration” may be created at the time of surgery. This communication between the systemic venous Fontan pathway and the pulmonary venous atrium allows a limited right-to-left shunt at the atrial level. This technique has been shown to improve outcomes of the surgery by better maintaining cardiac output in the perioperative period, at the expense of mild cyanosis.137,138 Secondary Fontan fenestration creation may be helpful later in the patient with a failing Fontan circulation, and has been performed both in the operating room139 and in the cath lab as an interventional procedure.140

Other issues are common in a failing Fontan patient: protein-losing enteropathy is a syndrome seen in some Fontan patients,141 in which serum proteins are lost through the stool. The exact mechanism for these losses is unknown, but in some cases may be related to bowel edema as a result of high venous pressures. These protein losses include albumin, resulting in lower serum oncotic pressure, worsening the patient’s fluid retention. Antithrombotic factors, such as antithrombin III, may also be lost, promoting hypercoagulable states.

Atrial arrhythmias, owing to stretching of the atria or to extensive atrial surgery, may be the chief presentation of a failing Fontan or may be one of the underlying causes of the physiologic derangement. Ventricular dysfunction is a common endpoint for Fontan patients. The mechanism of ventricular failure is unknown, but may be related to the amount of time prior to the Fontan, when the LV myocardium was both stretched owing to volume overload and oxygen deficient as the coronaries carried cyanotic blood.

Interestingly, Fontan patients cannot develop pulmonary venous congestion like other patients with poor left ventricular function. Mean left atrial/PA pressures cannot get high enough to cause pulmonary edema before systemic venous stasis occurs. These patients will present with “right heart failure” long before they develop typical symptoms of left heart failure. Because Fontan patients have begun to reach adult age in significant quantity, careful invasive assessment of the Fontan physiology will be required in the adult cath lab.

Hemodynamic Evaluation

Right and left heart hemodynamics should be obtained with particular focus on mechanical obstructions in the Fontan pathway. Ventricular end-diastolic pressure and PA wedge pressures should be compared to rule out pulmonary vein or atrioventricular valve obstruction. Pullbacks through both branch PAs should be done, looking for pressure gradients. Surgical anastomoses should be a site of particular attention. Cardiac output should be assessed using the Fick calculation. Saturations should be obtained in the central and distal PAs to rule out competitive aortopulmonary collateral flow.

Angiographically all of the limbs of the Fontan pathway should be imaged, particularly because of the difficulties in imaging these branches using echocardiography. Venous collaterals draining to the heart or via a pulmonary vein directly to the atrium and via the coronary sinus should be ruled out, particularly in a patient who has issues of systemic desaturation. An aortogram should be performed at the distal arch
to rule out aortopulmonary collaterals providing competitive flow and to exclude aortic arch obstructions that may be affecting ventricular afterload. Atrial pacing can be performed to assess its effect on cardiac output and on atrial filling pressures for patients in nonsinus rhythm.

The interventions that may be required to improve Fontan physiology include a virtual manual of the procedures outlined in this chapter. Branch PA stenosis should be ballooned or stented to relieve any pathway obstruction. Venous pathways and surgical anastomoses may also require enlargement/angioplasty. Aortopulmonary collaterals should be aggressively embolized. Fontan fenestrations may need to be occluded in a patient who is excessively cyanotic. The devices for atrial septal closure can be used for this purpose. In some patients, when there is little other relief available, the cath lab creation of a secondary Fontan fenestration has been shown to improve the symptoms of protein-losing enteropathy in some and to improve cardiac output in all. Pulmonary atrioventricular malformations may be present in patients who previously underwent a Glenn shunt and may need to be embolized.

SUMMARY

The above discussion covers only a few of the large array of interventional procedures performed in a cath lab that manages congenital heart disease. As important as familiarity with the procedures themselves is the need for a thorough understanding of the underlying anatomy and physiology. Like other expanding areas of interventional cardiology, existing specialists in congenital heart disease should play an important educational and collaborative role in training future specialists in adult congenital and structural heart disease.

REFERENCES


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The promise of cell therapy as a strategy to regenerate or repair myocardial tissue fulfills a true unmet need in cardiovascular (CV) medicine, and there is considerable interest in the potential of stem cells and other cell types to treat acute and chronic myocardial damage. Although major advances in medicine, interventions, and surgery have reduced all-cause mortality from CV disease, in the current era patients still endure morbidity and mortality from the irreversible injury caused by ischemic heart diseases. In this regard, revascularization (percutaneous coronary intervention or coronary bypass graft surgery) and medical therapy remain the mainstay of therapy of acute and chronic coronary artery disease, and medications such as 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, angiotensin-converting enzyme inhibitors (ACEI), beta blockers, antiplatelet and anticoagulant therapies reduce patient risk and are effective at primary and secondary prevention. Despite these therapies, patients remain at risk for ventricular remodeling and heart failure after coronary ischemic events. Prevention or reversal of ventricular remodeling remains a major challenge in patient management. A number of lines of evidence now indicate that stem cell therapies may offer unique efficacy at reversing the myocardial scarring and adverse remodeling of ischemic heart disease.

A critical aspect in the developing field of cell-based therapy for heart disease is that of appropriate and adequate cell delivery. This important issue holds the promise of transforming the field of interventional cardiology, and in this chapter we review the emerging technologies and approaches to cell delivery.

**STEM CELLS**

Stem cells are defined by the ability to self-replicate and by the capacity to differentiate into a variety of lineages. Adult stem cells under active investigation for myocardial disease include bone marrow derived stem cells, circulating stem cells, cells from a variety of nonhematogenous sources, tissue-resident stem cells (cardiac stem cells), and pluripotent stem cells.

Stem cells from the bone marrow include mesenchymal stem cells (MSCs) and hematopoietic stem cells. From dozens of small and large animal models, and increasing numbers of human trials, it is becoming clear that stem cells have therapeutic potential after acute myocardial infarction (AMI) and in chronic myocardial dysfunction late after infarction. The mechanisms underlying cell therapeutics appear to be multiple, involving both direct cell actions (engraftment, differentiation into myocardial and vascular lineages) as well as indirect actions mediated in part by activating other cells, cell-cell interaction and paracrine pathways; cell fusion, and the stimulation and regeneration of resident cardiac stem cell niches.

One strategy which may enhance the applicability of cell therapy is the concept of an “off-the-shelf” cell therapeutic, taking advantage of the immunoprivileged status of certain cell types, prototypically, MSCs which are both immunoprivileged and immunosuppressive. These stem cells can be cultured from healthy donors and expanded for storage and subsequent allogeneic use in a multitude of patients without the need for individual bone marrow aspiration in every
patient, and without the delay to treatment associated with cell expansion in vitro.

### DELIVERY APPROACHES AND SYSTEMS OF DELIVERY

There is accumulating clinical trial evidence employing a variety of methods of cell delivery for at least four distinct clinical indications:

1. Acute myocardial infarction (AMI).
2. Chronic ischemic cardiomyopathy.
3. Hibernating myocardium.
4. Chronic ischemia leading to intractable angina (IA).

Delivery approaches or strategies include stimulating endogenous precursor cell recruitment, cell delivery via intracoronary, intravenous, or direct intramyocardial injection.

1. The systemic approach—granulocyte stimulating factor (G-CSF): A prototypic approach to stimulating endogenous precursor cells involves administering G-CSF to mobilize circulating CD34 cells such as endothelial precursor cells (EPCs). A large number of preclinical and clinical studies have tested whether G-CSF can be employed to stimulate the recruitment of endogenous cells to the myocardium. Animal studies and several pilot human studies have shown some evidence of reverse ventricular remodeling with the administration of G-CSF when given in the perinfarct period. However, larger randomized placebo-controlled studies showed no improvement in infarct size or ejection fraction in patients who had recent ST elevation MI. Studies have shown that intra coronary injection of G-CSF improved ejection fraction in patients with acute MI but data is conflicting with regard to chronic myocardial damage. G-CSF is in clinical testing currently to mobilize EPCs that are subsequently collected by apheresis and then readministered by intramyocardial injection in patients with chronic chest pain syndromes.

2. The intracoronary route: Intracoronary delivery can be achieved with or without the use of a balloon occlusion catheter (the “stop flow” technique) to prevent backflow and prolong the residence of the administered cell suspension in the target coronary. Intracoronary administration has the advantage of targeting the ischemic and the perinfarct area by injecting the cells into the infarct-related artery. This route is less invasive than surgery and easy to perform. Potential disadvantages include inefficient cell retention (washout) as well as microvascular obstruction, which has particularly been noted with MSCs or skeletal myoblasts. The direct intracoronary infusion is clinically used especially within 4 to 9 days after acute MI. The technique is similar to that used for coronary angioplasty, typically with the use of an over-the-wire angioplasty balloon inflated in the infarct-related stent. Coronary blood flow is then stopped for 2 to 4 minutes and stem cells are infused under pressure to the coronary artery of choice.

3. The intravenous route: Intravenous administration is obviously a simple and low-cost route and has the potential to deliver cells to the largest population of patients. Disadvantages include early distribution to the lungs and poor myocardial retention. Peripheral venous infusion of stem cells (as performed in bone marrow transplants) represents a convenient way of delivering cells, and is based upon the principle that injury signals emanating from the damaged tissue recruit cells. A prototypic example is of SDF1 which binds to the CXCR4 receptors present on MSCs. A mouse model showed that transplanted human stem cells home to perinfarct areas; however, only a few cells reached the affected area, and the general belief is that this technique could be applicable only after acute MI, because it relies on physiologic homing stimuli only. Another issue is the fact that many of the injected stem cells will be trapped in the microvasculature of the lungs, liver, and the lymphoid tissues.

4. Transendocardial route: There is now major interest in developing catheter systems for intramyocardial transendocardial injection of cells or other biologics for therapeutic purposes. The NOGA Myostar Catheter and the Biocardia Helical Infusion Catheter represent two injection systems that have been widely used in human studies. The transendocardial stem cell injection (TESI) strategy offers the ability to administer cells directly and accurately into the damaged myocardial segment without the need for surgery, avoiding the potential microvascular obstruction associated with the intracoronary route, and permitting access to any territory, even if its coronary supply is occluded and impassable. The risk of ventricular perforation appears to be low with proper case selection and careful technique. In some ways the technique of TESI is more akin to interventional electrophysiology than to the endovascular operations performed by most interventional cardiologists; catheter manipulation and navigation within the cardiac chamber may also be familiar to operators who had experience with investigation of catheter laser channel burning (so-called percutaneous myocardial revascularization, or PMR). TESI devices generally consist of several components, including a core element for cell transport, terminating distally in an injection needle. The core element may be advanced and retracted within the outer elements of the device. The support catheters are multifunctional, serving to protect the core and to direct it toward the regions of the myocardium to be targeted.

Four intramyocardial catheter-based delivery systems have been used in clinical trials. All share the design that was described, but differ in the anatomic approach to the myocardium. The Helix (BioCardia Inc., South San Francisco, CA, USA), the MyoCath (Bioheart Inc., Sunrise, FL USA), the Myostar (Biologics Delivery Systems, Diamond Bar, CA, USA), and the Stiletto (Boston
Scientific, Natick, MA, USA), all approach the myocardium from within the left ventricular (LV) chamber, with a transendocardial approach that is achieved by retrograde entry into the ventricle by crossing the aortic valve.

The MyoCath and the Myostar (Figures 36.1 and 36.2) are “integrated systems” where the core and support catheters are joined to form a single unit. These two devices are manipulated through a combination of axial rotation and deflection of the distal aspect (in a separate control mechanism capable of inducing up to 180° of flexion). While the tip of the device is in contact with the endocardium, the core catheter is advanced forcing a straight needle to a controlled intramyocardial depth of 3 to 8 mm. The integrated design provides an ability to navigate and to repeat injections; however, in both systems there is no guidewire lumen that may help in control and navigation, and they must be advanced from the femoral artery across the aortic valve using the same navigation mechanisms that guide the device within the ventricular chamber. The Helix and the Stiletto (Figures 36.3 and 36.4) are not integrated and the core catheter is a separate device that can be inserted and removed from the support catheters. The intraventricular manipulation and navigation are handled by a single, deflectable catheter (the Morph guiding catheter for the Helix infusion catheter) or by two preshaped support catheters (the Stiletto). Both systems are characterized by the ability to insert the support catheters into the ventricle over a guidewire and by the configuration of the injection needles (helical or spring loaded). In the helical design (reminiscent of a screw-in pacemaker lead) the needle tip may be more stable during the injection.

The Biocordia Helical Infusion System was used by us in porcine models and by our group and others for clinical trials. Its steerable deflectable guiding catheter allows access to nearly all parts of the left ventricle, and its helical screw-in needle provides positive engagement into the myocardium. In the spring-loaded needle device (the Stiletto) the needle is set to a fixed depth of 3.5 mm and may better penetrate fibrotic tissues. The Stiletto catheter is guided fluoroscopically in two planes. The Stiletto system allows rapid injection delivery to a number of endocardial sites. Neither the Helical infusion catheter nor the Stiletto system offers real-time assessment of the target myocardium, so that preinterventional imaging (with echocardiography, magnetic resonance, or computerized tomography) seems to be valuable for injection site selection. Nonetheless, careful and well-opacified biplane LV angiography, performed with an isocentered position, offers a wealth of information to the operator and may prove adequate for targeting. In preclinical experiments TESI is also feasible with real-time cardiac magnetic resonance imaging (MRI), which permits three-dimensional online assessments of the full thickness myocardium and perfusion.

5. Epicardial delivery during surgery: Epicardial delivery was the first route of cell delivery that was tested. The advantage is the ability to inject the cells during heart surgery, although this fact is also the disadvantage of this method—it must coincide with a major operation.

6. Transcoronary-venous injection: The TransAccess Delivery System (Medtronic Vascular, Santa Rosa, CA, USA) (Figure 36.5) is a device that approaches the myocardium through the epicardial surface. A support catheter is positioned in specific branches of the cardiac venous system through the femoral vein. Guided by an intravascular ultrasound probe it is possible to localize the adjacent coronary artery and pericardium and to guide an injection catheter and needle into the myocardium through the epicardial surface. This delivery system

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Figure 36.1 The MyoCath catheter.
Figure 36.2  The Myostar catheter. A. With NOGA mapping capability. B. Needle extension. C. Intramyocardial injection catheter with protruded needle. D. and E. control of the needle length.

Figure 36.3  The Helix catheter. A. Non-integrated system with independent deflectable guide catheter. B. Removable helical shaped needle injection catheter.
Chapter 36 Cardiac Cell-Based Therapy: Methods of Application and Delivery Systems

has been used for skeletal myoblast delivery to scarred myocardium in patients with cardiomyopathy. Feasibility studies have shown a good safety profile for this technique. Infusion of stem cells through the coronary venous system (coronary sinus) under high pressure has been achieved in experimental models. The limitations include the lack of specific targeting and the variability and tortuosity of the coronary venous system.

### Which Route of Cell Delivery is the Best?

There is a limited dataset comparing methods of delivery, derived from experimental models, which to date do not uniformly support one approach over another. Perin et al. compared intracoronary (IC) versus transendocardial delivery in dogs with acute MI and found that transendocardial injections led to greater cell retention and a significant improvement in their LV ejection fraction compared with IC delivery. A small study that compared the transendocardial route to the IC and intravenous routes in ischemic swine heart found that the IC route delivered the highest amount of cells that were engrafted within the infarct zone. Engraftment of the cells delivered transendocardially was greater than the intravenous route delivery system. However, endocardial delivery had less engraftment to other organs other than the heart, and the IC route was associated with more microvascular obstructions.

A study that compared transendocardial injection using the Boston Scientific Stiletto catheter with IC infusion (using an inflated occlusive balloon to deliver the cells into the distal bed) and with intravenous delivery of identically prepared MSCs in a porcine MI model found that this protocol of IC delivery was the most efficient technique; however, this technique caused microvascular obstruction in some animals. The preclinical studies suggest that infusing large numbers of MSCs directly into the coronary circulation could be dangerous because of possible occlusion.

**Figure 36.4** The Stiletto device. A non-integrated system with 2 independent configured guide catheters and a removable spring-loaded needle.

**Figure 36.5** The TransAccess Delivery System catheter. A. The full system with the proximal connection for the IVUS component. B. The distal catheter tip with the internal intravascular catheter US imaging element (IVUS) and the extended needle and injection catheter (Core).
Despite advantages and disadvantages, the delivery of MSCs into infarcted myocardium by transcendocardial injection appears to be one of the most promising new approaches to cell-based therapeutics and is now supported by abundant preclinical studies and a growing clinical experience.

**CELL TYPES USED FOR TRANSPLANTATION**

Multiple candidate cells were suggested for regeneration of the injured heart, including embryonic stem cells, induced pluripotent stem cells, neonatal cardiomyocytes, skeletal myoblasts, EPCs, bone marrow mononuclear cells, MSCs, and cardiac stem cells.

*Embryonic stem cells* have the capacity for self-renewal, can be clonally expanded, and are capable of differentiation into any cell type in the body. However, this potential could be dangerous, because they can form teratomas, they may induce immune rejection, and there is the ethical problem since they are created from early human embryos.

*Skeletal myoblasts* have a contractile phenotype, can be used for autologous transplantation, and are resistant to ischemia. Several small nonrandomized phase I trials demonstrated a functional benefit, but with a high incidence of ventricular arrhythmias.

*Bone marrow derived cells* are stem cells derived from the bone marrow. The relative ease in accessibility of bone marrow, and the large number of unfraccionated autologous cells that can be obtained have been attractive for clinical use, and many human studies were done using these cells. They include rare hematopoietic, endothelial, and mesenchymal stem cells. Human hematopoietic stem cells can be defined as CD34+ cells capable of reconstituting all blood cell lineages and of transdifferentiating into cardiomyocytes, endothelial cells, and smooth muscle cells in vivo.

*Endothelial progenitor stem cells* are hematopoietic cells that promote neovascularization directly or indirectly through secretion of proangiogenic cytokines.

*MSCs* are defined as CD105+ CD90+ cells, with a tendency to adhere to a plastic or tissue culture, and the capacity for multilineage differentiation including osteogenic, chondrogenic, and adipogenic lineages. They exhibit low immunogenicity and are attractive for stem cell therapy due to these traits. As donor cells they can be transplanted into recipients’ hearts to promote the restoration of cardiac function. In addition bone marrow MSCs have the capacity for angiogenesis, a trait that could enhance cardiac functional recovery. MSCs are rare, representing only approximately 0.01% of the bone marrow mononuclear cell fraction, but are attractive for therapy due to their low immunogenicity and the ability to expand many fold in vitro, allowing their use as an allogeneic graft.

*Cardiac stem cells*, the c-kit-positive, lineage-negative cardiac stem cells (CSCs) have been shown to improve postinfarction LV dysfunction in animal models. In a phase I trial (Stem Cell Infusion in Patients with Ischemic cardiomyopathy (SCIP)) of autologous CSCs for the treatment of ischemic heart failure, post transplantation LV ejection fraction (LVEF) increased from 30.3% to 38.5% at 4 months ($P = 0.001$) in treated patients, while in controls LVEF did not change. At 1 year LVEF increased by 12.3 ejection fraction units versus baseline ($P = 0.0007$). In the seven treated patients in whom cardiac MRI could be done, there was a 24% decrease in infarct size at 4 months and a 30% decrease at 1 year.

**IMAGING FOR CATHETER GUIDANCE**

Several approaches have been employed to help guide intramyocardial cell delivery. These include MRI, MDCT, and systems that integrate imaging guidance such as electroanatomic mapping.

**Magnetic Resonance Imaging**

MRI is emerging as highly valuable as it provides detailed information of cardiac anatomy that can help guide a TESI procedure. MRI enables precise delineation between viable and nonviable myocardium (i.e., that injured by MI). Thus, a myocardial injection procedure can be planned based upon integration of MRI images with conventional ventriculography (Figure 36.6).

Cardiovascular magnetic resonance (CMR) is a rapidly evolving technology that is used for noninvasive imaging of the heart in different heart failure populations. CMR is performed at a magnetic field strength of 1.5 T. A CMR sequence generates its image by a series of radiofrequency pulses, magnetic gradient field switches, and timed data acquisitions. To prevent artifacts from cardiac motion most CMR images are gated to the R wave (of the ECG) and in order to overcome the respiratory motion CMR images are acquired in end expiratory breathhold.

For infarct/fibrosis imaging gadolinium contrast agents are injected intravenously, and the areas that are detected with late or delayed (DGE) gadolinium enhancement are areas of scarring and fibrosis. The abnormally prolonged washout is due to a decreased functional capillary density in the irreversibly injured myocardium. For perfusion imaging the dynamic passage of the contrast media (gadolinium) is followed through the cardiac chambers and the myocardium. Viability and nonviable myocardium are detected accurately, with highly specific patterns of fibrosis and scarring in ischemic and nonischemic cardiomyopathies.

Ischemic cardiomyopathy is characterized by area of scarring that involves the subendocardium and extends up to the epicardium (depending on the size of the infarct) in a pattern consistent with the “wave front phenomenon” of ischemic cell death. Today CMR has become the gold standard for...
noninvasive evaluation of an injured viable/irreversibly injured myocardium, assessing its transmural effect. The ability of the DGE CMR to predict functional recovery of a specific segment post vascular intervention is an important landmark in CMR use for CV management. DGE helps to define the location and extent of the infarction, and to differentiate areas that showed failure of recovery tissue perfusion after revascularization. Another important advantage of stem cell transplantation is detection of LV mural thrombi and defining the location of aneurysmal dilatation, by using the early postcontrast images.

CMR has high sensitivity to detect coronary artery disease (between 80% and 100%) in patients with poor LV contraction and to differentiate between idiopathic and ischemic cardiomyopathy (Figures 36.6 and 36.7).

The NOGA System

Another widely used imaging approach involves electroanatomic (EA) imaging that can be achieved using an electromechanical system for intramyocardial navigation and mapping.

Figure 36.6 Registration of SPECT/CT with MR images of the heart demonstrating focal uptake of MSCs in the periinfarcted region. (A) Short-axis view of alignment of CT (gold) with MRI (gray scale) and SPECT (red) showing focal uptake in the septal region of the MI in a representative dog. (B), Focal uptake on SPECT (red) in another animal demonstrating localization of the MSCs to the infarcted myocardium (MI) in the short-axis (B) and long-axis (C) views. (Reproduced with permission from Kraitchman DL, et al. Circulation 2005;112(10):1451–1461.)

Figure 36.7 MRI imaging. A CMR image in 2-chamber view showing an extensive area of delayed contrast enhancement indicative of a large anterior infarction extending from the base around the apex of the heart.
Catheter systems that allow for EA imaging have been developed and are incorporated into the Myostar system. To use this system, the operator creates a baseline three-dimensional endocardial map based using the electromechanical signal detection capability of the catheter (NOGA, Biological Delivery Systems). This color-coded map delineates regions of viable, ischemic myocardium, or infarcted myocardium. Once target areas are identified for injection, the system permits electronic marking of each injection site. The NOGA system has been widely used in both preclinical and clinical studies.

Principles of the Technique

EA mapping uses magnetic fields generated by a magnetic pad positioned beneath the patient. The magnetic fields intersect proximal to the tip of the mapping catheter, which is positioned in the left ventricle and helps to determine the location of the catheter tip inside the left ventricle in real time. The NOGA injection catheter (Myostar) is a nonfluoroscopic magnetic guiding catheter, and injections of stem cells are guided by a three-dimensional LV electromechanical map. The NOGA system uses algorithms to calculate the location of the catheter. Data can be acquired only when the catheter tip is in stable contact with the endocardium. The mapping catheter has electrodes that can measure endocardial electrical signals, and an electrical map can be drawn and used as a three-dimensional platform for catheter navigation in the left ventricle and provide the necessary orientation for TESI. The Myostar catheter enables detection of myocardial viability at each injection site, and the operator has the ability to target therapy to viable tissues. This technology has been widely tested in animal models and in human studies and has an excellent safety profile (Figure 36.8).

DISEASE APPROACHES

Cell Therapy in Acute Myocardial Infarction

Shortly after the appearance of animal studies indicating that bone marrow harbored potentially regenerative elements, human studies were conducted testing the hypothesis that IC autologous whole bone marrow could improve LV function after infarction. These early investigational clinical studies performed by Strauer et al., the transplantation of progenitor cells and regeneration enhancement in acute myocardial infarction (TOPCARE-AMI), the bone marrow transfer to
enhance ST-elevation infarct regeneration (the BOOST-trial), and two more reported an improvement in global LV ejection fraction by 6% to 9% with a reduction in LV end systolic volume at 6 months after the cell transplantation. These studies have shown that IC infusion of autologous bone marrow stem cells (BMSCs) was safe and feasible in patients with AMI and promoted functional recovery after AMI. The functional improvement was largely due to improved regional wall motion in the infarct border zone. The beneficial effects that were demonstrated in the pilot phase I/II studies were confirmed in the so far largest double blind, randomized multicenter reinforcement of enriched progenitor cells and infarct remodeling in acute myocardial infarction (REPAIR-AMI) trial that has demonstrated improved LV ejection fraction, a reduction in the combined clinical endpoint of death, AMI, or revascularization in BMSC-transplanted patients compared with placebo after 1 year of follow-up. Patients with lower baseline ejection fractions (less than 48.9%) had a more significant improvement in global LV ejection fraction as well as in clinical endpoints indicating that patients with more severe myocardial damage profit most from BMSC therapy (Figure 36.9). However, one study, the autologous stem cell transplantation in acute myocardial infarction (ASTAMI trial) did not show any benefit after stem cell transplantation, most probably due to a different cell isolation and storage protocol that affected the functional capacity of the cells. A comparison between the effect of autologous whole bone marrow cells and circulating progenitor cells was done in the TOPCARE study. Both cell types were delivered IC 4.3 days after coronary artery reperfusion, and found that both cell types had improved LV function at 4 months and 1-year follow-up. When these cell types were delivered IC 3 months after the AMI the autologous whole bone marrow cells proved to be more effective in improving LV function compared with the circulating mononuclear cells.

Mesenchymal Stem Cell Transplantation After Acute Myocardial Infarction

Chen et al. infused autologous MSCs through the IC route and found no side effects (including arrhythmias), and found an improvement in regional wall motion and global LV function with a decrease in LV end diastolic volume compared to the control group 6 months after cell transplantation. Our group also demonstrated that transplantation of allogeneic MSCs in the intravenous route was safe in patients after AMI with an improvement in LV ejection fraction and in reverse remodeling. Intravenous administration of allogeneic MSCs to human patients within 10 days of their first AMI was safe at different cell doses, and patients treated with cell therapy had less post-MI arrhythmias, a better pulmonary function, and improved quality of life compared with patients that were treated with placebo, and with a significant improvement in LV ejection fraction in patients who suffered an anterior infarction.

Adult Bone Marrow Stem Cells After Acute Myocardial Infarction

A meta-analysis by Abdel-Latif et al. summarizing 18 eligible studies with 999 patients found that BMSC transplantation (that included bone marrow nonnucleated cells, MSCs, and EPSCs) improved LV ejection fraction, reduced infarct size, and reduced LV end systolic volume. The BMC transplantation is associated with modest improvements in physiologic and anatomic parameters in patients with AMI beyond conventional therapy. In a study where cardiac MRI (CMR) was used to test the hypothesis that bone marrow progenitor cell injection causes functional recovery of scarred myocardium and reverse remodeling, autologous bone marrow progenitor cells (mononuclear or mesenchymal stem cells) were injected into the endocardium of eight patients (aged 57.2 ± 13.3 years) in the area of the LV scar and the border zone. No serious adverse events were reported, and CMR at 1 year demonstrated a decrease in end diastolic volume (208.7 ± 20.4 versus 167.4 ± 7.32 mL; P = 0.03), a trend toward a decrease in end systolic volume (142.4 ± 16.5 versus 107.6 ± 7.4 mL; P = 0.06), a decreased infarct size (P < 0.05), and improved regional LV function (~8.1 ± 1.0 versus ~11.4 ± 1.3; P = 0.04). There was a time-related effect so that the improvement in the regional LV wall function was evident at 3 months, but the change in chamber dimensions became significant only at 6 months. Improved regional function in the infarct zone strongly correlated with reduction of end diastolic volume and end systolic volume (Figures 36.10 and 36.11). These data suggest that autologous bone marrow progenitor cells injected intramyocardially improve contractility of a myocardial scar, and may predict subsequent reverse remodeling. These findings support the potential clinical benefits of this new approach and ongoing randomized clinical trials.

Mobilization of Bone Marrow Stem Cells with Granulocyte Colony-Stimulating Factor

Clinical studies and a meta-analysis that summarized clinical trials where BMSCs were mobilized with G-CSF found that G-CSF therapy in patients with AMI was safe but did not provide any clinical benefit.

Possible Side Effects of Cell Therapy for Acute Myocardial Infarction

None of the clinical studies with BMSCs reported an increased incidence of arrhythmias, bleeding complications, additional ischemic injury, inflammation, or myocardial damage. Restenosis (demonstrated in animal models after injecting MSCs or CD133+ cells IC) was not observed in any of the clinical studies. On the other hand, the REPAIR-AMI trial found a decreased rate of revascularization in cell-transplanted patients post AMI and a better survival (Figure 36.12). Intramyocardial calcification (reported in murine model)
Figure 36.9  LV angiography before CPC therapy (left panel, A) and at 4-month follow-up (right panel, B). C and D. Corresponding FDG-PET bulls-eye views of the left ventricle of the patient; LV angiography is illustrated in A and B. LAD indicates left anterior descending artery; LCX, left circumflex artery; and RCA, right coronary artery. (Reproduced with permission from Assmus B, et al. Circulation 2002;106:3009–3017.)
Autologous bone marrow progenitor cell injections increase regional function and precede reverse remodeling. A through I depict a patient injected with bone marrow progenitor cells. A. Baseline lateral wall infarct in delayed enhancement CMR (white arrows). B. One year postinjection infarct. C. Infarct mapped to corresponding segmented tagged CMR image with IZ defined by the presence of enhancing myocardium, neighboring myocardium as border zone (BZ), and normal myocardium as remote zone (RZ) (first segment of each map correlated by right ventricle insertion point; white arrowhead). Tagged harmonic phase CMR strain maps show significantly depressed regional function by peak Ecc at baseline in IZ (white arrows) D. Red/white indicates weak contractility (more positive Ecc) and green/blue indicates vigorous contractility (more negative Ecc) in harmonic phase strain maps. E and F. At 3 months after cell injection, the IZ contractility has improved (less red/white, more green/blue) (E) and by 12 months is contracting similar to the border zone (mostly green/blue) (F). G through I, ESV remains relatively stable between baseline (G) and 3 months (H); however, at 1 year, reverse remodeling is present (I). J and K. Changes in peak Ecc of the IZ had a strong correlation with the changes in EDV (J) and ESV (K) at 12 months compared with baseline (difference in peak Ecc between baseline and 1 year versus difference in normalized EDV and ESV, respectively). L. Decreases in EDV and ESV strongly correlate with each other, indicating parallel decreases in chamber sizes contributes to unchanging EF after bone marrow stem cell injections. (Reproduced with permission from: Williams AR, et al. Circ Res 2011;108:792–796.)

Figure 36.10
Impact of allogeneic MSC therapy on infarct size. DE-MRI images of (A) swine with chronic ischemic cardiomyopathy injected with 200 million allogeneic MSCs before and 3 months after therapy, showing a 17% reduction in scar size, and (B) a control animal showing no change in scar size (red arrows delineate the borders of gadolinium-enhanced scar). (Reproduced with permission from Williams AR, et al. J Am Heart Assoc 2013 May 17;2(3):e000140.)

was not documented in any of the human subjects that were transplanted (using MRI), and no increased cancer incidence was observed in any of the clinical trials.

**Which Cell Population to Use**

Bone marrow derived stem cells isolated from whole bone marrow aspirate remain the most commonly used cell type for human studies. However, unfractionated bone marrow cells are gaining more popularity since they are much more feasible, with no requirement of an in vitro expansion and the availability of mixed populations of cells. In addition, there are no ethical issues. MSCs are also important because of their inherent properties of transdifferentiation into cardiomyocytes and their tolerance by the immune system.

**When to Transplant**

Seven days post AMI VEGF concentrations peak and cell adhesion molecules start to decline.\(^{89,84}\) By 2 weeks,
there is already scar formation and less efficiency in cell transplantation. Therefore the best time for cell transplantation would be between days 7 and 14. In the REPAIR-AMI trial patients that were treated earlier than 4 days post AMI showed no benefit, whereas later treatment (between days 4 and 8) enhanced LV function.

Using the intravenous route, the cells have the advantage of reaching the tissue and the vessels near the damaged area and other vascular areas in need of repair. Since intravenous administration is safer than coronary catheterization, this approach has to be studied further in clinical trials. Hare et al. used this intravenous approach to deliver allogeneic MSCs to the infarct region with positive results.

The LateTIME trial was designed to explore whether delayed BMC delivery 2 to 3 weeks following MI to patients with impaired LV function could improve global and regional LV function. IC infusion of $150 \times 10^6$ autologous BMCs (total nucleated cells) or placebo was performed within 12 hours of bone marrow aspiration after local automated cell processing. No significant change in LV volumes and infarct volumes was observed; both groups decreased by a similar amount at 6 months versus baseline.

### Cell Therapy in Angina Pectoris

Tse et al. injected autologous BM-MNCs to eight angina pectoris (AP) patients using the NOG A system to find the ischemic still-viable tissue for cell injections. No complications were reported during and after the procedures, including arrhythmia, perforation, myocardial damage, or intramyocardial tumor growth.

The use of hematopoietic stem cells to enhance bone marrow function and angiogenesis was studied in a phase II trial, the Autologous Cellular Therapy CD34-Chronic Myocardial Ischemia (ACT34-CMI) trial. 167 patients with refractory AP who failed to respond to medical maximal therapy received placebo or one of two doses of mobilized autologous CD34+ stem cells. The cells were administered by intramyocardial injection into ischemic-viable myocardium (using the endocardial electromagnetic mapping system, NOGA). The weekly AP frequency rate was reduced significantly at 6 and 12 months in the low-dose cell-treated group compared with placebo. The high-dose cell-treated group showed improvement that did not reach statistical significance. Exercise duration was also significantly improved in the low-dose group. Mortality was 5.4% in the placebo arm, with no death in the cell-treated group. Based on this and other pilot human studies more than 250 patients with AP were treated with cell therapy.

Losordo et al. transplanted intramyocardial G-CSF mobilized CD34+ cells in 24 AP patients. Patients that were cell injected had favorable trends in AP frequency, nitroglycerin usage, exercise tolerance, and in perfusion defects compared with placebo-treated patients. In another study 112 AP patients received IC transplantation of autologous bone marrow derived CD34+ cells. Both groups showed improvement in AP symptoms and in exercise tolerance at 3 and 6 months of follow-up, however, the CD45+ stem cells treated group experienced a greater reduction of symptoms.

Tse et al. randomized 28 “no option” AP patients to receive low-dose ($1 \times 10^6$ cells/0.1 mL) or high-dose ($2 \times 10^6$ cells/0.1 mL) autologous bone marrow cells or placebo through endomyocardial injections guided by the NOGA system (electromagnetic mapping). A significant improvement in exercise time, LV function, and functional class were observed in the cell-treated group at 6 months without short- or long-term complications (Figure 36.13).

Van Ramshorst J. et al. found in a randomized, double blind, placebo-controlled trial with intramyocardial injection of $100 \times 10^6$ autologous bone marrow derived mononuclear cells or placebo (guided by NOGA electromagnetic mapping) that bone marrow injected patients significantly improved their angina symptoms, quality of life, and exercise capacity.

Vicario et al. reported good outcomes with the retrograde delivery through the coronary sinus (via the brachial vein), but this is the only clinical experience in AP and its role in therapeutic angiogenesis is unclear. In the IC delivery method, cells are injected directly into the artery of the ischemic area (most often used after AMI). The most promising approach is the direct intramyocardial injection that enables injecting the cells in the ischemic territory of interest. This achieved the greatest local concentration of cells of interest.

A multicenter study that investigated intramyocardial transplantation of CD34+ stem cells for intractable AP found
a promise for that approach and for that cell type.88 Patients with refractory AP who received intramyocardial injections of autologous CD34+ cells had a significant improvement in angina frequency and exercise tolerance.88 Other studies85,86 provided evidence for the therapeutic potency of cultured EPCs for ischemia. A significant improvement in clinical parameters and in myocardial perfusion following delivery of autologous bone marrow CD34+ cells through the IC route has also been reported.90

**Cell Therapy in Ischemic Heart Failure**

Several small studies have examined percutaneous catheter injections of autologous myoblasts in patients with heart failure.95 Percutaneous transcatheter intramyocardial injection of skeletal myoblasts has been evaluated in small clinical trials,95-96 In the CAUSMIC study, transcatheter injection into viable myocardium of 12 patients with severe ischemic heart failure showed a significant improvement in functional classification, quality of life, and evidence of reversed ventricular remodeling compared with controls at 1-year follow-up.96 The multicenter study of the safety and cardiovascular effects of myoblasts in congestive heart failure (MARVEL Trial) will enroll 330 patients with class II or III heart failure in North America and Europe. It will study the safety and efficacy of intramyocardial injection of skeletal myoblasts in patients with chronic ischemic heart failure.

A few studies have assessed the IC delivery of BMSCs in patients with chronic ischemic heart failure. In the TOPCARE-AMI trial, BMSCs were delivered IC and proved to be a safe route of administration with an improvement in LV function97 and no major cardiovascular adverse effects (Figure 36.9).

Autologous bone marrow mononuclear cells (ABMMNC) were delivered by injections into the myocardium (transendocardial delivery) of 20 no-option patients with chronic severe heart failure. 10 age, sex matched patients in the same condition served as the control group. The procedure was safe. The Canadian Cardiovascular Society angina score improved significantly in cell treated patients, and quality of life score was improved significantly at 6 months after the cell transplantation, while patients in the control group did not have any improvement.98 Single PET CT suggested a trend towards improved perfusion in cell treated patients, and the proportion of fixed defects was significantly increased in controls but not in treated patients. Cell treated younger patients had a significant improvement in maximal myocardial oxygen consumption compared with age matched controls. No procedural or acute complications were noted, or any other long-term side effects like ventricular arrhythmias or ectopic tissue growth.99 Previous studies (the Brazilian study) showed a significant improvement in functional capacity (assessed by MVO2) in treated patients.100

Other studies have assessed the therapeutic benefit of transendocardial injection of BMMNCs in patients with advanced heart failure or in patients with normal LVEF and found improvement in global left ventricular function and/or improved myocardial perfusion (SPECT)91,92,101 (Figure 36.9).

Assmus et al.102 delivered intracoronary progenitor cells and found that the patients who received a higher number of hematopoietic progenitor cells had a lower mortality rate (TOPCARE-CHD trial).

Since there are different delivery systems for patients with ischemic heart failure and poor LV function a study was designed to answer this question. The randomized controlled trial to compare the effects of G-CSF and autologous bone marrow progenitor cell infusion on quality of life and LV function in patients with heart failure secondary to ischemic heart disease (REGENERATE-IHD) study103 will compare the efficacy and safety of delivering BMSCs using three different methods—indirect mobilization using peripheral G-CSF infusion, direct injection of cells via the IC route, or the intramyocardial route.

In our recent pilot study, 8 patients (aged 57.2 ± 13.3 years) received transendocardial, intramyocardial injection of autologous bone marrow progenitor cells (mononuclear or mesenchymal stem cells) in the LV scar and in the border zone. All patients tolerated the procedure with no serious adverse events. At 1 year, a decrease in end diastolic volume (208.7 ± 20.4 versus 187.4 ± 7.32 mL; P = 0.03), a trend toward decreased end systolic volume (142.4 ± 16.5 versus 117.6 ± 7.4 mL; P = 0.06), a decreased infarct size (P < 0.05), and an improved regional LV function by peak Eulerian circumferential strain were observed in the treated infarct zone. Improvements in regional function were evident at 3 months, and the changes in chamber dimensions were not significant until 6 months. Improved regional function in the infarct zone strongly correlated with reduction of end diastolic volume and end systolic volume.60

We are currently completing recruitment in two clinical trials. In the Transendocardial Autologous Cells in Heart Failure Trial (TAC-HFT), 68 patients will be enrolled in a blinded and randomized fashion to receive adult stem cells to treat ischemic heart failure.60 In this trial, cells are taken from the patient’s own bone marrow before being processed and administered at target sites near damaged tissue in the heart. The second trial is a Phase III, randomized pilot study of the comparative safety and efficacy of transendocardial injection of autologous MSCs versus allogeneic MSCs in patients with chronic ischemic LV dysfunction secondary to MI, The Percutaneous Stem Cell Injection Delivery Effects on Neomyogenesis Pilot Study (The POSEIDON-Pilot Study).

In general, we feel that the best and most effective delivery approach in ischemic heart failure is the TESI method.

**Cell Therapy in Dilated Cardiomyopathy**

The first pilot study of IC injection of BMSCs in 24 patients with dilated cardiomyopathy (DCM) showed a significant improvement in LV ejection fraction and in functional class
6 months after transplantation.\textsuperscript{104} The largest study to date (TOPCARE-DCM) included 33 patients and showed that IC administration of BMSCs was associated with regional and global wall motion improvement 3 months after treatment (Figure 36.14).\textsuperscript{105} A recent study started to recruit patients with DCM to study and confirm these preliminary encouraging findings. This is the first randomized, double-blind, placebo-controlled study to compare the effects of G-CSF and autologous bone marrow progenitor cell infusion on quality of life and LV function in patients with idiopathic dilated cardiomyopathy (REGENERATE-DCM).

We are also enrolling patients in an ongoing clinical trial of patients with idiopathic DCM who will receive percutaneous stem cell injections, using the NOGA delivery system the percutaneous stem cell injection delivery effects on neomyogenesis in dilated cardiomyopathy (POSEIDON-DCM trial).

### Cell Therapy in Hibernating Myocardium

A recent trial has demonstrated no effect of surgical revascularization on death from any cause in ischemic heart failure.\textsuperscript{106} Viable dysfunctional myocardium is common and arises secondary to hibernating myocardium and repetitive stunning, as well as from myocyte loss and cellular hypertrophy due to LV remodeling.\textsuperscript{107,108} In contrast to avascular fibrotic scar, there is residual perfusion, which permits the distribution of IC cell-based therapy by standard cardiac catheterization approaches. A study that was conducted on swine with chronic hibernating myocardium to test the hypothesis that MSCs mobilize bone marrow progenitor cells and may improve function by stimulating myocyte proliferation in collateral dependent hibernating myocardium found that in hibernating myocardium, MSCs increased LV function in the area supported by the left anterior descending artery, even though the artery itself was still occluded. Circulating cKit\(^+\) and CD133\(^+\) bone marrow progenitor cells increased transiently after MSC administration, with a corresponding increase in myocardial cKit\(^+\)/CD133\(^+\) and cKit\(^+\)/CD133\(^−\) bone marrow progenitor cells. These results show that MSC transplantation can improve LV function in the hibernating myocardium independent of the coronary flow or the reduced scar volume (Figure 36.15).\textsuperscript{109} The assumption is that this improvement was induced by the MSCs that affected myocyte proliferation with an increase in cKit\(^+\)/CD133\(^+\) bone marrow progenitor cells and cKit\(^+\)/CD133\(^−\) resident stem cells, resulting in increased myocyte number and reduced cellular hypertrophy.\textsuperscript{109}

A randomized, double-blind, placebo-controlled human study examined the transplantation of blood-derived circulating progenitor cells (CPC) via IC infusion after recanalization of chronic occluded coronary arteries (26 patients enrolled). CPC transplantation resulted in an increase in coronary flow reserve by 43%. At 3 months the number of hibernating segments in the target region declined in the treatment group, but no such change was observed in the control group.\textsuperscript{110} MRI revealed a reduction in infarct size by 16% and an increase in LV function by 14% in the treated group due to improved wall motion in the target region.\textsuperscript{110}

![Figure 36.14](image_url) Dilated Cardiomyopathy. Individual changes of the extent of hypokinetic area (A), severity of hypokinesia (B), and ejection fraction (C) between baseline and 3-month follow-up. (Reproduced with permission from Fischer-Rasokat U, et al. \textit{Circ Heart Fail} 2009;2:417–423.)
Figure 36.15 icMSCs increase regional function in hibernating myocardium. LAD wall thickening (WT) was depressed compared with remote myocardium, and coronary flow reserve was critically impaired and unable to increase in response to adenosine. There was no spontaneous improvement in flow or function in untreated animals (n=7). After icMSC administration, regional LAD wall thickening increased significantly, whereas coronary flow reserve remained critically impaired, which indicates the absence of functional collateral development. Increases in LAD%WT were significant in animals studied 2 weeks (n=6) and 6 weeks (n=4) after icMSC administration. (Reproduced with permission from Suzuki G, et al. Circ Res 2011;109:1044–1054.)

FUTURE DIRECTION

With the accumulating dataset supporting the possibility of cell-based therapies for cardiac disease, the field of CV medicine can anticipate the inclusion of this exciting approach in the therapeutic armamentarium in the not too distant future. As discussed in this chapter an essential component of the approach is targeted delivery. Cell delivery requires not only sophisticated navigation but also safe and effective deployment strategies. Coupled with ongoing biological insights, delivery of the appropriate quantity of cells to the optimal location within the heart, using the best strategy will facilitate the therapeutic outcome. We can now anticipate a new branch of interventional cardiology, one in which highly potent and transformative treatments are delivered using a variety of devices in conjunction with diverse imaging systems (Figure 36.16) to treat CV diseases that at present continue to pose a major burden of morbidity and mortality.
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Endovascular Aortic/Aneurysm Repair (EVAR) and, in particular endovascular abdominal aortic aneurysm repair has rapidly progressed over the last two decades. Since the first reported case by Juan Parodi in 1991, the combination of new graft material, design, as well as progress in endovascular techniques and radiologic imaging modalities have allowed steady improvement in outcomes.

At the same time, the role of the physician who performs EVAR has evolved. Physicians have learned the engineering behind endovascular repair, have a better understanding of the physical properties of the grafts, and they have learned ways to manage the challenges of endovascular hemodynamics while taking into consideration the complexity and spatial configuration of aneurysm pathology.

Preoperative planning of endovascular repair is the key to its success. Determination of the access site, choosing the adequate endograft type for a given anatomy, and deployment techniques are all important aspects of a successful repair.

This chapter focuses on endovascular abdominal aortic aneurysm repair. It reviews the significant steps in analyzing preoperative and intraoperative imaging required to plan an EVAR and overcome different anatomic challenges that may be encountered during and after repair.

**INDICATION FOR REPAIR**

The goal of EVAR is an intraluminal exclusion of the aneurysmal sac, which reduces sac pressure in order to prevent dilation and potential rupture of the aneurysm. Persistence of blood flow in the sac contributes to a resultant pressurized aneurysm sac and continuous aneurysm dilation.

EVAR is recommended for abdominal aortic aneurysms larger than 5.5 cm, aneurysm growth of more than 0.5 cm/year, or symptomatic aneurysms. Indications are the same for endovascular and open repair. Multiple randomized studies have shown no survival benefit in treating abdominal aortic aneurysms smaller than 5.5 cm. Although three-quarters of the small aneurysms in the surveillance group will progress and ultimately result in aneurysm repair, the cost of early aneurysm treatment is significantly higher with no survival benefit. The 12-year follow-up of the small aneurysm UK trial, the small aneurysm US trial, and the “Positive Impact of Endovascular Options for Treating Aneurysms Early” (PIVOTAL) trial do not support a policy of early elective repair prior to the aortic diameter reaching 5.5 cm.

Although long-term survival of patients undergoing EVAR and open repair are similar, early outcomes in EVAR are better as demonstrated by overall lower physiologic stress for the patient, faster recovery, and shorter hospital stays. Compared to the traditional open approach, EVAR avoids large surgical incisions, decreases pulmonary complications and hernias, and reduces cardiac stress due to extended aortic cross clamp during the aortic anastomosis. This modality is particularly attractive in patients with significant medical comorbidities, who would otherwise not tolerate an open surgical procedure.

Over the last two decades, multiple randomized studies have examined the short- and long-term efficacy and safety of EVAR. Three large randomized clinical trials that have compared EVAR to open surgical repair are worth mentioning: Dutch Randomized Endovascular Aneurysm Management (DREAM), EVAR 1, and Open versus Endovascular Repair (OVER). In the DREAM trial, there was a strong trend toward a 30-day mortality benefit in the EVAR group when compared to open surgery (1.2% EVAR versus 4.6% open surgery; P = 0.10). However, the mortality benefit from EVAR was lost at 2-year follow-up. In the EVAR 1 study, 1,082 patients with aneurysm ≥5.5 cm were randomized to EVAR or to open surgical repair. Also in this study, perioperative mortality was lower in the EVAR group when compared to open surgery (1.7% EVAR versus 4.7% open surgery; P = 0.009).

The benefit in mortality in the EVAR group was associated with a shorter length of hospital stay and a lower use of blood products. At the end of the 4-year study, there was a reduction in aneurysm-related death in the EVAR group.
(3.5% EVAR, 6.3% open surgery; \( P = 0.02 \)), but there was no difference in all-cause mortality. Long-term complications and reinterventions rates were higher in the EVAR group. A similar benefit in perioperative and 30-day mortality with EVAR was observed in the OVER study (0.5% EVAR versus 3.0% open surgery; \( P = 0.004 \)). However, also in this study the benefit was lost over time (2-year mortality 7.0% versus 9.8%, \( P = 0.13 \)).

In summary, these trials highlight a trend toward an early benefit with EVAR when compared to open surgery, with similar long-term survival between the two treatment modalities. This is particularly important when dealing with patients who have a relatively long life expectancy since EVAR is generally more expensive, and these patients would be exposed to life-long surveillance involving radiation and possible reintervention.

**ENDOGRAFTS DESIGN**

Endografts have improved in their design, material, mechanical fixation, and delivery system size.

Seven different endografts have been approved by the Food and Drug Administration (FDA) for EVAR. They are classified into two general configurations:

1. Unibody endografts (Powerlink, Endologix) consisting of a main body with two limbs, completed with a proximal extension graft to the neck. The endograft is “built from bottom up” (Figures 37.1 and 37.2).
2. Bifurcated modular endografts consisting of two or three different pieces (Excluder-C3 Gore, AneuRx-Talent-Endurant Medtronic, Zenith Cook). The infrarenal aortic neck is sealed first and graft limbs are secondarily extended into the iliac arteries. The endograft is “built from top to bottom” (Figure 37.2).

Graft fixation and prevention of migration is obtained either proximally at the neck of the aneurysm for modular grafts, or distally on the aortic bifurcation for the unibody device. Some grafts have a suprarenal bare metal component with additional proximal fixation.

Endografts have different radiopaque markers attached to their graft material. The markers define the top and end of each piece, the spatial orientation, and the location of the graft’s contralateral gate. These are extremely important during positioning and implantation of the endografts.

**PREOPERATIVE EVALUATION**

Adequate preoperative imaging is crucial to determining whether a patient is a candidate for endovascular repair, and for planning the intervention.

The course the endograft will take before deployment, assessment of the proximal and distal sites of fixation, as well as the nature of the arterial walls are all important factors to be evaluated. Preoperative imaging will also guide the operator in choosing the graft type and design best suited to the anatomical requirements of a given aneurysm.

Thin-cut (1.5 to 3.0 mm) spiral computed tomography angiography (CTA) of the abdomen and pelvis is preferable for accurate distance and diameter measurements guiding endograft sizing. Each manufacturer has its own defined criteria for graft sizing and selection, but in general they all
recommend 10% to 20% graft diameter oversizing. Excessive oversizing (>30%) may lead to graft material infolding that can result in a perigraft leak.

In addition to the axial, coronal, and sagittal images, a three-dimensional CTA reconstruction of the aortoiliac vasculature is recommended in order to clearly visualize vessel tortuositites and anticipate graft positioning, deployment, and gate cannulation (Figures 37.3 and 37.4). These reconstructions also allow virtual endograft simulation.

Instead of CTA imaging, magnetic resonance angiography (MRA) can be performed in order to avoid exposure to iodinated products. This modality is however lengthy, can overestimate stenotic lesions, and does not reliably depict calcifications. Moreover, gadolinium-associated nephrogenic systemic fibrosis in patients with chronic renal failure has made this modality less attractive than in the past (see also Chapter 2).

In patients with severe renal failure a CT without contrast combined with intravascular ultrasound imaging (IVUS) can occasionally be used for adequate endograft placement,8 IVUS is rarely used preoperatively for planning, but it is of particular help intraoperatively with respect to identifying the renal artery ostia without the need for contrast administration. The endograft can then be deployed under both fluoroscopy and IVUS monitoring.

Another alternative in patients with renal failure is to combine CT imaging without contrast and use an intraoperative CO₂ angiogram.9 The use of CO₂ should not exceed 1,000 to 2,000 cc in 30 minutes due to the risk of ischemic colitis secondary to accumulation of CO₂ bubbles. As discussed in Chapters 2 and 19, this modality requires meticulous care to avoid contamination with air, which can result in gas embolization and debilitating complications such as spinal cord ischemia. CO₂ angiography can therefore be used only below the diaphragm and cannot be used for thoracic stent grafting.

**ENDOVASCULAR STRATEGY AND ENDOGRAFT IMPLANTATION**

EVAR can be performed under general anesthesia, epidural or spinal anesthesia, and even with sedation and local anesthesia. General anesthesia is preferred since chest and abdominal movements during respiration can be controlled during imaging and graft deployment. This allows precise graft positioning. Moreover, the patient is more comfortable during the procedure and ready for a potential open conversion if needed.

Endograft implantation can be divided into three phases: (1) access and graft delivery; (2) deployment; and (3) completion imaging. Each phase should be thoroughly planned by reviewing the preoperative imaging and by anticipating potential difficulties and complications.

**Choice of Access Site and Graft Delivery**

Although graft delivery from an axillary or subclavian artery access can be done, a transfemoral approach is most commonly used. Occasionally, a large superficial femoral artery can be used as an access site when dealing with a “hostile” groin.

CTA evaluation of the iliofemoral arteries should detail the diameter of the vessels, tortuosity of the iliac system and presence of stenosis, circumferential calcification, or thrombus.

Common femoral artery access can be obtained either by a percutaneous approach (Chapter 6) or by direct surgical arterial exposure (Chapter 8). Percutaneous access with suture-mediated devices using the Perclose Proglide device (preclose technique)10 or the Prostar device11 avoids common surgical wound complications and shortens operative time. This technique is growing in popularity, and due to its adaptability it allows percutaneous closure of arterial access using sheaths as large as 24F. However, this approach has a risk of failure, and an open approach is still recommended when the anterior surface of the femoral artery is calcified, fibrotic, the femoral artery is small, or when dealing with deep femoral arteries in obese patients. Open femoral exposure allows arterial control and accurate vessel closure under direct visualization. Occluded or severely stenotic common
femoral arteries should be treated with endarterectomy to prevent access site complications and prevent compromising graft limb patency.

Simple unibody or modular endografts are composed of a large main body delivery system and a smaller graft limb delivery system. The choice of the main body entry side, known as the ipsilateral access side, should take into account the size of the iliofemoral arteries. The larger access vessel should be favored for the larger sheath access side.

Once femoral access is obtained the iliac arteries and the aorta are accessed with a wire and catheter. Usually a catheter is then advanced up to the renal arteries and an angiographic image is obtained to locate the aorta, iliac vessels, and branches and confirm endograft sizing. Then, the endograft is delivered over a stiff wire to the desired position before graft deployment.
In the unibody configuration, the contralateral graft limb is snared through the femoral access, the endograft is then brought down to sit on the aortic bifurcation, and is finally completely deployed. The aneurysm is then totally excluded by proximal extension of the graft up to the aneurysmal neck. In the modular configuration, the main body graft is positioned and deployed at the neck, the contralateral graft limb is then cannulated from femoral access, and the aneurysm exclusion is completed by distal extension of the graft limbs into the iliac arteries.

Tortuous iliac arteries can be challenging to maneuver and particular attention should be paid to avoid unfortunate arterial dissection while accessing the aorta. This tortuosity can be counteracted once a stiff wire is placed in the system, but in severely tortuous iliac arteries endograft delivery may be compromised. Occasionally, a “dental floss technique” may be necessary to permit endograft advancement: a wire is snared and pulled from a left brachial access allowing the iliac-aorta system to straighten under wire traction.

Delivery sheath, system and device flexibility play an important role during the delivery phase. Tremendous emphasis has been put on device flexibility and profiling by different manufacturers to overcome these challenges.

Another challenging aspect when dealing with tortuous iliac arteries is the contralateral gate cannulation in modular grafts. In such cases, a body-wire technique can help cannulation: before deploying the endograft, the contralateral iliac system is straightened by placing a stiff wire through the iliac artery up into the aorta. A large sheath is advanced up to the distal aorta. The main-body endograft is then deployed from the ipsilateral side, while the contralateral iliac system is kept straight with the aforementioned stiff wire behind the endograft and contralateral access sheath already placed in the distal aorta. A more flexible guidewire and adjunct catheter are then advanced through the sheath, along the stiff wire, allowing cannulation of the contralateral limb. Once cannulation is completed, the guidewire is exchanged for a second stiff wire in order to deliver the endograft limb. The first stabilizing stiff wire is removed from behind the main-body endograft before completion of EVAR.

Alternatively, an “up and over” approach can be used. This approach involves advancing a guidewire over the endograft bifurcation and across the gate from the ipsilateral side. The guidewire is then snared from the contralateral side and exteriorized. A catheter is advanced from the contralateral side over the guidewire, through the contralateral gate and limb into the body of the graft. The guidewire is then slowly retracted from the ipsilateral, with the catheter still through the gate and in the body. A new stiff guidewire can then be inserted through the contralateral side in the catheter. The catheter is removed, and the contralateral endograft limb is advanced over the stiff wire; it is positioned and deployed in a standard fashion.

If the “up and over” approach fails, a brachial access can be used for an antegrade gate cannulation. This method also uses a snaring technique from the contralateral access side.

Small iliac arteries or iliac artery stenosis along the endograft delivery path may prevent advancement of the endograft. The most common site of stenosis is the external iliac artery. It is important to know the outer diameter of the access sheath and delivery system in order to anticipate potential difficulties advancing the device in smaller-diameter iliac segments. Most delivery systems traverse vessels 7 mm in diameter. Several maneuvers can help overcome the challenge: the lesion can first be serially stretched with a rigid dilator. It can also be predilated with an angioplasty balloon and/or stented to create a passage large enough for delivery. A certain number of manufacturers have their own delivery system that uses a hydrophilic coated surface, which allows better trackability. In addition, providing the lowest-profile delivery system that would allow easy navigation in calcified tortuous vessels is an important goal in endograft manufacturing. Low-profile devices can also potentially allow safer placement of totally percutaneous endografts.

Table 37.1 EVAR Anatomic Exclusions

<table>
<thead>
<tr>
<th>Inadequate proximal landing zone</th>
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<tbody>
<tr>
<td>Aortic neck length too short</td>
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<tr>
<td>Aortic neck diameter too wide or too narrow, ( \geq 32 \text{ mm and } \leq 18 \text{ mm respectively} )</td>
</tr>
<tr>
<td>Aortic suprarenal neck angulation ( \geq 45^\circ )</td>
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<tr>
<td>Aortic neck angulation ( \geq 60^\circ )</td>
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<tr>
<td>Conical aortic neck ( -10% ) increase in diameter or 15 mm</td>
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<tr>
<td>Irregular calcification, plaque, or thrombus at proximal neck</td>
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<tr>
<td>Inadequate distal landing zone</td>
</tr>
<tr>
<td>Nonaneurysmal iliac length ( &lt; 10 \text{ mm} )</td>
</tr>
<tr>
<td>Inadequate visceral blood supply to compensate for loss of IMA</td>
</tr>
<tr>
<td>Excessive tortuosity of the aorta and iliac system</td>
</tr>
<tr>
<td>Iliofemoral vessels too small, tortuous, or angulated to accommodate device</td>
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Aortic Neck

The aortic neck’s role is to provide a secure circumferential proximal sealing zone for both modular and unibody endografts. The neck is particularly important for modular endograft fixation; the endograft-neck apposition is key to preventing graft migration.

In unibody devices, fixation and seal are achieved separately. The neck provides proximal sealing and the aortic bifurcation acts as the anatomical fixation site. Once deployed, the endograft will sit on the bifurcation and aneurysmal exclusion is completed by graft extension proximally up to the sealing zone at the neck.

Aortic neck length, diameter, tortuosity, and nature should be evaluated by CTA. Most manufacturers recommend an aortic neck length of 15 mm below the lowest renal artery to assure adequate seal. The Talent and Endurant devices (Medtronic) are however approved by the US FDA for a 10 mm aortic neck length. Current endografts can treat necks up to 32 mm in diameter.

Neck angulation and tortuosity can be very challenging for precise endograft placement. Devices can be difficult to deliver up to the desired position. They can also get “kinked” after deployment in very angulated and/or tortuous neck anatomies, in extreme cases, resulting in graft collapse. The maximum neck angulation recommended for EVAR is 60 degrees. Angulation and tortuosity can be particularly challenging in short necks. Endografts deployed in an angulated zone deal with significant hydrodynamic forces that may cause graft bascule. This potential transfer may displace the graft, occlude the renal arteries if the graft moves proximally, or even drop into the aneurysmal sac if it moves distally.

Tapered, conical necks are also more susceptible in graft displacement, distal migration, and sac enlargement. A 10% increase in neck diameter from proximal to distal puts the endograft at higher risk of migration.

Some endografts have suprarenal bare metal components allowing additional fixation anchoring in the proximal normal aorta. Some of them are equipped with “hooks.” The suprarenal component theoretically prevents not only migration, but also hypothetically supports the graft angulation in the neck contour and neck apposition in the tortuous neck anatomy.

Before deployment of an endograft in the aortic neck, a magnified-view angiogram should be obtained to clearly visualize the renal arteries’ ostium and endograft radiopaque markers. When dealing with an angulated neck, craniocaudal and oblique views should be adjusted. “Endograft parallax” can be assessed for precise endograft placement. This is done by positioning the proximal radiopaque markers of the graft, which must be aligned by correcting the C-arm angulation adjustment.

Other considerations with respect to the nature of the neck are also important. The rough surface in circumferential neck calcification may not allow adequate seal. Presence of thrombus in the neck and in the aorta above the neck can be dangerous, due to the risk of distal embolization to the legs or proximal to the visceral arteries.

Aortic Bifurcation

A thorough evaluation of the distal aorta and aortic bifurcation is very important for graft selection and successful EVAR. As stated, the aortic bifurcation is the key anatomic structure in graft fixation and migration prevention, particularly in unibody devices. The aortic bifurcation location is important also when planning EVAR using a modular device. Modular devices are composed of a main body and a contralateral limb. Placement of the latter involves cannulation of the contralateral gate. Depending on the graft, the gate can open at a minimum distance of 7 to 8 cm (even longer for the Cook Zenith device) from the top of the endograft. Exact measurement of the distance between the lowest renal artery and the aortic bifurcation is important and must be long enough to ensure that the contralateral gate opening will not be blocked by the aortic bifurcation after main body deployment. Similarly, a very narrow distal aorta (less than 2 cm) just above the bifurcation may not allow gate opening and cannulation, or may severely compress the endograft limbs. In such cases, the use of an aorto-uniliac device with femoral crossover bypass should be considered. Alternatively, a unibody device can be used; residual stenosis, due to aortic external compression on the endograft, can be treated by a balloon-expandable Palmaz stent.

Iliac Deployment

The distal sealing zone for the endograft should be located and vessel diameter determined on the preoperative CTA. The landing zone could be in the common iliac or external iliac artery, depending on the aneurysm involvement of the iliac arteries. Particular attention should be paid to the internal iliac arteries and preserving their patency when possible. An adequate distal iliac landing zone is necessary to avoid retrograde aneurysm sac filling. Most manufacturers recommend a 10 mm minimum sealing zone in the iliac artery.

When dealing with aneurysmal common iliac arteries, the landing zone should extend into the external iliac artery and the internal iliac artery should be covered. The internal iliac artery should be embolized to prevent a type II endoleak after endograft deployment. Before such repair, accurate knowledge of the patient’s mesenteric vasculature and surgical history (such as colon resection) is important to avoid catastrophic bowel ischemia after endograft deployment. Marginal mesenteric blood supply and poor mesenteric collateralization combined with coverage of the inferior mesenteric artery and internal iliac arteries can have harmful consequences for the patient. In such cases, an attempt at internal iliac artery revascularization and/or mesenteric revascularization should be strongly considered (see also Chapters 34 and 46).
Coverage of a single internal iliac artery is usually well tolerated with ipsilateral buttock claudication that should improve with time and collateralization. Coverage of bilateral internal iliac arteries is feasible if adequate collateralization exists. Therefore, a staged embolization of the internal iliac artery before implantation of endograft will allow pelvic collateralization to develop. Up to 50% of patients undergoing internal iliac embolization will report symptoms including buttock claudication and erectile dysfunction (20%). The newer fenestrated or branched endografts allow maintenance of internal iliac artery flow and patency. Already used in Europe for some time, these grafts will most probably be readily available in the United States in the near future and thus help with maintenance of pelvic perfusion for extensive EVAR.

Tortuous iliac arteries are challenging not only during the delivery phase but also once the graft is deployed (Figure 37.5). Endograft limbs can kink and thrombose. If a limb kink or stenosis is suspected, the delivery stiff wire can be exchanged for a floppy wire, which will allow the endograft to take its final resting conformation. Pressure gradient can then be measured across the suspected stenosis and if significant mean pressure drop is found (> 10 mmHg) the segment should be treated. Placement of a large balloon expandable stent with significant radial force, such as a Palmaz stent, at the suspected stenosis can sometimes expand the narrowing and prevent catastrophic acute endograft limb thrombosis. In extreme cases, conversion to an aorto-uni iliac and femoral crossover should be considered.

Presence of circumferential calcification or thrombus in the iliac arteries can compromise the aneurysm seal and a longer landing zone should be considered. Severe calcification and thrombus can also result in complications, such as distal embolization, dissection, and iliac artery rupture. Control of the femoral arteries and adequate arterial forward flush before arteriotomy closure is recommended to avoid embolization.

Weak femoral pulses due to suspected arterial dissections found on angiograms should be aggressively treated with stent coverage. The entire endograft limb patency depends on adequate outflow. Iliac artery rupture can be treated with additional graft or covered stent deployment. Placement and inflation of a large compliant balloon (such as a Coda balloon) in the aorta or iliac artery will prevent excessive blood loss, while preparing the new graft or stent for delivery.

**COMPLETION IMAGING**

After endograft placement, a completion angiogram is performed to assess accurate endograft positioning, migration, aneurysm exclusion, renal and mesenteric artery patency, as well as the adequacy of the iliofemoral artery outflow.

**Renal Artery Patency**

Proximal migration or inaccurate deployment of the endograft, especially in a hostile aortic neck, may inadvertently cover partially or completely the renal or mesenteric arteries. In such cases, the graft can sometimes be pulled downward using an inflated compliant balloon. This maneuver is however hazardous when dealing with very short necks since the graft may actually “fall” into the aneurysm sac. It can also be dangerous and damage the aortic wall and renal ostia when suprarenal fixation is present.

Renal artery stenting is another way to maintain vessel patency. When the artery is totally covered, stenting is more difficult but feasible. A guidewire and catheter can be used through a brachial artery approach to create a path in between graft material and the aortic wall leading into the renal artery. The wire is then replaced with a stiffer wire, such as a Rosenwire, and a delivery sheath is advanced to the renal artery. A covered stent is then deployed from the renal artery up to the aorta. Placement of a covered stent avoids leaks through the stent cells behind the endograft material. This technique is also known as “chimney” or “smorkel.”

Alternatively, during graft deployment one can preemptively maintain a wire or a flush catheter between the endograft and aneurysmal neck. Thus, an access is maintained behind the endograft at all times; in case of accidental renal artery coverage, a balloon can be advanced over the wire. The balloon is inflated, creating space between the aorta and the graft. This maneuver will provide enough space for wire access to the renal arteries from a brachial approach. Subsequently, a covered stent can be delivered to maintain renal artery perfusion in “chimney” configuration. The wire and
flush catheter behind the graft can also be snared from the contralateral side and used to anchor the proximal graft edge, to pull it down and uncover the renal artery.

If these maneuvers fail, open revascularization of the renal artery should be initiated.

**Endoleaks**

Persistent blood flow into the aneurysm sac outside the endograft is called an endoleak (Figures 37.6 and 37.7). This can be demonstrated at the completion of the angiography; at this point the source of the endoleak can usually be identified.

Incomplete proximal seal or distal endograft migration will result in a type Ia endoleak (Figure 37.7). Similarly, an incomplete seal at the iliac artery level will result in a retrograde endoleak or type Ib endoleak (Figure 37.6). Type I endoleaks must be treated when identified since they maintain a pressurized aneurysm sac leaving the patient at risk of aneurysm rupture. Repeat balloon angioplasty of the sealing zone can be attempted. If the endoleak persists, a proximal or distal endograft extension can be added in cases where the landing zone permits it, without obstructing aortic branch arteries. Ultimately, an uncovered balloon-expandable stent, such as a Palmaz stent, can be placed at the landing zone and extended beyond the endograft (Figure 37.8). The stent will apply a high radial force over the endograft in order to obtain a seal. The stent can be extended proximally beyond the renal arteries’ ostium. If an endoleak persists and it is found to be small, the patient can be monitored, and follow-up imaging obtained. The sac may thrombose once heparinization is reversed.

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**Figure 37.6** Schematic demonstrating the different types of endoleak after endovascular aneurysm repair. Type I endoleaks occur because of inadequate graft seal resulting in perigraft flow and include (Ia) perigraft flow occurring proximally, (Ib) perigraft flow occurring distally, and (Ic) perigraft flow around an iliac artery occlusion device. Type II endoleaks occur when branch arteries backbleed because of collateral flow. These endoleaks include (IIa) backbleeding inferior mesenteric artery and (IIb) backbleeding lumbar artery. Type III endoleaks occur when flow persists between the segments of a modular graft and include (IIIa) leaks between iliac limbs or an iliac limb and main body component and (IIIb) leaks between main body components. Type IV endoleaks (IV) occur when flow is present through endograft material (graft porosity). Type V endoleak, or, “endotension” (V), occurs when persistent or recurrent pressurization of the aortic aneurysm exists in the absence of demonstrable endoleak. Drawings prepared by H. Fischer, MFA. (Reproduced with permission from Eliason JL, Upchurch GR. Endovascular abdominal aortic aneurysm repair. *Circulation* 2008;117:1738–1744.)
Figure 37.7 Type 1a endoleak shown on computed tomography angiography (CTA) and angiogram (arrows). Presence of a large lumbar artery, accessory renal artery, or inferior mesenteric artery may result in retrograde filling of the aneurysm sac. This is a type II endoleak. They can be recognized during completion angiogram by the delayed retrograde filling of the sac from the aortic branches (Figure 37.9). Type II endoleaks are usually benign. The collateral vessels feeding the sac usually thrombose when anticoagulation is reversed. Large patent inferior mesenteric arteries, large accessory renal arteries, or other aortic branches arising from the aneurysmal sac should however be embolized before endograft deployment.

Figure 37.8 Palmaz stent (short arrow) reinforcing the proximal seal of the endograft (long arrow). The Palmaz stent is extended proximally beyond the renal arteries.

Figure 37.9 Delayed type 2 endoleak on CTA (arrow).

Ineffective sealing of overlapping graft joints or, less frequently, fabric tear caused by a severely calcified aortic wall results in an early type III endoleak. Contrast flush between the modular component or graft material can be identified on the angiogram. In order to clearly identify a type III endoleak, the flush catheter can be brought down into the endograft and a focused angiogram obtained that will reveal the contrast blush. The modular graft junction can be balloononed again, and if unsuccessful, or if graft material is damaged, the leak should be covered and relined with an additional endograft.

Type IV endoleaks are rare and caused by graft material porosity or needle holes in the graft material used to fix different components of the endograft. They usually disappear when heparin is reversed.

It is worth mentioning that there is also a type V endoleak. Radiographic imaging at completion or during follow-up will not demonstrate any flow in the aneurysmal sac. However, the sac continues to enlarge without any obvious radiographically demonstrable leak. Most type V endoleaks need to be treated by an open approach.
POSTOPERATIVE FOLLOW-UP

After graft implantation, the aorta undergoes a slow remodeling process involving the aneurysm sac and most importantly the aortic neck. This can result in late graft migration and other late complications. Routine surveillance is needed to monitor aortic remodeling, graft migration, as well as progression of persistent endoleaks, and development of new endoleaks. Multiple large series, in particular data from the large Eurostar registry, reported incidence of secondary intervention after endograft implantation of 6.0%, 8.7%, 12%, and 14% at 1, 2, 3, and 4 years, respectively—the majority of them being transfemoral. Similarly, data from the Lifeline Registry of the EVAR trial reported a 22% secondary intervention at 5 years.21

Imaging is commonly obtained at 1, 6, and 12 months, then yearly. A triphasic CTA is the most common imaging modality used during follow-up. The unenhanced images reveal vessel wall calcifications and metallic endograft material and allow them to be differentiated from the intraluminal contrast. The arterial phase shows an immediate endoleak and the delayed phase may reveal late aneurysm sac fillings. CT imaging is reproducible, sensitive, and specific for endoleak detection. The main inconveniences are the potential nephrotoxicity, the radiation exposure, and long-term cost.

Other imaging modalities, such as unenhanced CT combined with duplex imaging, can be used in follow-up of patients with renal failure. Duplex imaging can detect blood flow within the sac. A continuous biphasic or monophasic flow pattern predicts persistence of the endoleak. This modality is however operator dependent and difficult to perform in large patients.22

COMPLICATIONS DURING FOLLOW-UP

During follow-up, complications can manifest in the early and late postoperative period. They can either be related to the prosthetic graft or to hemodynamic changes in the patient’s vasculature, resulting mostly in ischemic symptoms.

Early Complications

Early postoperative graft complications include iliac graft limb thrombosis resulting in acute limb ischemia. The overall late and early graft limb thrombosis rate is between 0.7% and 6.4%, and up to half of them occur during the first month.23 Common factors playing a role in limb thrombosis are severe iliac artery tortuosity, compromised iliofemoral arterial outflow, graft extension to the external iliac artery, incomplete graft expansion due to mural calcification or thrombus, and traumatic dissection of the iliac outflow during the access or delivery phase. As stated, intraoperative pressure gradient measurement at suspected graft narrowing should be obtained and stenosis corrected by stents.27,28

Early limb thrombosis can usually be thrombectomized, and its etiology should be identified and corrected. Poor iliac artery outflow or dissections should be treated by stenting and femoral artery stenosis should be treated by surgical endarterectomy. Ultimately, treatment might consist of conversion to aorto-uniliac conformation with femoral crossover bypass.

Early ischemic symptoms after EVAR can also be related to vessel coverage by graft material, or they can be secondary to thromboembolic events.29 Adequate collateral blood flow is extremely important for spinal, intraabdominal, and pelvic organ viability; any previous intestinal resection, mesenteric artery stenosis, or previous thoracic aortic aneurysm repair puts the patient at higher risk of ischemic complications after EVAR. It is also very important to obtain a completion angiogram at the end of the procedure to assess internal iliac artery patency, since it is an inherent part of the collateral flow.

Interruption of flow through the inferior mesenteric artery, infrarenal lumbar arteries, and internal iliac arteries may result in colonic ischemia, mostly affecting the sigmoid colon. Postoperative left lower quadrant pain, bloody bowel movements, or diarrhea should be taken very seriously and a sigmoidoscopy should be performed to look for ischemic changes.

Embolization of renal and mesenteric vessels is more commonly atheroembolic and thromboembolic in nature. The visceral arteries may be patent at completion of the angiogram, but the injury can result in intrinsic organ damage in the early postoperative period. The patient may complain of nausea, vomiting, food intolerance, and/or worsening renal function. Unfortunately, this outcome has a very poor prognosis and most patients become dialysis dependent. Bowel ischemia is also associated with poor outcomes and high mortality.10

Paraplegia is another devastating complication estimated to occur in 0.21% of elective EVAR cases.31 Embolization of the internal iliac arteries in patients whose spinal cords are dependent on pelvic circulation (particularly patients with previous thoracic aneurysmal repair) puts them at much higher risk of paraplegia. A lumbar drain should be placed in patients with a history of previous thoracic aneurysm repair and the patient’s systemic blood pressure should be kept above a mean of 90 mmHg to maintain adequate spinal perfusion pressure.

Lower extremity thromboembolization should always be ruled out at the end of the case with a peripheral pulse check. A lower extremity angiogram should be performed if embolization is suspected.

Late Complications

Late graft-related complications are mainly related to late graft limb thrombosis, the aneurysm remodeling process, aneurysm disease progression, endograft wear, and infections. The expected result after EVAR is the total interruption of blood flow in the aneurysmal sac, resulting in sac thrombosis and
shrinkage. This outcome is however not uniform and close follow-up with radiologic imaging is necessary after EVAR if complications arise.

It is generally agreed that persistent type II endoleaks with a progressive aneurysm sac enlargement of more than 0.5 cm should be aggressively treated. Several different therapeutic modalities have been reported, and in particular endovascular embolization with an overall 8.6% complication rate. Commonly performed through a transfemoral approach with coil, glue, or Gelfoam, embolization of the feeding vessel is successful in the early phase, but a significant number of patients require more than one procedure, and many have delayed sac growth at their 5-year follow-up. This late growth underlines the importance of lifelong surveillance after EVAR.

Among the different modalities, endovascular glue embolization may be the most effective because of its liquid properties, which allow it to disperse beyond the original feeding vessel into the sac and potential outflow vessels. However, in the presence of short inferior mesenteric or lumbar arteries or an abundant lumbar collateral network, the glue may progress beyond the targeted vessel and result in bowel or spinal ischemia. Direct CT-guided sac embolization with glue is another alternative, but there is a risk of spinal or colonic ischemia. Conversion to an open repair is the ultimate treatment for persistent type II endoleaks with sac enlargement.

Distal migration of the implanted endograft with a resulting type Ia endoleak is a dangerous complication leading ultimately to aneurysm growth and rupture (Figure 37.10). A much higher rate of migration (of more than 10 mm or requiring repair due to endoleak Ia) was reported with the older generation of endografts, but currently most manufacturers report less than 5% migration rates at 2 years. Multiple factors play a role in migration. Aneurysm enlargement and neck anatomy—in particular tortuosity, angulation, length, and device apposition zone length—are important factors to consider. Aneurysm sac enlargement may be secondary to a persistent endoleak (i.e., type II), progressive aortic neck degeneration, or aortic remodeling after EVAR. In the presence of a short and angulated neck, even a small sac enlargement may result in migration and a type Ia endoleak. Late migrations can be treated with simple aortic cuff endograft overlap and endograft relining.

In more advanced cases the endograft may migrate and “fall” into the aneurysm sac. In such cases, the distance between the lowest renal artery and the endograft flow divider

**Figure 37.10** (A) 3D reconstruction demonstrating distal migration of an Excluder endograft (WL Gore & Associates, Inc.). Note the low position in relationship to the renal arteries. Proximal aneurysmal dilation of the aortic neck may be responsible for graft migration. (B) Angiography demonstrating distal migration of an AneuRx endograft (Medtronic, Inc.). Note the lower most renal (thin arrow) and the top of the graft (thick arrow). (Reproduced with permission from Vandy FC, et al. Aortic endovascular grafting. In: Mosucci M, ed. Complications of Cardiovascular Procedures: Incidence, Risk Factors and Bailout Techniques. Lippincott & Wilkins; 2011.)
is usually too short for the placement of another bifurcated endograft for realignment. The preferred treatment is therefore the placement of an aorto-uniliac endograft and femoral crossover bypass.

The high pulsatility of the aortic blood flow, as well as aortic remodeling may cause torsional, radial, and circumferential pressure on the endograft. Although endograft material has drastically improved over the last few years, these constant forces can create an opportunity for late graft component separation, or progressive graft material wear with stent fracture, fabric erosion, and suture breakdown. They all result in a type III endoleak, which, in most cases, can be treated by covering defects with luminal graft extension and realignment.

Endograft infection is rare with a rate of 0.16% at 2 years and an overall mortality of 20% to 40%. Most infections occur within the first 2 years after implantation.34 The etiology of these infections is not clear, but patients with nosocomial infections, blood stream septicemia, and surgical site infections in the perioperative period seem particularly susceptible to graft infection.35 Presence of perigraft gas or fluid during follow-up imaging, despite absence of infection symptoms, should prompt further investigation. Graft explantation and revascularization is the standard care option, but it has a high mortality rate (up to 36%).36,37 Nonoperative treatment is an option in high-risk patients, comprising percutaneous drainage and/or instillation of antibiotics through drains and intravenous antibiotics.

ENDO VASCULAR REPAIR COMAPRED WITH SURVEILLANCE FOR PATIENTS WITH SMALL ABDOMINAL AORTIC ANEURYSMS


REFERENCES


CONCLUSION

Although early outcome of EVAR is superior to open aortic aneurysm repair, one must be more cautious with long-term follow-up. The significant rate of secondary reintervention and potential complications related to EVAR should be taken into consideration before offering this treatment modality to patients. Preoperative planning, identification of important anatomic challenges during repair, as well as sound familiarity with the endograft being used, and in particular its deployment and behavior during repair, are key for a successful EVAR.


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Although early outcome of EVAR is superior to open aortic aneurysm repair, one must be more cautious with long-term follow-up. The significant rate of secondary reintervention and potential complications related to EVAR should be taken into consideration before offering this treatment modality to patients. Preoperative planning, identification of important anatomic challenges during repair, as well as sound familiarity with the endograft being used, and in particular its deployment and behavior during repair, are key for a successful EVAR.


The pericardium consists of both a visceral and a parietal component, each composed of an inner layer of mesothelial cells covering an underlying fibrosa. The visceral pericardium is attached to the heart by loose connective tissue and surrounds the epicardial fat pads and coronary arteries. At the pericardial reflections, it extends onto the pulmonary veins, superior and inferior vena cavae, and several centimeters of proximal pulmonary artery and aorta, before folding around to continue as the parietal (or free) pericardium. The parietal pericardium then envelops the heart and visceral pericardium as a separate 1 to 2 mm-thick layer (Figure 38.1). The pericardial space lies between the visceral and parietal layers and normally contains 15 to 35 mL of serous pericardial fluid—an ultrafiltrate of plasma. If outward pressure is exerted by chronic pericardial effusion or cardiac chamber dilation, the pericardial layers can stretch slowly over time, but over shorter periods, the pericardium behaves as a fixed-capacity sac. Both the parietal and visceral pericardium are supplied by nerves, arteries, and lymphatics and are metabolically active, producing prostaglandin E, eicosanoids, prostacyclin, and growth factors. Inflammatory cytokines, complement myocardial cellular enzymes, and other factors may appear in the pericardial fluid in response to inflammation or transmural myocardial ischemia and necrosis, and may affect the underlying myocardium, cardiac nerves, and coronary arteries.1

The pericardial pressure is usually subatmospheric (−5 to +5 mmHg) and tracks with intrathoracic pressure during the respiratory cycle.1 During inspiration, intrapleural pressure and pericardial pressure fall more than systemic venous pressure, thus increasing the right atrial filling gradient and right ventricular stroke output (see chapter 23). In contrast, the falling intrapleural pressure during inspiration reduces pulmonary venous pressure, and decreases the left atrial filling gradient and left ventricular filling. Together with an increase in left ventricular afterload (owing to an increase in the relative difference between left ventricular end-diastolic and aortic pressure), this reduces left ventricular stroke output during inspiration. These effects are reversed during expiration. Therefore, under normal conditions, the hemodynamic effects of respiration cause cyclical changes in ventricular stroke output that are nearly 180° out of phase between the right and left ventricles.

The parietal pericardium also contributes to the diastolic compliance characteristics of the heart, especially over the thin-walled atrial and right ventricular chambers.2,3 The pericardium thus limits acute cavity dilation in situations such as right ventricular infarction, massive pulmonary embolism, and acute aortic insufficiency. If excess pericardial fluid accumulates in the pericardial space beyond its limited capacity to stretch, the pericardial pressure rises and begins to progressively compress the underlying cardiac chambers. Since this pressure is applied equally to all chambers, a rising pericardial pressure couples the diastolic behavior of the left and right ventricles together and creates ventricular interdependence whereby changes in pressure and volume in one ventricle thus produce changes in diastolic filling, contraction, and relaxation in the other ventricle.1 For example, acute increases in right ventricular
infarction or pulmonary embolism) will increase the intrapericardial pressure, cause an increase in the stiffness of both ventricles, and reduce their compliance. Whenever right ventricular diastolic pressure exceeds left ventricular diastolic pressure, the common external pericardial constraint can cause the intraventricular septum to shift leftward and impede left ventricular filling.

As described in detail in Chapter 44, pericardial disease can manifest with a variety of presentations, of which acute fluid accumulation leading to tamponade physiology and chronic fluid accumulation are relatively common. In addition, the growth in the performance of complex coronary interventions and catheter-based procedures for ablation of arrhythmias and for structural heart disease has been associated with an increase in coronary artery and cardiac perforation, and pericardial tamponade as a complication of these procedures. Thus, familiarity with elective or emergency management of pericardial effusion and tamponade continue to be important components of contemporary interventional cardiology. More recently, there has been a renewed interest in the pericardial space as a site for drug administration and as a new access site for mapping and ablation of ventricular arrhythmias. In this chapter, we will review indications and techniques of pericardiocentesis, balloon pericardiotomy, and pericardial access to the epicardium.

PERICARDIOCENTESIS

The etiology of pericardial effusion varies, and the role of pericardiocentesis in its management depends on the presence of tamponade physiology, the size of the effusion, and the ability to obtain the appropriate diagnosis on the basis of clinical history and other noninvasive diagnostic tests. Figure 38.2 depicts a proposed algorithm for the management of pericardial effusion. Pericardial tamponade is a Class I indication for pericardiocentesis (level of evidence B according to the European Guidelines for the Diagnosis and Management of Pericardial Disease). Pericardiocentesis can also be considered for effusions >20 mm in size on echocardiography and for the diagnosis of smaller effusions when obtaining pericardial fluid is felt to aid in the diagnosis (level of evidence B, Class IIa indication; Table 38.1).

Fluoroscopy-Guided Pericardiocentesis

At most centers, pericardiocentesis is performed in the cardiac catheterization laboratory using a combination of echocardiographic and fluoroscopic guidance. It is highly recommended that a two-dimensional echocardiogram be obtained just prior to the procedure to document the presence, location, and size of the effusion; to determine the presence of loculation or significant stranding; and to determine the location on the body surface where the effusion lies closest to the surface and at which the fluid depth overlying the heart is maximal. Once an entry location is selected, the echo can indicate the optimal direction for needle passage and the approximate depth of needle insertion that will be required. We believe that in the cardiac catheterization laboratory, access to pressure measurement, continuous ECG and vital sign monitoring, and fluoroscopy with the ability to inject radiographic contrast is highly preferable, particularly in difficult or challenging cases, in patients with small or localized effusions, or when complications ensue. It is important to have access to adequate ancillary support and other technologies in hemodynamically unstable patients, unless an emergency requires a bedside procedure. Performing the procedure in the catheterization laboratory in conjunction with right heart pressure measurement is also required if the diagnosis of effusive-constrictive pericarditis is suspected, if the effusion is small or loculated, or if the patient is hemodynamically unstable.

The patient’s torso is propped up to a level of about 45° using a bolster or other mechanism, and the transducers are

**Table 38.1** Utility of Diagnostic Tests for the Etiologic Diagnosis of Pericarditis According to Targeted Causes

<table>
<thead>
<tr>
<th>Test</th>
<th>General</th>
<th>Tuberculous</th>
<th>Systemic Disease</th>
<th>Neoplastic</th>
<th>Purulent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auscultation</td>
<td>++</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>ECG</td>
<td>++</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Markers of inflammation</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Markers of myocardial lesion</td>
<td>++</td>
<td>+/-</td>
<td>+</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Tumor markers</td>
<td>–</td>
<td>–</td>
<td>+/-</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Tuberculin skin test</td>
<td>–</td>
<td>+/–</td>
<td>+/–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Quantiferon-TB</td>
<td>–</td>
<td>+/–</td>
<td>+/–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>ANA, ENA (anti-SSA)</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>HIV testing</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Viral serology</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Blood culture</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Chest x-ray</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
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<tr>
<td>CT</td>
<td>–</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>CMR</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Mammography</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>++</td>
<td>–</td>
</tr>
<tr>
<td>Pericardiocentesis</td>
<td>–</td>
<td>++</td>
<td>+/-</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Pericardial biopsy</td>
<td>–</td>
<td>++</td>
<td>+/-</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

ANA, antinuclear antibody; CT, computed tomography; CMR, cardiac magnetic resonance; ENA, antibodies anti-extractable nuclear antigen; SSA, Sjogren Syndrome type A; ++, very high; ++, high/good; +, discrete; +/-, low/insufficient; and –, not useful. Quantiferon-TB is an interferon-γ release assay used in tuberculosis diagnosis.

The window is thus very useful to confirm the optimal direction toward the pericardial entry point and the approximate depth between the syringe and the needle, it can be used to introducing leakage currents through the needle. With the use of fluoroscopy and the ability to inject radiographic contrast and monitor pressure to confirm entry into the pericardial space, most operators no longer use ST segment monitoring during fluoroscopy-guided pericardiocentesis. Importantly, it should be emphasized that ST segment monitoring alone is inadequate as a safeguard from complications. A blunt-tip epicardial needle (Tuohy-17) can also be used to minimize risk of right ventricular puncture. This technique may be modified to enable access to the normal pericardium for drug delivery and epicardial mapping.

When the needle enters the pericardial space, a distinct pop is usually felt and it is possible to aspirate fluid. If there is an interposed stopcock connected to a pressure transducer, turning the stopcock will allow display of intrapericardial pressure, which should be superimposable on the simultaneously displayed right atrial pressure from the right heart catheter. The waveform should emphatically not resemble that of right ventricular pressure. If the pericardial needle tip displays a right ventricular waveform, the tip is quickly but smoothly withdrawn under continuous hemodynamic monitoring until the overlying pericardial space is entered. Entry into the pericardial space can be confirmed by injection of radiographic contrast or agitated saline echo contrast, or the advancement of a 0.035 inch J wire in the characteristic path wrapping around the heart (Figure 38.5A,B). An 8F dilator is then introduced over the guidewire, followed by a drainage catheter (straight or pig-tail shaped, with multiple side holes) (Figure 38.6). If difficulty is encountered in advancing the drainage catheter, the dilator can be reintroduced and used to substitute an extra-stiff J wire for better support. We usually attach a 50 mL syringe and a three-way stopcock to the drainage catheter, connecting an extension tube from the other port of the three-way stopcock to a drainage bag or vacuum bottle. This allows fluid to be aspirated into the syringe and transferred to the bottle. Removal of as little as 50 mL of fluid is often sufficient to relieve frank tamponade and improve hemodynamics. After removal of 100 to 200 mL of fluid, it is informative to measure the pericardial and right atrial pressures before resuming aspiration. Resolution of tamponade physiology usually occurs after aspiration of 50 to 200 mL of fluid. It is recommended that pericardial fluid be removed slowly, as rapid removal can precipitate the development of acute postprocedure ventricular dysfunction (Complications” below). Occasionally, patients will experience pericardial pain when the effusion is tapped dry. In this
Figure 38.4  Diagram showing the subxiphoid approach to pericardiocentesis with pressure and ST segment monitoring. A hollow, thin-walled, 18-gauge needle is connected via a three-way stopcock to an aspiration syringe filled with 1% Xylocaine and to a short length of fluid-filled tubing connected to a pressure transducer. A sterile V lead of an electrocardiographic recorder may be attached to the metal needle hub. The needle is advanced until pericardial fluid is aspirated or an injury current appears on the V-lead electrocardiographic recording. Once fluid is aspirated, the stopcock is turned so that needle-tip pressure is displayed against simultaneously measured right atrial pressure from a right heart catheter. When needle-tip position within the pericardial space is confirmed, a J-tipped guidewire is passed through the needle into the pericardial space, the needle is removed, and a catheter with end and side holes is advanced over the guidewire and subsequently connected via the three-way stopcock to both the transducer and the syringe. This permits, first, thorough drainage of the pericardial effusion using a catheter rather than a sharp needle and, second, documentation that tamponade physiology is relieved when right atrial pressure falls and intrapericardial pressure is restored to a level at or below zero.

Figure 38.5  A, B. Guidewire advanced in the pericardial space with its characteristic path wrapping around the heart.
case, parenteral narcotic analgesics and benzodiazepines can be administered, and if the pain is severe, 50 mL of pericardial fluid, sterile saline, or 10 to 20 mL of 1% Xylocaine can be reintroduced to help ease the pain. The patient should be laid flat and a final set of pericardial and right heart pressures measured. A fall in pericardial pressure to a level ≤0 mmHg and separation from the right atrial pressure, with a return of the normal diastolic y descent, indicate relief of tamponade physiology. These changes will be accompanied by a resolution of pulsus paradoxus. In previously hypotensive patients, systemic arterial pressure usually rises in association with an increase in mixed venous oxygen content, indicative of an increase in cardiac output. Failure of pericardial pressure to fall close to 0 mmHg indicates that the reference height of the transducers is incorrect or that free or loculated pericardial fluid is still under pressure. If the pericardial pressure falls appropriately but the right atrial pressures remain elevated with prominent x and y descents, the diagnosis of effusive-constrictive pericarditis must be entertained, with an ongoing element of constriction after the tamponade physiology has been relieved (see chapter 23).

The drainage catheter is then sewn in place and attached to a sterile fluid path (stopcock, syringe, and drainage bag) to allow the postprocedure nursing staff to periodically attempt additional aspiration. Sterility must be strictly maintained with this technique, because regularly interrupting the integrity of the drainage circuit may introduce infectious agents. Some institutions rely on continuous or intermittent suction applied via a water-seal device. The pericardial catheter is removed when the drainage has decreased to <25 to 50 mL per 24 hours and there is no echocardiographic evidence of reaccumulation of fluid. Subsequently, periodic echo reassessment for fluid reaccumulation should be performed. Larger effusions may benefit from slightly more prolonged drainage, but >48-hour dwell time should be avoided to reduce the risk of infection. Analysis of pericardial fluid can aid in the diagnosis of infectious pericarditis (fungal, bacterial, viral, and tuberculous), as well as in the diagnosis of malignant and cholesterol effusions. Table 38.2 summarizes recommended diagnostic tests to be performed on pericardial fluid, as indicated.

Echocardiography-Guided Pericardiocentesis

When performing pericardiocentesis, the ideal entry site would be the point at which the distance from skin to maximal fluid accumulation is minimal, with no intervening vital organs. Echocardiographic guidance has emerged as a technique to identify the ideal entry site and to perform pericardiocentesis safely without fluoroscopy. In a large series of 1,127 patients managed with echocardiography-guided pericardiocentesis, the chest wall entry site was the most commonly used site (79% of patients). Importantly, the para-apical approach was used in 80% of patients managed with chest wall entry (714/890), while the remaining chest wall entry sites included the left and right parasternal, left
Table 38.2 Diagnostic Tests of Pericardial Fluid

| Suspected Malignant Effusion | Cytology and tumor markers (carcinoembryonic antigen—CEA), alpha-fetoprotein (AFP), carbohydrate antigens (CA 125, CA 72-4, CA 15-3, CA 19-9, CD-30, CD-25, etc.). Differentiation of tuberculous and neoplastic effusion is virtually absolute with low levels of adenosine deaminase (ADA) and high levels of CEA. |
| Suspected Tuberculosis | Acid-fast bacilli staining; mycobacterium culture or radiometric growth detection (e.g., BACTEC-460); adenosine deaminase (ADA), interferon (IFN)-gamma, pericardial lysozyme, and PCR analyses for tuberculosis (level of evidence B, indication I). Very high ADA levels have prognostic value for pericardial constriction. PCR analysis is as sensitive (75% versus 83%), but more specific (100% versus 78%) than ADA estimation for tuberculous pericarditis. |
| Suspected Bacterial Infection | At least three cultures of pericardial fluid for aerobes and anaerobes as well as blood cultures are mandatory (level of evidence B, indication I). Gram stains in pericardial fluid have a specificity of 99%, but a sensitivity of only 38% for exclusion of infection. |
| Viral Infections | PCR analyses for cardiotropic viruses discriminate viral from autoreactive pericarditis (indication IIa, level of evidence B). |
| Nonspecific Tests | Specific gravity (>1.015), protein level (>3.0 g/DL; fluid/serum ratio >0.5), LDH (>200 mg/dL; serum/serum ratio >0.6), and glucose (exudates versus transudates: 77.9 ± 41.9 versus 96.1 ± 50.7 mg/dL) can separate exudates from transudates but are not directly diagnostic (class IIb). However, purulent effusions with positive cultures have significantly lower fluid glucose levels (47.3 ± 25.3 versus 102.5 ± 55.6 mg/dL) and fluid-to-serum ratios (0.28 ± 0.14 versus 0.84 ± 0.23) than those of noninfectious effusions. |
| Cell Counts | White cell count (WBC) is highest in inflammatory diseases, particularly of bacterial and rheumatologic origin. Very low WBC count found in myxedema. Monocyte count is highest in malignant effusions and hypothyroidism (79 ± 27% and 74 ± 26%), while rheumatoid and bacterial effusions have the highest proportions of neutrophils (78 ± 20% and 69 ± 23%). |
| Cholesterol Levels | As compared with controls, both bacterial and malignant pericardial fluids have higher cholesterol levels (49 ± 18 versus 121 ± 20 and 117 ± 33 mg/dL). |
| Epithelial Membrane Antigen, CEA, Vimentin | Combination of epithelial membrane antigen, CEA, and vimentin immunocytochemical staining can be useful to distinguish reactive mesothelial and adenocarcinoma cells. |


Complications of Pericardiocentesis

The safety and success of percutaneous pericardiocentesis is related to the choice of entry site as well as to the size of the effusion. Pericardiocentesis is most likely to be uncomplicated if both anterior and posterior echo-free spaces are at least 10 mm. In smaller effusions, there is an increased risk of cardiac injury, so pericardiocentesis should usually be avoided in minimally symptomatic patients with small incidental effusions, unless there is clear echocardiographic evidence of hemodynamic compromise. The risk is also higher in patients who are anticoagulated with warfarin, so pericardiocentesis should be deferred if possible until the international normalized ratio (INR) is within normal range. If hemodynamic status demands urgent pericardiocentesis in the patient with elevated INR, fresh frozen plasma should be administered in the catheterization suite immediately after catheter access to the pericardium is achieved by an expert operator and drainage is initiated (to avoid conversion of a free hemorrhagic effusion into a mixture of fluid and gelatinous clot).
In the Mayo Clinic series of 1,127 echocardiography-guided pericardiocenteses,4 drainage was successful in 97% of cases with a 1.2% rate of major complications and a 3.5% rate of minor complications. As summarized in Table 38.3, pericardiocentesis can cause complications that include laceration of a chamber wall or laceration of a coronary artery or vein, which can result in hemopericardium, worsening tamponade, or circulatory collapse. Perforation of the ventricular myocardium with just the needle usually does not result in significant bleeding and is usually well tolerated, but reflex hypotension can occur. Ventricular and atrial arrhythmias may occur as a result of mechanical irritation from the needle, guidewire, or catheter, but are usually transient and not life threatening. Pneumothorax can occur as the result of entry into the pleural space, and laceration of the liver and penetration of the stomach, colon, or spleen have also been described as complications of pericardiocentesis via the subxiphoid route. Right and left ventricular failure, pulmonary edema, and exacerbation of bleeding from an ascending aortic dissection have been described following pericardiocentesis.12–16

Acute transient left ventricular and/or right ventricular dysfunction is a rare though serious complication that has been described in association with rapid removal of large amounts of pericardial fluid. It can manifest with acute pulmonary edema and cardiogenic shock.13–16 Several hypotheses have been proposed regarding its pathogenesis. The first hypothesis relates to a reduction in coronary blood flow in the setting of tamponade, which results in myocardial stunning.17,18 It has also been suggested that, in some cases, resolution of the catecholamine surge associated with tamponade can unmask underlying ventricular dysfunction.19 The third hypothesis relates to sudden changes in wall stress. The resolution of tamponade leads to a sudden increase in venous returns, which results in rapid diastolic volume overload.10 The diastolic volume overload in association with the increase in vascular resistance and the resultant increase in wall stress lead to ventricular systolic dysfunction. The general agreement is that rapid removal of large amounts of fluid contributes to the development of left ventricular dysfunction and should be avoided. As discussed further in case 3 of Chapter 44, this might be particularly relevant in patients with pulmonary hypertension and with systemic sclerosis.

**Figure 38.7** Parasternal long-axis echocardiogram recorded in a patient with a large posterior pericardial effusion (PEF). Pericardiocentesis is being undertaken with echocardiographic guidance. **A.** There is a large posterior pericardial fluid collection. **B.** Agitated saline has been injected via the pericardiocentesis needle. There is now echo contrast in the previously clear pericardial space confirming that the pericardiocentesis needle is in the pericardium. LA, left atrium; LV, left ventricle; RV, right ventricle.

**PERCUTANEOUS BALLOON PERICARDIOTOMY**

Percutaneous balloon pericardiotomy is an alternative approach to the treatment of cardiac tamponade in patients with large recurrent malignant effusions20 or idiopathic effusions that have recurred or not abated after prolonged catheter drainage (e.g., catheter drainage of >100 mL/day for 3 days). Of the patients who undergo pericardiocentesis for malignant effusion, 66% has recurrence after simple drainage by pericardiocentesis.21,22 In comparison, in most series of cardiac tamponade not related to malignant effusion, pericardiocentesis with prolonged catheter drainage23 was effective without further intervention in >80% of patients. An analysis by Vaitkus et al.24 has suggested that balloon pericardiotomy, surgical pericardiecotmy, pleuropericardial window, and subxiphoid window are all superior in terms of freedom from recurrence to repeat simple pericardiocentesis, instillation of sclerosing agents, radiation, or prolonged catheter drainage.
Patients with recurrent tamponade from malignant effusions often are poor surgical candidates. Hence in this patient population, percutaneous balloon pericardiomy has emerged as an alternative to a subxiphoid window. The technique begins with pericardioctesis via the subxiphoid approach. After pericardioctesis, approximately 20 mL of contrast is injected to aid visualization of the pericardial space. A 0.035 inch J-tip guidewire is then introduced and looped in the pericardium. The pericardiomy catheter is withdrawn, the tract is dilated with a 10F dilator, and a 10F to 12F sheath is inserted under fluoroscopy. A 20 mm-diameter by 3 to 4 cm-long dilating balloon (e.g., Mansfield, Z-Med) is advanced over the guidewire. The balloon is positioned to straddle the pericardial border, and the sheath is withdrawn to uncover the balloon. The balloon is slightly inflated to define a waist at the parietal pericardial border as illustrated in Figure 38.8, and then fully expanded to create a rent in the pericardium. Depending on the stiffness of the pericardium, the balloon may “watermelon seed” into the pericardium and requires strong counter-traction. In thin patients, the skin and subcutaneous tissues may need to be retracted inferiorly to avoid dilating through the skin. If the 20 mm balloon cannot be successfully inflated, we have found that moving to a 12 or 18 mm balloon may allow dilation, with subsequent upsizing of the balloon to 20 to 22 mm in diameter. Balloon dilatation across the pericardium tends to cause severe pain, and adequate prophylactic narcotic analgesics should be administered prior to inflation to minimize discomfort.

The balloon is removed, the pericardial catheter is reintroduced, and about 10 mL of contrast may be injected to confirm free exit of fluid through the rent in the pericardium. Any remaining fluid is evacuated, and the catheter is left in place for drainage for 24 hours or until the catheter drainage is <50 to 75 mL/24 hours. Sometimes more than one site must be dilated to ensure rapid emptying of the pericardial space, or balloon pericardiomy may need to be repeated for recurrent tamponade. Chest roentgenography must be performed within 24 hours to evaluate for left pleural effusion, which is common, or pneumothorax, which is uncommon. Echocardiography should be performed 48 hours after catheter removal to confirm resolution of the pericardial effusion.

Modifications of the procedure include the use of a double balloon technique and the use of the Inoue balloon catheter. With the double balloon technique, two J-tip guidewires are advanced into the pericardial space through the same sheath after initial drainage of fluid. An 8 to 12 mm-diameter by 2 cm-long balloon and a second 8 to 12 mm-diameter by 4 cm-long balloon are advanced over the guidewires. The advantage of using two guidewires relates to the fact that the pericardial border can be identified as the point of separation of the two guidewires as they enter the pericardial space, thus facilitating positioning of the two balloons (Figure 38.9).
Figure 38.8  A. Illustration of the percutaneous balloon pericardiotomy technique. After partial drainage of the pericardium using a pericardial catheter, a 0.038 inch stiff J-tip wire is introduced into the pericardial space. A 3 cm-long dilating balloon is then advanced over the guidewire to straddle the parietal pericardial membrane and is manually inflated to create a rent in the pericardium. B. Still frames from a percutaneous balloon pericardiotomy. (From Ziskind AA, Pearce AC, Lemmon CC, et al. Percutaneous balloon pericardiotomy for the treatment of cardiac tamponade and large pericardial effusions: description of technique and report of the first 50 cases. J Am Coll Cardiol 1993;21:1.)

The Inoue balloon catheter is unique in that its inflation is sequential; that is, inflation of the distal portion is followed by inflation of the proximal portion. This sequential inflation dynamics can allow optimal positioning of the balloon across the pericardium. The technique requires inflating the distal portion of the balloon, pulling the balloon back against the parietal pericardium, and then full inflation, thus locking the pericardium in the middle of the balloon (Figure 38.10). In 11 patients who underwent Inoue balloon pericardiotomy for treatment of recurrent large effusion, the procedure was successful in 10 patients (91%), who remained free of recurrent effusion for a follow-up period of 4 months.

It has been established that balloon pericardiotomy causes drainage and absorption of fluid within the peritoneal cavity and the pleura. 20, 29 Given the experience with subxiphoid surgical pericardial window, it is unlikely that the communication between the pericardium and pleura or peritoneum produced by balloon pericardiotomy stays open for the long term as inflammatory fusion of the opposed parietal and visceral pericardium occurs over time and obliterates the potential space.

A multicenter registry of 130 patients undergoing balloon pericardiotomy has been reported. 31 The procedure was performed without major complications in all patients; minor complications included fever, which occurred with lesser frequency later in the series when prophylactic antibiotics were routinely administered. There was no recurrence of pericardial effusion or need for surgery in 85% of patients followed for a mean of 5.0 ± 5.8 months. After percutaneous balloon pericardiotomy, 15% required chest tube placement for pleural effusion. In a recent series of 94 patients treated with subxiphoid pericardiotomy for cardiac tamponade of which 64% were malignant effusions, the procedure was successful in all patients with no operative deaths and associated with a rate of recurrent tamponade of 1.1%, in comparison with a recurrence rate of 30% in a nonrandomized concurrent series of 23 patients managed with percutaneous catheter pericardiocentesis. 32 With regard to patients with recurrent malignant effusion, there are multiple small series that discuss the use of intrapericardial sclerosing agents, but there are no prospective randomized series comparing the risks and benefits of catheter pericardiocentesis with and without instillation of sclerosing agents, or comparing balloon pericardiotomy with pericardiocentesis or subxiphoid window.

The pericardial mesothelium actively secretes and metabolizes bioactive molecules, including prostaglandins, nitric oxide, atrial natriuretic peptide, and endothelin-1, which have the potential to modulate cardiac performance via paracrine signaling. 33 In addition, growth factors with the potential to modify underlying myocyte and smooth muscle cell growth appear to be diffused between cardiac tissue and the pericardial space and concentrated in pericardial fluid. Fujita and coworkers 34 demonstrated that concentrations of basic
fibroblast growth factor (bFGF) are about 10-fold higher in the pericardial fluid of patients with unstable angina as compared to patients with nonischemic heart disease, raising the possibility that growth factors concentrated in the pericardial space may mediate collateral blood vessel growth in humans. Thus, the pericardial space may serve as a potential drug delivery reservoir, bathing the cardiac structures with increased myocardial delivery and reduced systemic recirculation. In addition, intrapericardial delivery of FGF-2 has been shown to result in functional angiogenesis in animal models of acute and chronic myocardial ischemia, and percutaneous intrapericardial drug administration in patients with normal pericardium (and in the absence of significant pericardial effusion) has been shown to be feasible.

For these reasons, there is interest in the development of techniques for minimally invasive access of the pericardial...
Anatomy of the Pericardial Space and Its Relation to Epicardial Access

As previously mentioned, the pericardial cavity is a potential space between the parietal and visceral layers of the serous pericardium. It is continuous with the epicardium and reflects around the roots of the great vessels and onto the visceral surface of the fibrous pericardium, which is continuous with the adventitia of the great vessels superiorly and related posteriorly to the bronchi, esophagus, descending thoracic aorta, and mediastinal surface of each lung (Figure 38.1). The phrenic nerves descend between the pericardial cavity and the mediastinal pleural layers that adhere to its lateral sides. 51

The oblique sinus, a recess located behind the left atrium, is formed as the pericardium envelopes the pulmonary veins and vena cava. Within it lies the vein of Marshall, connected by the fetal remnant of the duct of Couvier to the highest left intercostal vein, and draining into the coronary sinus. The transverse sinus is located superior to the heart between the arterial mesocardium, which envelopes the ascending aorta and pulmonary trunk anteriorly, and the venous mesocardium, which covers the superior vena cava (SVC), left atrium, and pulmonary veins posteriorly and inferiorly. 51

Although most of the pericardial cavity can be easily mapped using standard mapping catheters, mapping the posterior wall of the left atrium (LA) can be challenging given the complex pericardial reflections that form the pulmonary vein (PV) recesses and the two major sinuses. On the other hand, the epicardial surfaces of both ventricles are free of reflections and, in the absence of prior severe pericarditis or cardiac surgery, are accessible. This allows for simple manipulation of the mapping/ablation catheter during ventricular epicardial ablation. The inferior and anterior approaches taken during percutaneous epicardial access allow for easier access to the respective surfaces of the heart. 51

Technical Aspects

The technique for safely accessing the normal pericardial space for the purpose of epicardial intervention was first described by Sosa and colleagues using a modification of the traditional method. This approach allows free access to the entire ventricular surfaces, the right atrium, and the majority of the left atrium. 45

Conceptually, entering the pericardial space is as simple as draining pericardial effusions. However, in the absence of an effusion, epicardial access can be intimidating since there is little room for error. The normal pericardial cavity contains only 15 to 35 cc of physiologic fluid with only virtual space. Thus, there is an increased risk of perforating the RV wall and/or of damaging epicardial vessels when attempts are made to access the space percutaneously with a regular pericardiocentesis needle. In a series of 200 patients, Sosa et al. reported a bleeding rate of 10% and “dry” RV puncture rate of 4.5%, which decreased with experience. 45-48 A step-by-step approach is illustrated in Figure 38.11.

After a 3-mm incision is made on the skin of the subxiphoid area using an 11 blade, a blunt-tipped epidural needle (Tuohy) designed to enter virtual spaces is routinely employed. The skin incision is often made to allow easy entry of the needle into the deeper tissues, and this also helps in transmitting the tactile sensation of various structures encountered on the way, especially the contracting walls of the heart. The needle is then advanced gently at an angle (depending on whether an anterior or inferior approach is required) aiming for the left scapula with the patient in the supine position. The preferred entry point is 2 to 3 cm below a line that joins the xiphoid process and the costal margin, left of the midline. Under fluoroscopic guidance, the needle is continually advanced until the operator can feel cardiac motion. X-ray can be deceiving, especially in single view. As the border of the heart is approached, small injections of contrast are made to delineate proximity to the pericardium. 45

It is preferable to perform percutaneous access after induction of general anesthesia as this allows to puncture during apnea, allowing for a more controlled puncture. Some operators prefer the use of conscious sedation to maximize the chance of arrhythmia induction (general anesthesia may potentially limit arrhythmias inducibility in the EP laboratory). A small amount of contrast may then be injected to demonstrate entry of the needle into the pericardial space. Occasionally, the parietal pericardium can be stained and tenting of the pericardium can be seen before the needle suddenly enters the space. The appearance of layering of the contrast medium within the pericardial space indicates that the needle is correctly positioned within the pericardial cavity. This transition into virtual space is usually accompanied by a sensation of “give,” which is noted with experience. 45

Once within the pericardial space, a guidewire is passed through the needle. This step again allows confirmation of entry in the pericardial space. Occasionally, in some patients
Determine the need for epicardial access

Prior h/o cardiac surgery/severe pericarditis

Yes

Surgical subxiphoid access

Insert catheter into space

Advance sheath over catheter into space

Catheter can be carefully manipulated to allow further access

No

Skin incision/manual pressure over skin

Determine anterior vs. inferior approach

Confirm needle tip location with contrast

Confirm needle tip location with contrast

Confirm needle tip location with guidewire

Advance sheath +/- double wire epicardial space

Figure 38.11 Percutaneous epicardial access: a step-by-step approach. As the needle is advanced toward the heart border, location of its tip is confirmed with small injections of contrast.

cardiac motion and/or the sensation of “give” is difficult to perceive and direct entry into the RV cavity may occur inadvertently. In such cases, aspiration of blood or passage of the guidewire into the RV/right ventricular outflow tract accompanied by salvos of premature ventricular contractions indicates entry into the RV cavity. If this occurs, the needle should be slowly withdrawn a few millimeters and the guidewire pulled back into the needle tip and readvanced. This can be repeated until one gains entry into the pericardial space as opposed to withdrawing the needle entirely.

As a general rule, when the guidewire is advanced, it should slide unrestricted over the epicardial surface until it outlines the fluoroscopic left heart border. This is usually achieved and confirmed in the left anterior oblique (LAO) view by advancing the guidewire, forcing it into a loop and observing the loop glide across the various chambers until it outlines the cardiac silhouette. Once the wire position within the pericardial space is confirmed beyond any doubt, the introducer and sheath are advanced over the wire under fluoroscopy maintaining adequate length of guidewire distal to the sheath tip. The introducer/guidewire is then removed and a standard ablation/pig-tail catheter is advanced through the sheath and manipulated into the pericardial space. Double wiring of the epicardial space to avoid inadvertent loss of pericardial access during sheath manipulation is often helpful. The pig-tail catheter is particularly useful to accurately assess the presence of hemopericardium as it has implications for subsequent anticoagulation with heparin.

The guidewire is always advanced under fluoroscopy typically in the AP/LAO projection (Figure 38.12). When the AP projection is chosen, it is difficult to discriminate whether the guidewire is actually in the pericardium along the lateral surface of the LV, or is instead being advanced into a dilated RV and pulmonary artery. The operator can be sure that the guidewire is wrapping around the heart only in the LAO projection. When it does occur, inadvertent RV puncture with the epidural needle or the guidewire does not cause severe complications. However, if the sheath is inadvertently advanced into the RV, surgical repair may be required to control the resulting hemopericardium. Thus, until the location of the guidewire is confirmed by fluoroscopic visualization in an LAO projection, the sheath should not be placed.

Special care should be taken when contrast is injected as it can obscure relevant fluoroscopic details if too much...
Antero-posterior (AP) view of guide-wire through the epicardial needle during an anterior approach forming a large loop (white dashed line) that lies along the cardiac silhouette suggesting pericardial location.

Contrast is used. In this situation, the operator should consider waiting until the contrast dissipates allowing for clear visualization of the cardiac silhouette before attempting another puncture. Some operators try not to use contrast since if no contrast is used the views are preserved. However, it can be difficult to confirm the correct access without contrast, using the current tools.

Contact forces on the epicardial surface can be suboptimal leading to ineffective radiofrequency lesion generation. Although soft-tip long vascular sheaths (e.g., Brite-tip, Johnson & Johnson) are often adequate in most situations, deflectable sheaths (AgilisTM EPI steerable sheath, St Jude Medical) can be used to enhance contact. An important measure when using sheaths is to ensure that the lumen of the sheath is always occupied either with an ablation catheter or a pig-tail catheter so as to prevent the distal edge of the sheath from causing local trauma.

Finally, while the subxiphoid is the most widely used approach, accessing the pericardium across the esophagus, the left lower lobe bronchus, the right atrium, and the anterior mediastinum (reached from a needle directed substernally from a subxiphoid puncture) have been done in experimental animal work or in patients with pericardial effusion. Some of these alternate accesses may have potential for future clinical application in epicardial intervention but at this stage remain experimental.

Anterior and Posterior Approach

Depending on the indication and/or the location of the potential ablation target, either an inferior or an anterior approach to pericardial puncture may be chosen. Typically, an inferior puncture allows for better mapping and ablation of the infero-lateral wall of the ventricles and the posterior wall of the LA and for epicardial LV lead placement. Conversely, an anterior puncture may be preferable when the anterior walls of the heart, such as the anterior RV or the left and right atrial appendages, are the target regions. When needle access is attempted in patients with history of prior cardiac surgery, posterior access may be chosen. In order to enter at the inferior surface of the pericardium, the puncture can be performed in LAO projection because it gives the operator a better view of the inferior wall of the heart. When an anterior puncture is chosen, the entry point should be 3 to 4 cm below the junction of the xiphoid appendage and the costal bone, and the needle should be advanced in a slightly shallow approach angle, often with gentle downward pressure to keep the left lobe of the liver away from the needle path. In this situation, the antero-posterior (AP) projection may facilitate visualization of the free wall of the right ventricle.

When performing an epicardial left atrial appendage (LAA) closure procedure, the anterior approach is mandatory and a more lateral angulation is preferred so as to approach the LAA with the catheters from a more favorable and stable position.

Fluoroscopic Navigation of the Epicardial Space

The right anterior oblique (RAO) and left anterior oblique (LAO) positions project the heart in its anatomic sagittal and coronal planes such that in RAO the left and right sides are superimposed but there is good atrioventricular differentiation, whereas in LAO there is left–right differentiation but the atria and ventricles are superimposed. A catheter placed in the coronary sinus marks the mitral valve annulus from the interatrial septum medially. These landmarks can be used to determine the position of the epicardial catheter as it is navigated within the pericardial space. Once a catheter is inserted into the pericardial space, it can be moved freely laterally, anteriorly, and inferiorly over various parts of the ventricle ranging from the right ventricular outflow tract (RVOT) to the posterior crux. Damage to the coronary arteries during ablation is a major concern, particularly when it becomes necessary to ablate at the base of the heart or septum, for example, the case of accessory pathways that cannot otherwise be ablated with an endocardial or intravenous approach. Fluoroscopic identification of anatomic landmarks, supplemented by intracardiac catheters, including retrograde placement at the aortic root, will help avoid this.
The mitral and tricuspid annuli are intimately related to the major arteries and veins of the heart. The mitral annulus is outlined by the coronary sinus catheter and the tricuspid annulus is identified by the endoluminal diagnostic quadripolar RV catheter, while the septum is defined fluoroscopically by the diagnostic catheter placed in the His-bundle area. Any remaining doubt regarding proximity to a coronary artery should prompt performing coronary angiography. Also it is important to appreciate the close relation of the RVOT to the proximal coronary arteries and distal coronary veins. The LAA is easily reachable and is the first atrial structure to be encountered when a catheter is advanced laterally and cranially; it is identifiable by the characteristic change in intracardiac electrograms. Understanding its fluoroscopic anatomy is important because of its proximity to the RVOT and the proximal coronary arterial system. It should be noted that the left ventricular outflow tract (LVOT) cannot be reached using this approach because it is covered by the RVOT anteriorly and the mitral valve or the left atrium posteriorly.56

The blind-ending oblique sinus, its opening being bounded by the two inferior pulmonary veins, can be reached by passing the catheter superiorly behind the heart. Its importance in the contemporary practice of atrial arrhythmias ablation is related to its unique anatomic location behind the pulmonary venous atrium and the posterior left atrial wall. Within it rests the vein of Marshall, which can itself be a source of arrhythmia amenable to ablation. The esophagus is directly behind the left atrium and is vulnerable to thermal injury.56

The transverse sinus lies superior to the oblique sinus and can be reached by passing the catheter around the lateral wall of the left ventricle and left atrium, and then under the pulmonary arteries. It is of functional importance because a catheter placed at this site may ablate the roof of the left atrium or Bachmann’s bundle which are important sites for certain atrial arrhythmias. It is intimately related to the aorta, which arches around it; the pulmonary arteries; and the left atrium. The floor of the transverse sinus is formed by the pericardial reflection between the right and left superior pulmonary veins, which separates it from the oblique sinus and the roof of the left atrium, which is the location of Bachmann’s bundle. It allows access to the anterior LVOT as it communicates with the epicardial aspect of the noncoronary and right coronary aortic cusps via the inferior aortic recess. It also communicates with the superior vena cava by way of the aortocaval sinus, a small virtual space between the SVC and the ascending aorta, which in some individuals is large enough to bypass with a catheter and reach the right heart border.56

Epicardial Access in Patients with Prior Cardiac Surgery

Postoperative pericardial adhesions were initially thought to be contraindications to percutaneous epicardial access. However, it is possible to perform percutaneous access in these patients although with caution. In this situation, an inferior approach should be used because of the higher density of the adhesions anteriorly, where the pericardial sac is typically opened during cardiac surgery. The amount of exposure to the epicardial surface is often limited when using this technique, typically along the infero-lateral region. Multiple attempts are often needed, and the incidence of complications is usually higher; hence this technique is best reserved for extreme situations where open surgical access is not an option.

A limited surgical approach to gain epicardial access in patients with prior cardiac surgery is safe and feasible.37 The cardiac surgeon typically makes a 3 inch vertical incision along the midline of the epigastrium but veering to the left of the xiphoid process. The pericardium is subsequently opened horizontally, parallel to the diaphragmatic reflection, and the incision is extended to improve visualization of the ventricle. This is followed by blunt dissection of pre-existing adhesions inferiorly so as to expose the maximum possible area of the epicardial surface without either excessive bleeding risk or damage to the bypass grafts. After the ablation procedure, the incision is closed and a pericardial drain is left in place overnight, which is removed the next morning.

In conclusion, the percutaneous epicardial puncture technique is now well established and has been embraced by electrophysiologists owing to the importance of epicardial substrate for arrhythmia ablation and other interventional procedures such as percutaneous LAA occlusion. In experienced hands, it has an acceptable complication rate. It is important to note that this safety profile reflects practices at centers that specialize in arrhythmia management and may not be applicable to less experienced operators or centers. With up to a 20% risk for ventricular perforation, careful patient selection is important, and the procedure should be performed solely by experienced operators with surgical backup.56

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INTRODUCTION

In the three decades since the first report of a catheter-based ablation procedure for medically refractory arrhythmias by Scheinman et al., 1 tremendous advances have been made in the field of interventional cardiac electrophysiology (EP). These advances have been predicated on a dramatic increase in our understanding of arrhythmia mechanisms, normal and abnormal cardiac anatomy, and ablation biophysics. Once these principles were established for any given arrhythmia, surgical procedures were developed to target and interrupt critical portions of the arrhythmia machinery. Following this, catheter-based procedures have been developed to recapitulate the success of the operative approach. This paradigm of progress in EP has occurred for both supraventricular and ventricular arrhythmias.

This chapter focuses on the current state of catheter-based interventions for cardiac arrhythmias, including present and evolving indications, periprocedural considerations, technical issues, outcomes, and complications.

CLASSIFICATION AND MECHANISMS OF ARRHYTHMIAS

All arrhythmias arise as a consequence of disordered electrical impulse formation or disordered impulse propagation. In terms of bradyarrhythmias, the commonest manifestation of the former mechanism is sinus node dysfunction, and of the latter, atrioventricular (AV) block. Permanent pacemaker (PPM) implantation is an adequate therapy for the majority of cases of bradycardia where intervention is required, 2 and is not further addressed here. In terms of tachyarrhythmias, disorders of impulse formation result in focal tachycardias in which centripetal wavefronts emanate from a point-source. The mechanism of the disordered impulse formation may relate to either abnormal automaticity or to triggered activity. Tachyarrhythmias caused by abnormal impulse propagation result from reentry of wavefronts around anatomically and/or functionally determined circuits, and are much more common than focal tachycardias. Reentry requires the presence of longitudinal dissociation of a tissue by either functional or anatomic means such that there are two possible paths for a propagating wavefront to activate. It also requires the presence of unidirectional conduction block to allow for conduction to occur down the nonblocked path in isolation. And, crucially, it also requires the presence of significant slow conduction to allow for recovery of the blocked path by the time the wavefront returns to the original site of block.

Apart from mechanism, tachycardias are also classified into narrow- and broad-complex tachycardia based on the width of the surface 12-lead QRS complex. This in turn is determined by the presence or absence of ventricular activation exclusively over a normal conducting AV nodal His-Purkinje axis. Almost all regular narrow-complex tachycardias are due to supraventricular tachycardia (SVT) in which the tachycardia mechanism involves the atrial and/or subatrical junctional tissue, although it may involve the ventricles in addition. Also, atrial fibrillation (AF) and atrial flutter (AFL) usually present as narrow-complex tachycardia, although they are typically distinguished by marked cycle length irregularity in the former or by the presence of characteristic flutter waves in the latter. Broad-complex tachycardia can be due to ventricular tachycardia (VT), SVT with fixed or functional bundle branch block (also known as aberrant conduction), preexcited tachycardias (in which ventricular activation occurs partially or completely over a manifest bypass tract), paced rhythms, and artifacts. Invariably, the first aim of any procedural intervention for arrhythmias is to categorize and define the precise mechanism for the targeted arrhythmia.
GENERAL PRINCIPLES AND PERIPROCEDURAL CONSIDERATIONS

Most patients with clinical arrhythmias requiring procedural intervention now undergo diagnostic EP studies to define the precise arrhythmia mechanism and then subsequent catheter ablation at the same sitting. Consequently, after case selection, the most important periprocedural consideration is careful examination of all available clinical electrocardiograph (ECG) traces. In many cases, such as with atrial tachycardia, atrial flutter, Wolf-Parkinson-White (WPW) syndrome, or idiopathic VT, an intracardiac ablation target may be defined with great precision before commencing. In SVT and idiopathic VT cases, the ECG of the clinical tachycardia may help in procedural planning such as identifying the need for transseptal puncture, arterial access for left ventricular (LV) ablation, or pericardial access for epicardial ablation. Documentation and diagnosis of clinical arrhythmia events may be essential to accurately interpret the results seen at electrophysiologic testing. Detailed consideration of ECG interpretation is beyond the scope of this chapter but has been extensively reviewed elsewhere.  

One of the reasons for the success of the surface 12-lead ECG in localization of arrhythmias is, in the absence of significant structural cardiac disease, the relatively constant anatomic relationship between the heart, various intracardiac structures, and the thoracic wall. Successful ablation of many arrhythmias requires a thorough spatial understanding of this three-dimensional (3D) geometry. In simple arrhythmias that can be dealt with by focal ablation, such as most forms of SVT, this geometry is generally predictable to the point that advanced individual preprocedural imaging is not required, although most patients undergo noninvasive transthoracic echocardiography to definitively exclude structural heart disease. In these cases, intraprocedural imaging with fluoroscopy alone is usually sufficient.  

For more complex arrhythmias, a transthoracic echocardiogram is a mandatory minimum to confirm the status of valve structures and cardiac function. It will also exclude LV thrombus if catheters are to be placed in that chamber in patients with LV structural heart disease (Figure 39.1).  

For patients with persistent AF a transesophageal echo is required to exclude left atrial appendage thrombus before cardioversion or AF ablation procedures. More complex arrhythmias, such as AF, atypical AFL, and scar-related VT, are often caused by various degrees of myocardial scarring, and usually require additional tools for successful ablation. Chief among these are 3D electroanatomic mapping (EAM) systems. Utilizing either magnetic or impedance-based catheter localization, these allow for the position and orientation of intracardiac mapping catheters to be registered in a virtual 3D geometry of the patient’s heart. The two most commonly used systems are CARTO XP/3 (Biosense Webster, Diamond Bar, CA) and NavX (St Jude Medical, Sylmar, CA). At each registered position of the catheter, the electrical mapping information it contains, for instance the bipolar voltage or local activation time, can be plotted on color-coded 3D maps to allow for rapid assessment of arrhythmia mechanisms, reentrant circuit locations, and substrate characteristics (Figure 39.2).  

The systems allow for significantly lower ionizing radiation exposure for both the patient and the operator. For complex arrhythmias, preprocedural imaging with computed tomography (CT) or cardiac magnetic resonance (CMR) imaging has become widely used. The latter is particularly useful in view of the ability to directly visualize fibrosis by employing delayed gadolinium enhancement (DGE) techniques. The CT or CMR geometry may also be imported into the virtual geometry created by the EAM system, a process known as image integration. Also, real-time imaging during the procedure with intracardiac echocardiography (ICE) has become increasingly deployed. This assists with catheter manipulation, defining manipulation, obtaining transseptal or pericardial access when required, visualizing catheter contact, assessing lesion formation, and continuous online monitoring for complications such as cardiac perforation, pericardial tamponade, and pulmonary vein stenosis.  

Interventional EP procedures are generally performed via the femoral venous route, although sometimes jugular, subclavian, arterial, or percutaneous direct pericardial access may be required. The initial aims are to study the arrhythmia substrate and then to induce the clinical tachycardia so that its precise mechanism can be defined. This is accomplished by means of an EP study in which multipolar intracardiac recording catheters are placed in strategic locations such as in the coronary sinus (CS) and at the His bundle recording position.
The baseline properties of refractoriness and conduction in the atrium, ventricle, atrioventricular (AV) junction, and His-Purkinje system are then defined using a sequence of pacing maneuvers known as programmed stimulation. The clinical tachycardia is often induced during process, but sometimes beta adrenergic stimulation using isoproterenol is required before induction attempts are repeated. After arrhythmia induction, the patient is examined for evidence of hemodynamic tolerance before proceeding further. The tachycardia is first studied in its unperturbed state to attempt to reach a diagnosis. For this, the mode of induction, the surface ECG morphology and characteristics, the cycle length and any irregularity, zones of transition, the AV relationship, the atrial and ventricular activation sequence, and the mode of termination are all carefully examined. Thereafter, the response of the tachycardia to well-established pacing maneuvers is studied and a diagnosis established.

Clinical management of patients during these procedures is often complex. The demands of patient tolerance and catheter stability have to be balanced with the detrimental effects of sedation and anesthesia on tachycardia inducibility and hemodynamic stability. The latter is of particular concern during scar-related VT ablation in patients with dilated ventricles and poor systolic function. Outside of the pediatric setting, the majority of adult EP procedures are carried out under conscious sedation, with one noticeable exception being AF ablation where a randomized comparison has shown better outcomes with general anaesthesia. While hemodynamic tolerance is not an issue for most SVT procedures, either inotropic or mechanical circulatory support is often required for scar-related VT ablation, both to allow for catheter mapping during VT or to improve the patient’s general circulatory status during what are often long and complicated procedures. This may be in the form of an intracardioc balloon pump (IABP) or a percutaneous ventricular assist device (VAD).

While right-sided arrhythmia mechanisms are readily accessible to transvenously placed catheters, mapping and ablating arrhythmias in the left atrium or left ventricle require either a retrograde transaortic approach (usually via the common femoral artery) or a transseptal puncture. Retrograde approaches are technically more demanding for the ablation of most left-sided SVTs and hence electrophysiologists have become very comfortable with obtaining transseptal access with the assistance of one or more of (i) a His-bundle recording catheter to mark the position of the noncoronary aortic sinus of Valsalva; (ii) radiocontrast administration to stain the interatrial septum and to ensure safe advancement of the needle/sheath assembly; (iii) ICE or transesophageal (TEE) online imaging guidance; and (iv) needle tip manometry. Further technical descriptions of transseptal techniques are found in Chapter 6.

Some complex EP procedures require access to the pericardial space to enable epicardial mapping and ablation. The percutaneous approach to pericardial access was pioneered by Sosa et al.11 in the context of Chagas disease (and its associated epicardial VTs) and is now performed routinely by electrophysiologists. Under fluoroscopic guidance and after complete reversal of any anticoagulation, a 17G Tuohy needle (with anatraumatic curved tip) is advanced via the subxiphoid space into the triangle of Larry until a characteristic pop is felt as the fibrous pericardium is breached. A small volume of radiocontrast is then injected to confirm the characteristic pericardial layering of contrast and then a super-stiff, exchange-length 0.035 inch guidewire is advanced. Crucially, as during routine pericardiocentesis, guidewire placement is then confirmed in the left anterior oblique projection to ensure that it is contained within the outline of the pericardium and that it has crossed the boundaries between all four cardiac chambers, hence excluding the possibility of it being intracardiac (Figure 39.3). A sheath is then advanced and its side arm aspirated to exclude significant bleeding. If inadvertent right ventricular (RV) puncture occurs, the needle is simply withdrawn slightly and the pericardial space rewired. Apart from RV laceration, additional risks of pericardial access and epicardial ablation include intra-abdominal bleeding, coronary artery injury and occlusion, phrenic nerve injury and failure of access due to prior surgery, radiation, or pericarditis. However, the risk of these complications is

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**Figure 39.2** Electroanatomic activation mapping of a reentrant left atrial tachycardia revolving around the right-sided pulmonary veins is displayed. A preoperative CT of the left atrium has been integrated with the map by acquiring fiducial points, such as at the pulmonary vein ostia, and merging these landmarks as well as chamber surfaces with the segmented CT geometry. Activation times relative to a fixed intracardiac reference (usually a coronary sinus recording from a stable multipolar catheter placed there) are displayed in color-coded format with earliest times being shown in red and later times in blue.
pulmonary veins. Appropriate balloon sizing, placement, and pacing are required to avoid right phrenic nerve injury associated with right superior pulmonary vein isolation. Although not an energy source per se, there is a niche role for intracoronary ethanol in the treatment of select intramural VT substrates not accessible by either endocardial or epicardial ablation.

### SUPRAVENTRICULAR TACHYCARDIA

In adults, three main tachycardia mechanisms comprise the vast majority of SVT cases: atrioventricular nodal reentrant tachycardia (AVNRT), atrioventricular reentrant tachycardia (AVRT), and atrial tachycardia (AT). Junctional ectopic tachycardia is a rare diagnosis in adults and is seen much more frequently in the pediatric context. Recent data from a large center showed that AVNRT accounted for 56% of SVT, with AVRT seen in 27%, and AT in 17% overall, although there was a significant age and gender influence observed.

Most patients with palpitations and SVT have a benign prognosis, particularly if there has been no history of syncope or hemodynamic compromise. This also applies to patients with WPW syndrome. These patients are given a choice of management strategies including (i) ongoing observation only; (ii) regular medication to suppress SVT such as verapamil, metoprolol, or flecainide; (iii) intermittent medication to be taken at the time of an episode (the so-called pill-in-the-pocket approach); or (iv) electrophysiologic evaluation with a view to catheter ablation if the target can be appropriately identified. Most patients who come to medical attention are symptomatic enough that they would like treatment. The very high success rate of catheter ablation in treating most underlying mechanisms of SVT and WPW and the low incidence of complications mean that the vast majority of patients prefer this approach to lifelong medication. The joint American College of Cardiology (ACC) and American Heart Association (AHA) Task Force guidelines give catheter ablation a class I indication for symptomatic SVT or WPW that is “drug-resistant or the patient is drug intolerant or does not desire long-term drug therapy.”

#### Atrioventricular Nodal Reentrant Tachycardia

The exact mechanism of AVNRT remains unclear despite many decades of detailed research, and despite the existence of a routine ablation procedure that has a 98.5% long-term cure rate. While it is generally agreed that the AV node has functional longitudinal dissociation in patients with AVNRT, the degree of involvement of subnodal atrial tissue in the reentrant circuit is still debated. The footprint of this longitudinal dissociation during EP testing is the presence of AV...
node duality in which at least one discontinuity is seen in the curve representing the output of the AV node to increasingly premature atrial extrastimulus testing. This is represented schematically as a so-called fast pathway that displays rapid conduction velocity but relatively longer refractoriness, and a slow pathway that has slower conduction but shorter refractoriness. In the basal state, conduction proceeds down both pathways but only fast pathway activation is manifest on the surface ECG. Classically, at a critical prematurity of atrial extrastimulus, unidirectional conduction block occurs in the fast pathway due to its longer refractory period and activation proceeds only down the slow pathway resulting in a long PR (or AH) interval. If the fast pathway has recovered excitability by this time, retrograde conduction to the atrium can occur over it, resulting in an “echo beat” with a very short RP interval, and sustained AVNRT if the cycle repeats itself. The very short RP interval means that atrial and ventricular activation is simultaneous and the narrow retrograde septal P wave is either difficult to discern on the surface ECG, or is seen as a small terminal inscription on the QRS complex (pseudo-S-wave in lead II and R’ in V1).

Catheter-based interventions for selective ablation of the AVNRT circuit without producing AV nodal block have been sought from the time Ross et al. pioneered the surgical technique of dissection in the triangle of Koch (which is formed by the CS os, the tricuspid annulus, and the tendon of Todaro) at the site of earliest atrial activation during tachycardia. Initial attempts targeted the fast pathway located in the anterior portion of the triangle. This was effective but resulted in an unacceptable incidence of AV block. The standard technique in use today is selective ablation or modification of the slow pathway with a procedural endpoint of tachycardia noninducibility. This was first described in 1992 by Jackman et al. They mapped and targeted high-frequency potentials located in the posterior region of the triangle of Koch (between the CS os and the tricuspid annulus) during sinus rhythm. Although these and other investigators found evidence linking these abnormal potentials to the tachycardia circuit, subsequent high-density array mapping of the triangle of Koch during surgical slow pathway ablation by McGuire et al. proved these potentials to be related to asynchronous muscle bundle activation around the CS os and not pathogenic for tachycardia. Currently, the most widely used method of slow pathway mapping is largely anatomic with the ablation catheter positioned just outside the CS against the septal tricuspid annulus in a position where a sharp but low-amplitude atrial electrogram is located along with a large ventricular signal. If RF applications (40 to 50 W power) here are not successful, the catheter is moved slightly superiorly in the triangle and energy delivery is repeated. At successful sites, longer and slightly faster runs of junctional rhythm are usually obtained compared to unsuccessful sites where only isolated junctional beats or slow junctional rhythm is seen. Very fast junctional rhythm during ablation may be a risk for impending AV block however, and applications are ceased immediately if this is seen. Ablation is also immediately discontinued if VA block is seen during junctional rhythm as this is a marker of impending antegrade heart block. After successful RF applications have been delivered, EP testing is repeated to assess for residual slow pathway function on and off isoproterenol. Multiple series have shown that AVNRT recurrence after slow pathway ablation (which is less than 2%) is not predicted by the presence of either residual slow pathway conduction or single echo beats. Consequently, AVNRT noninducibility remains the most important procedural endpoint. The success and safety of slow pathway RF ablation is not less favorable in the elderly either and is a first-line option across all age groups.

Aside from more minor complications such as venous access site bleeding, the main material risk to patients undergoing slow pathway ablation for AVNRT is inadvertent AV block. Various studies initially suggested this to be less than 1% but more recent, large single-center series have shown an even lower rate of persistent AV block requiring permanent pacing of 0.07%. Strategies to minimize the risk of AV block with RF ablation include the use of long preformed sheaths to increase catheter stability and, in difficult cases, the use of general anesthesia to allow for reduced cardiac motion with respiratory excursion. Alternatively, and particularly in the pediatric context, cryoablation may be considered a safer, although less effective option for slow pathway ablation.
present as broad-complex tachycardias on ECGs since they do not activate the ventricle over the normal AVCS. One of these is a form of AVRT that, in contrast to ORT, displays antegrade activation down the manifest BT and through the ventricle before proceeding back to the atrium via retrograde conduction up the normal AVCS. This is known as antidromic tachycardia (ART) and presents clinically as a broad-complex tachycardia resembling some basal forms of VT. In a variant of ART, retrograde conduction may be up a second BT rather than the AVCS. Apart from ART, other forms of preexcited tachycardias involve bystander activation of the ventricle over the BT. These include preexcited AVNRT, preexcited AT, and preexcited AF. The latter rhythm in particular may be lethal if the antegrade conduction characteristics of the BT allow for extremely rapid ventricular activation that may degenerate to ventricular fibrillation. This probably accounts for the small incidence of sudden death seen with WPW, though this risk is not high enough to justify routine ablation of asymptomatic patients with preexcitation.31,32

Adequate preprocedural planning, ECG interpretation, and anatomic understanding are important factors in catheter ablation of BTs. Due to reasons of embryogenesis, the AV valve annuli are the commonest locations of BTs, although less common sites such as the right and left atrial appendage, the aortic sinuses of Valsalva, and the coronary venous system can be involved. BTs are 5 to 10 mm in length and 0.1 to 7 mm in diameter, and generally traverse the epicardial AV groove subjacent to the overlying fat pad.33,34 The majority of BTs are related to the mitral annulus, although rightsided and septal BTs account for up to 46%.35 To eliminate a left-sided BT the operator must decide between transseptal and retrograde approaches, both of which have been shown to be equally effective.36 However, once at the mitral annulus, catheter stability is easily maintained and mapping and ablation are generally uncomplicated. In contrast, right free wall BTs, while easily accessed from the venous approach, are technically much more challenging due to the difficulties associated with stable catheter contact on the highly mobile tricuspid annulus. This is reflected in the lower acute success rate of ablation and higher recurrence risk compared to left-sided BT.37 Importantly, there is a well-described association between right-sided BTs (often multiple) and Ebstein anomaly, a situation of much greater anatomic and electrophysologic complexity because of the shift in the anatomic location of the tricuspid valve and the ventricularization of atrial myocardium. A lower acute and chronic success rate for catheter ablation in this context is minimized by careful identification of the AV groove.38

Although surface ECG algorithms can regionalize the BT site well enough to guide and streamline the mapping process,3 precise localization requires intracardiac mapping with an EP catheter. The most commonly used technique for this relies on the determination of the site of the earliest atrial electrogram during retrograde BT conduction, or of the site of earliest ventricular activation pre–delta-wave during antegrade conduction over a manifest BT. At such sites, the relative timing of the local atrial and ventricular activation may be short or fused. A short AV interval is not used as a mapping criterion for precise localization because synchronous activation of late signals on either side of the annulus may also give rise to such short intervals away from the BT location. If mapping occurs during atrial or ventricular pacing, a degree of fusion may occur between wavefront conduction down the BT and the normal AVCS. This may not be a problem for BTs located far from the AVCS but can complicate mapping paraseptal BTs. If earliest electrograms are mapped during orthodromic tachycardia, fusion of wavefronts will not be a problem since retrograde activation occurs entirely over the BT. As sudden tachycardia termination with ablation may result in catheter movement from the site before fulguration is complete, ablation may be best performed during pacing and not SVT. The second technique for BT localization relies on recording a sharp bipolar potential between the atrial and ventricular electrograms that represents depolarization of the BT itself. Such potentials are usually obscured if the interval between atrial and ventricular signals is short. As the majority of BTs actually pursue an oblique course across the AV groove, changing the direction of pacing wavefronts can result in lengthening of the local VA or AV interval, unmasking the obscured BT potential.39

There are several special situations in BT ablation where particular difficulties and risks are encountered. Septal BTs are an obvious example where the risk of AV block can be significant. Due to their proximity to the compact AV node, this risk is probably greatest for midseptal BTs.39 Anteroseptal BTs are often located in very close proximity to the penetrating bundle of His, where they are sometimes called parahisian BTs. This is particularly the case if a His potential is seen on the ablation catheter at the successful ablation site. Although there are no conclusive data, the risk of AV block is probably less than it is with midseptal BTs as the fibrous tissue sheath in which the His bundle resides may exert a protective effect. Due to the contiguous proximity of the His bundle and the aortic root, anteroseptal BTs can be mapped and ablated from the noncoronary aortic sinus of Valsalva.40

Notwithstanding the risk of AV block with midseptal and anteroseptal BTs, it is widely considered that posteros- septal BTs are the most challenging to ablate. They account for around 25% of BTs in most series, and they cause difficulty due to the anatomic complexity of the 3D region in which they reside, the pyramidal space. This is located at the inferior crux of the heart and is a region where all four cardiac chambers (or five if the CS with its contractile muscular coat is also considered a chamber) abut each other. It contains autonomic ganglia, epicardial fat, the left and right posterior extensions of the AV node, and most critically, the branches of the distal right coronary artery including the AV nodal artery.41 Most posterosseptal BTs course obliquely through the pyramidal space from the right
atrium to the posterosuperior process of the left ventricle. Some posteroseptal BTs result from epicardial muscular connections between the coats of the coronary venous system (the CS and the middle or posterior cardiac veins) and the left ventricle. The Oklahoma group found that 21% of these epicardial sinoventricular connections were associated with a CS diverticulum. While some posteroseptal BTs may be readily ablated from the inferoseptal tricuspid annulus, below the CS os, many require extensive mapping from transseptal, retrograde, subclavian, CS, middle cardiac vein, or even percutaneous epicardial approaches. Some posteroseptal BTs have decremental conduction and may be responsible for a near incessant orthodromic tachycardia, more commonly in children, known as the permanent form of junctional reciprocating tachycardia (PJRT). This can cause a tachycardia-mediated cardiomyopathy and ablation has been well documented to reverse the depressed LV function.

Atriofascicular BTs account for no more than 2% to 3% of all BTs but are notable for their fascinating anatomy and physiology, best described as a duplicated accessory AV nodal conduction system located on the free wall of the tricuspid annulus. They are usually long fibers that extend from the posterolateral tricuspid annulus to their commonest insertion into the distal ramification of the right bundle branch. These BTs are known colloquially (and incorrectly) as Mahaim fibers. They are notable for having antegrade-only, decremental conduction, sometimes with marked longitudinal dissociation. Their very slow conduction generally means that sinus rhythm ECGs have minimal or absent signs of preexcitation as most of the ventricular mass has been depolarized by the wavefront preceding down the normal AVCS before the atriofascicular wavefront can manifest. The absence of retrograde conduction means that orthodromic tachycardia is not possible, and the clinical arrhythmia they most commonly cause is an antidromic tachycardia in which antegrade activation is over the atriofascicular fiber and retrograde conduction is via the AVCS. This is manifest on the surface ECG as a late-transition left bundle branch block (LBBB) morphology broad-complex tachycardia. These atriofascicular pathways are mapped by searching for the large BT potential (analogous to a His potential) that they exhibit on the posterolateral tricuspid annulus, usually with the assistance of a multipolar catheter placed around the annulus. The main challenge in catheter ablation for atriofascicular BTs is, like all right free-wall BTs, catheter stability on the mobile tricuspid annulus that can be aided by using sheaths to support the flippier catheter tip. In addition, these BTs are superficial structures that are extremely vulnerable to catheter trauma, which can frustrate mapping attempts by causing them to transiently disappear during the procedure.

The overall success rate in catheter ablation of BTs approaches 93% to 98% long-term with a 2.2% redo rate for recurrence. However, success rates can be as low as 88% for posteroseptal BTs. The rates of major complication range from 0.6% to 1% in large, multicenter series with cardiac tamponade and heart block (parahisian BTs) being the commonest serious adverse events.

**Focal Atrial Tachycardia**

Focal AT accounts for 5% to 15% of SVTs in patients undergoing catheter ablation. The electrophysiologic mechanism can be a result of abnormal automaticity, triggered activity, or microreentry, and a variable response of the tachycardia focus to adenosine has been described as a result. Focal ATs do not arise randomly from all over the atria and are instead clustered around classic sites of anatomic heterogeneity. In the right atrium these include the crista terminalis, the tricuspid annulus, the CS os, the right atrial appendage, and the parahisian/perinodal regions. The latter can often be successfully and safely ablated from the noncoronary aortic sinus of Valsalva (Figure 39.4). In the left atrium, commonest sites of origin are the pulmonary veins, followed by the fossa ovalis and mitral annulus at the aortomitral continuity, the rest of the mitral annulus and CS, and the left atrial appendage.

Some focal ATs can be notoriously difficult to induce, particularly those due to triggered activity and liberal doses of catecholamines may be required in addition to burst pacing or programmed stimulation. This is often the biggest challenge in successful ablation as mapping can be almost impossible with noninducible or nonsustained tachycardia, and the ablation endpoint is uncertain. On the other hand, some focal AT sites of origin, particularly the atrial appendages, are associated with incessant tachycardia and the risk of development of tachycardia-mediated cardiomyopathy.

The most important step once focal AT has been proven by pacing maneuvers as the tachycardia mechanism is to analyze the P wave morphology. Transient AV block may need to be induced by rapid ventricular pacing if the P wave is obscured by the preceding T wave. In the absence of structural heart disease, the P wave morphology is a very reliable guide to the site of origin of focal AT. Also, the P wave onset must be defined relative to a fixed intracardiac fiducial reference signal (e.g., the CS os) as most successful ablation sites precede the P wave onset by 20 to 30 ms. Point by point activation mapping can then be targeted to the site of origin defined by the P wave, often assisted by 3D mapping systems. At successful sites the onset of RF energy delivery is often marked by an acceleration of the tachycardia, bipolar signal attenuation, and then abrupt termination. The published success rates of catheter ablation for focal AT are variable (69% to 100%) and largely reflect difficulties related to reliable induction of sustained tachycardia, catheter stability at some sites such as the tricuspid annulus or right atrial appendage, and proximity to sensitive structures such as the AV node.
Ablation of a focal parahisian atrial tachycardia from the noncoronary aortic sinus of Valsalva. The P wave morphology is shown in Panel A with a multiphasic configuration in V1. Panel B displays an electroanatomic activation map merged into a preacquired CT geometry with the segmented ventricle removed. The red zone in the noncoronary aortic sinus of Valsalva represents the earliest breakthrough of the tachycardia with later activation seen on either side of the interatrial septum. The fluoroscopic catheter position at the successful ablation site is depicted in Panel C, in close proximity to the His catheter.

**MACROREENTRANT ATRIAL TACHYCARDIAS**

**Nomenclature**

A number of different names have been given to tachycardias whose basic mechanism consists of large loop reentry around the right or left atria, referred to here as macroreentrant atrial tachycardia (MRAT). They can be divided into two main groups, cavotricuspid isthmus (CTI)-dependent tachycardia and non-CTI-dependent. The former group accounts for the vast majority of MRAT, and consists of typical AFL, reverse typical AFL, and lower loop reentry. Broadly speaking, non-CTI-dependent MRAT is often called atypical flutter, and is due to large right or left atrial circuits related to the presence of atrial scarring. The use of the term “atrial flutter” in describing MRATs has come to describe a surface ECG atrial activation pattern of continuous undulation of the baseline.

**Cavotricuspid Isthmus-Dependent Flutter**

The reentrant circuit of typical AFL has been well characterized. It consists of a large loop rotating around the counterclockwise tricuspid annulus and confined entirely to the right atrium with left atrial activation being passive. The wavefront exits the narrow protected slow zone just posterior to the coronary sinus os, travels up the septum, down the free wall anterior to the crista terminalis, and then travels through the CTI before exiting toward the coronary sinus os again. This circuit determines the classic P wave morphology of typical flutter with an isoelectric/positive pattern in V1.
and steep negative forces in the inferior leads. Reverse typical flutter utilizes the same circuit in the opposite clockwise direction. Since the circuit is constrained by the same anatomic barriers in all patients, in the absence of conduction-slowing medication, human AFL has remarkably constant cycle length around 200 to 240 ms.

Also known as the subeustachian isthmus and being formed by thick trabeculated muscle bundles extending from the bottom of the crista terminalis, the CTI is the narrow rim of tissue that lies between the os of the inferior vena cava (IVC) and the tricuspid annulus. This is the narrowest portion of the typical flutter circuit and the point where it is most vulnerable to interruption. Anatomic studies have shown the variability of CTI anatomy with the frequent presence of thick ridges and pouches.

Ablation of typical and reverse typical AFL (as well as a related rhythm called lower-loop reentry which rotates around the IVC) targets the CTI. Since the target is already known, and if the diagnosis has been made by the surface ECG morphology, patients do not need to be in flutter at the time of the procedure and ablation can occur in sinus or atrial paced rhythm. Using either a large tip or irrigated catheter, a linear lesion is created between the tricuspid annulus and the IVC. Flutter will usually terminate toward the end of this process if it was present at the start of the procedure. Acute termination and noninducibility of AFL is not a satisfactory endpoint however, as recurrence is common in this setting. Ablation is thus continued until conduction block is proven across the CTI from both medial and lateral to the linear lesion, the so-called bidirectional block.62 With the use of this endpoint, CTI-dependent AFL recurs in less than 4% of patients during long-term follow-up60 with an incidence of serious complications of less than 0.5%.20 This means that catheter ablation can be offered as an upfront alternative to less effective long-term suppressive drug therapy for typical AFL. Given the fact that most episodes of clinical typical AFL are induced by a burst of AF however, it should be remembered that patients with successful CTI ablation are still at risk for the development of AF over the subsequent years.62 This has implications for their long-term thromboembolic risk and thus close surveillance is warranted after AFL ablation.

**Atypical Atrial Flutter**

The common pathogenic factor underlying most MRAT not involving the CTI is the presence of some form of atrial scarring. It is well recognized that congenital and valvular heart disease, as well as the surgical procedures performed to correct them, can cause significant atrial fibrosis, as can surgical or catheter ablation procedure to treat AF.64-66 It is less recognized that some patients may have idiopathic spontaneous right or left atrial scar (perhaps related to prior episodes of atrial myocarditis) that forms the substrate for atypical flutter.67,68 MRAT circuits can be formed by fixed or functional barriers within a patch of scar, between patches of scar, or between scar and anatomic barriers such as the IVC or a valve annulus. Often in this context, simultaneous dual-loop or figure-of-eight circuits are present with two reentrant loops sharing a common isthmus such as occurs with a circuit revolving around a free-wall atriotomy scar coexisting with CTI-dependent typical flutter.

Ablation of atypical flutter requires a flexible, tailored approach to each individual case. In most cases, tachycardia induction is first performed using programmed stimulation or burst pacing. The P wave morphology is often unhelpful in the presence of significant structural atrial disease, and so close attention is paid to the recordings from multipolar catheters in order to deduce general facts about the rhythm. For example, a distal-to-proximal coronary sinus activation sequence largely excludes a right atrial MRAT. Overdrive pacing and entrainment maneuvers can be used to try to determine the specific regions likely to be involved in the reentrant circuit. In many instances, a detailed 3D electroanatomic activation map is constructed with point-by-point signal acquisition and annotation during tachycardia (Figure 39.5). Analysis of the voltage data contained in these maps also allows precise reconstruction of the atrial scar and any higher voltage conduction channels contained within it.65 Some combination of entrainment and activation mapping usually allows the reentrant circuit to be characterized. Since most of the MRAT are sizeable, entrainment from four sites including the CTI area, the proximal and distal CS, and a roof site between the pulmonary veins can quickly establish the mechanism and location of the reentry circuit.
of the circuit. The ablation strategy to eliminate MRAT usually consists of linear lesion delivery to interrupt the circuit (or circuits) at the narrowest or most vulnerable location. Often multicomponent, long-duration, low-amplitude fractionated electrograms are recorded at these sites, reflective of the slow scar-related conduction present here. The linear lesions need to be extended to achieve block between fixed anatomic and scar barriers. For example, right atrial free-wall MRAT revolving around an atriotomy scar usually requires a linear lesion connecting the bottom of the scar with the IVC, while perimital flutter revolving around the mitral annulus, is treated with a mitral isthmus linear lesion connecting the mitral annulus with the left inferior pulmonary vein or less commonly the right or left superior pulmonary vein. Usually the CTI line is also ablated at the same sitting due to the high incidence of typical flutter coexisting in these patients. And similar to the situation with typical flutter, the best electrophysiologic endpoint for these procedures is bidirectional conduction block across the particular linear lesion deployed. In the context of right atrial free-wall MRAT, this has been shown to predict complete freedom from flutter recurrence at medium-term follow-up.69

**ATRIAL FIBRILLATION**

The indications for catheter ablation in patients with AF are currently more conservative than they are for SVT, reflecting the fact that it is a more extensive procedure with a lower single-procedure success rate compared to most SVT ablation. Current recommendations suggest that most patients with symptomatic AF fail treatment with at least one antiarrhythmic drug before being offered AF ablation.70 With ongoing procedural evolution and improving efficacy, catheter ablation will be offered earlier to a wider array of patient groups. The question of whether there are long-term benefits of AF catheter ablation on stroke risk and mortality is currently the focus of large randomized trials.

A complete understanding of the complexities and mechanisms underlying human AF remains elusive despite more than a century of research. This has hampered efforts to develop a procedure with uniformly durable success rates, although great progress has been made. The modern era of catheter ablation for AF began with the seminal realization by Haissaguerre et al. in the late 1990s of the central role played by pulmonary vein muscle sleeve triggers in initiating most episodes of paroxysmal AF.71 Fifteen years later, the elimination of these triggers remains the sine qua non for every AF catheter ablation procedure. This was initially achieved through the mapping and ablation of these triggers deep within the pulmonary veins but this was associated with a high rate of pulmonary vein stenosis. The deployment of antral lesion sets to electrically isolate the veins has greatly reduced the risk of this complication22,73 (Figure 39.6).

Pulmonary vein isolation (PVI) can be performed under sedation or general anesthesia, although some recent randomized data suggest improved outcomes with the latter, perhaps due to increased catheter stability.9 Many operators employ some form of preprocedural imaging that can be integrated with the EAM system in order to help with anatomic definition and reduce fluoroscopic screening times.74 The use of ICE also helps in this regard,9 Thromboembolic risk during the procedure is minimized by the use of therapeutic levels of warfarin (with the role of novel oral anticoagulants undefined at present), unfractionated heparin to target an ACT of >350 seconds or even >400 ms if there are risk factors such as a very large left atrium (LA) or spontaneous echo contrast, and continuous irrigation of long sheaths. After placement of two sheaths in the left atrium by transseptal puncture, a circular mapping catheter is deployed to record pulmonary vein potentials along with an irrigated ablation catheter. An online virtual 3D geometry of the left atrium (and especially of the pulmonary vein antra) is then acquired and integrated with any preoperative CT or MR images. Point-by-point lesions are then deployed in a proximal, circular or oval fashion with lower power and esophageal temperature monitoring and direct echo imaging of the posterior wall where the esophagus is in close proximity. Along the anterior wall of the right veins the phrenic nerve may be damaged and pacing is routinely performed before lesion placement to identify phrenic nerve stimulation and the potential for injury with ablation. Newer balloon-based technologies for this purpose are also being developed, including the cryoablation and laser balloon
catheters. The procedural endpoint for PVI is the achievement of pulmonary vein entrance and exit block, ideally persistent through a waiting period and durable despite provocation with isoproterenol and adenosine. Although nearly 100% of patients leave the laboratory with electrically isolated veins, a significant clinical AF recurrence rate of up to 30% is noted during follow-up, including late after the index procedure where an up to 7% per year recurrence risk has been noted. The mechanism of recurrent AF in essentially all these patients is pulmonary vein reconnection and repeat PVI alone is effective.

Persistent AF is a more complicated electrophysiologic phenomenon than paroxysmal AF and it is characterized by a greater degree of substrate evolution favoring AF maintenance (“AF begets AF”). The abnormal substrate manifests initially as ion channel remodeling with changes in refractoriness and conduction followed by increased left atrial stretch and progressive diffuse fibrosis throughout the chamber. Elimination of pulmonary vein triggers by segmental isolation alone has been shown to have a lower success rate in this context than in paroxysmal AF. However, antral isolation in some series has been associated with reasonable outcome for persistent AF, possibly due to some degree of substrate modification with more proximal isolation. Most laboratories deploy additional lesions for persistent AF ablation compared to paroxysmal AF. These include ablation of non-pulmonary-vein triggers, debulking of complex fractionated atrial electrograms, linear ablation such as mitral isthmus or roof lines, superior vena cava isolation, autonomic ganglion ablation, and, more recently, rotor mapping and ablation. Many laboratories incorporate various combinations of these but systematic data showing the superiority of any given approach are lacking. There is universal agreement, however, that durable PVI remains the cornerstone of any AF ablation strategy.

As the worldwide experience with the procedure has increased, the complications of AF ablation have become rarer and better understood. The most recent worldwide multicenter survey suggested a major complication rate of 4.5%. Stroke and atrioesophageal fistula (due to the close proximity of the esophagus to the posterior left atrial wall) remain the most feared complications and obsessive vigilance to anticoagulation and lesion delivery respectively are needed to prevent them. Of note, in young patients with paroxysmal AF and no structural heart disease, major complications are very rare.

VENTRICULAR TACHYCARDIA

The management of VT has evolved considerably over the past four decades, and a deeper understanding of its classification, natural history, mechanisms, and pathogenesis has underpinned this progress. The majority of VT occurs in the presence of structural heart disease where it can cause sudden cardiac death.

Indications for Ventricular Tachycardia Ablation

Implantable Cardioverter-Defibrillator (ICD) Shocks and Storm

The majority of patients requiring catheter ablation for scar-related VT have an ICD in situ and the indication in this context is usually recurrent appropriate ICD shocks. Given its clinically demonstrated success in reducing or eliminating recurrent ICD shocks, the main indication for catheter ablation in these patients remains the presence of frequent appropriate ICD therapies for VT despite antiarrhythmic drug use. However, an increasing body of evidence supports an earlier approach to catheter ablation to prevent ICD shocks.

The presence of three or more shocks in a 24-hour period is known as electrical storm and along with antiarrhythmic drugs, intubation, and deep sedation, and in selected patients neuraxial modulation with either thoracic epidural blocks or stellate ganglionectomy, catheter ablation is an important management option for these patients. Carbucicchio et al. treated 95 patients with VT storm and were able to acutely suppress arrhythmias in all of them, achieving a 92% rate of freedom from recurrence of electrical storm and a 66% rate of VT suppression over a median 22-month follow-up. Despite these outcomes, patients with scar-related VT are usually not referred for ablation until late and often only after recurrent ICD shocks on amiodarone, with a recent series showing electrical storm as the indication for VT ablation in 58% of patients.

Sustained Monomorphous Ventricular Tachycardia

Sustained monomorphic scar-related VT may also be treated with ablation early in its clinical course prior to ICD insertion. Though controversial and not yet supported by randomized data, some investigators have suggested that selected patients with hemodynamically tolerated VT, circumscribed infarction, and relatively preserved ejection fraction generally have a sufficiently good prognosis to undergo ablation as a stand-alone therapy without placing an ICD. Idiopathic VT generally has a benign prognosis and in the absence of structural heart disease, can undergo stand-alone ablation or medical therapy without need for an ICD. Catheter ablation is a first-line option for patients with idiopathic VT and no structural heart disease because of its high success rates and low complication rate.

Polymorphic Ventricular Tachycardia and Ventricular Fibrillation

Some patients with polymorphic VT (PVT) and VF seem to have a monomorphic triggering premature ventricular complex (PVC), and these often originate from Purkinje fibers or from the RV infundibulum. Such focal triggers of PVT and VF can be seen in the context of coronary disease.
channelopathies, and in patients with idiopathic VF. Mapping and ablation of these triggering foci is not only acutely effective, but has also shown excellent long-term freedom from PVT and VF recurrence.

Symptomatic Premature Ventricular Complex versus Ectopy-Mediated Cardiomyopathy

In most cases, ventricular ectopy is a benign phenomenon but can be associated with significant patient symptoms that may be refractory to antiarrhythmic medications. In such instances, PVCs may be targeted and ablated for symptomatic reasons. However, in two situations, PVC ablation may be considered for prognostic reasons: first, when PVCs are triggering PVT or VF as outlined above, and second, when frequent PVCs may be the putative mechanism behind a reversible form of cardiomyopathy. This ectopy-mediated cardiomyopathy may have several mechanisms including cardiomyocyte calcium overload (similar to tachycardia-mediated cardiomyopathy), effective bradycardia, or ventricular dyssynchrony although the exact determinants are uncertain. Catheter ablation of frequent PVCs has been documented to lead to improvement of ventricular systolic performance and cardiomyopathy resolution.

Preoperative Ventricular Tachycardia Localization

The utility of the ECG in planning VT ablation procedures cannot be overstated. Three aspects of this deserve meticulous attention. First, if available, the QRS configuration during VT is generally a very accurate guide to either the site of origin of a focal idiopathic VT or to the site of scar exit for a scar-related VT. This topic has been reviewed in detail elsewhere. Second, the ECG during sinus rhythm may contain clues to the underlying VT substrate, including the site of any prior myocardial infarction, the typical basal substrate of nonischemic dilated cardiomyopathy (DCM), or the epsilon waves, parietal block, or anterior T wave inversion typical of arrhythmogenic RV dysplasia. Third, in patients with ICDs, VT is usually terminated promptly by the device before a surface ECG can be recorded. In this situation, the intracardiac electrograms stored by the device are a useful surrogate for the ECG morphology and can even be used in some cases for pacemapping.

Periprocedural Imaging

With the ever expanding experience with VT ablation has come an appreciation of the critical role played by normal and abnormal anatomy in the pathogenesis and origination of VT. An understanding of this anatomy and accurate imaging/definition has assumed a central role in VT ablation. Preoperative imaging of ventricular scarring with echocardiography, magnetic resonance imaging (MRI), CT, and positron emission tomography (PET) is important in procedural planning and in defining likely regional ablation targets. Modern mapping systems allow integration of this preprocedural imaging into a virtual online geometry of the patient’s ventricles, thereby facilitating accurate localization of sites critical to VT perpetuation.

While this image integration with previously acquired imaging data has proved useful, it still does not provide truly real-time anatomic visualization. The most frequently used technique for this purpose is currently ICE as this provides precise online anatomic definition, visualization of catheter manipulation within the chamber, reduction of fluoroscopy time, assistance with transseptal and pericardial puncture if required, assessment of catheter-tissue contact, monitoring of lesion formation, and rapid notification of complications such as thrombus formation, steam pops, and pericardial tamponade. It has also recently been shown to help in defining epicardial VT substrate in DCM as well as in helping to localize and ablate endocavitary sites of VT origin such as the papillary muscles.

Endocardial Left Ventricular Access and Anticoagulation

Both the retrograde transaortic approach and transseptal approach are possible routes to the endocardial LV with the former used more commonly due to easier catheter manipulation. This has to be balanced however with the embolic risks associated with aortic arch atheroma or aortic valve calcification. Other considerations such as the presence of aortic or mitral valve prosthesis and the anticipated site of origin of the VT may dictate the required or preferred route of accessing the LV. A basal septal origin may be best targeted with a transseptal approach, whereas a basal lateral origin may be best targeted via a retrograde aortic strategy (Figure 39.7). Regardless of the access chosen, anticoagulation is important to prevent thrombus formation, targeting an ACT of at least 250.
Ablation of Unmappable Ventricular Tachycardia Mapping Methods

Conventional Mapping

The ability to ablate any given idiopathic or scar-related VT relies on accurate mapping and localization of its machinery. If the patient can be maintained in sustained VT, activation mapping to find the earliest presystolic breakout of electrical activity can be performed, particularly for focal idiopathic VTs. These may be particularly difficult to induce and care to minimize sedation and local anesthesia may be required as well as the infusion of occasional high-dose isoproterenol up to 20 μg/min. Generally, for focal VTs, activation at the site of origin will be at least 10 to 60 ms earlier than the surface QRS complex. However, in reentrant scar-related VT, critical components of the VT machinery are found at mid-diastolic rather than presystolic times during the cycle length as a result of continuous circuit activation. In sinus rhythm, clues to the proximity of VT components can be elicited by pacing mapping in which a threshold pacing stimulus is delivered from various sites with the aim of mimicking the QRS morphology of the VT. Once again, this has higher technical accuracy in the context of idiopathic VT where homogenous myocardium lacking significant fibrosis allows for point source breakout of a paced wavefront to resemble the focal generation of wavefronts during VT. Activation and pacing mapping probably have similar resolution in localizing focal VT. With scar-related reentrant VT, sites of good QRS match can provide a guide as to VT exit sites from scar, but in these cases there is additional value in seeking proximal slowly conducting circuit components by identifying sites of long stimulus to QRS delay.

For tolerated, sustained scar-related reentrant VT, the preferred mapping method is by entrainment. This is because it allows the identification of specific components of the VT circuit, including sites that are most susceptible to interruption with ablation lesions. Entrainment mapping is predicated on interpreting the interaction of a series of paced wavefronts with the arrhythmia circuit, in this case scar-based VT. The specific questions that entrainment can answer include the following: (i) Is reentry the mechanism of VT? (ii) Is the ablation catheter close to the VT circuit? (iii) Is the catheter located in a constrained isthmus of diastolic conduction that may be vulnerable to radiofrequency ablation lesions? The technical details of entrainment mapping are beyond the scope of this review but have been dealt with extensively elsewhere.

Ablation of Unmappable Ventricular Tachycardia

VT may be unmappable for various reasons including noninducibility, hemodynamic nontolerance, spontaneous termination of nonsustained runs, and lack of uniform morphology or cycle length. The majority of patients will have at least some unmappable VTs, and contemporary data indicate that only around one-third of patients will have exclusively mappable VT morphologies. Conventional activation and entrainment mapping may not be possible in these situations. Strategies to identify the sinus rhythm footprints of VT circuit components have been devised based on the most successful form of surgical VT ablation, subendocardial scar resection, which prevented VT recurrence in more than 90% of patients. Using similar concepts to target the VT machinery deep within the scar, Marchlinski et al. described the concept of sinus rhythm substrate modification for catheter ablation of unmappable VT.

This relies on the accurate identification of myocardial scar and it is greatly facilitated by the use of EAM, which relies on a magnetic field-based or electrical impedance-based triangulation of a catheter's location in 3D space. The electrical information recorded by the catheter at each location as it roves can be used to create color-coded substrate maps in sinus rhythm or activation maps during VT. In sinus rhythm, a bipolar voltage of <0.5 mV corresponds to dense scar while 0.5 to 1.5 mV corresponds to patchy scar, often near the border zone (Figure 39.8). Dense scar is also identified by being electrically unexcitable and also having a lower voltage than surrounding scar tissue. Once the substrate has been mapped, ablation targets within the scar are selected on the basis of sites of good pacemaps, sites with good pacemaps and long stimulus QRS times, and sites with isolated late components to their sinus rhythm electrograms. The latter may represent diastolic conducting channels during VT but many are bystander sites. Extensive ablation is usually required, generally with the aim of maximal substrate modification to render all VT morphologies noninducible. Newer technologies including remote magnetic navigation may assist in this. Unmappable VT may also be mapped by noncontact mapping using the multielectrode array, which theoretically allows for targeting of a VT circuit after just one beat but long-term results with this approach are mixed.

Epicardial Access and Ablation

The critical targets for a proportion of VTs reside on the epicardium, either a focal site of earliest activation breakout or one or more circuit components. The technique of percutaneous epicardial access using a Tuohy epidural needle and ablation of these epicardial targets was pioneered by Sosa et al. and described earlier in this review (see also Chapter 38). The risks of pericardial puncture include RV laceration, intrapericardial and intraabdominal bleeding, as well as failure of access due to prior pericarditis or surgery. With epicardial ablation, specific risks to the coronary arteries and phrenic nerve are encountered. If found to be near an intended ablation site, the latter can be protected by lifting the parietal pericardium away from the epicardium by instilling air and/or saline into the pericardial sheaths.
Panels A and B depict the endocardial and epicardial voltage maps respectively of a patient with arrhythmogenic right ventricular dysplasia with normal voltage depicted in purple. As commonly seen, the endocardial substrate is located in the basal, periannular region with patchy left ventricular involvement not unexpected. A significantly larger area of scarring is seen on the epicardium overlaying the right ventricle with widespread isolated late potentials (ILP) tagged by black dots on the map. This patient’s clinical VT exited the border of the epicardial scar and was successfully ablated here after coronary angiography confirmed the right coronary artery and marginal branches to be a safe distance away. PV, pulmonary valve; MV, mitral valve; TV, tricuspid valve.

-space, or by inflating an intrapericardial balloon to achieve the same result. Caution should be deployed since the air in the pericardial space may cause a dramatic increase in energy requirements for successful defibrillation or termination of rapid VT.

IDIOPATHIC VENTRICULAR TACHYCARDIA

Outflow Tract Ventricular Tachycardia

Focal idiopathic VTs arise predominantly from the endocardium of the right ventricular outflow tract (RVOT), predominantly its so-called anterosetal corner (which is in reality opposite the aorta, not the interventricular septum). A combination of activation and pacing mapping, often with EAM assistance, is the usual mapping strategy. VT arising from here is readily recognized by its LBBB configuration with right inferior axis, negative in aVL, and a precordial QRS transition at V4 or beyond. Clues that the VT might be arising from the free wall of the RVOT include a wider QRS with later precordial transition and notching on the downstroke of the inferior limb leads. Earlier precordial transitions suggest non-RVOT sites of origin and recent data demonstrate a high accuracy in predicting left-sided origins when the relative transitions of sinus and VT beats are examined. Tachycardia acceleration is often seen at successful ablation sites with the delivery of RF energy prior to termination.

Other RVOT sites of origin of focal VT include the pulmonary artery and parahisian regions. The incidence of the former site is probably underestimated in that most series of RVOT VT have not used angiography or ICE to define the successful site in relation to the pulmonary valve. Parahisian sites of origin are remarkable for their positive forces in lead aVL due to their caudal distance from the pulmonary valve and their obvious risk of heart block with ablation.

On the left side, “outflow tract” VTs are typically ablated at what seem like widely disparate sites including the aortic sinuses of Valsalva (Figure 39.9), the mitral annulus, the aortomitral continuity, and epicardial coronary venous system. Of course, though a commonly used term, there is no true LV outflow tract due to the contiguous apposition of the mitral and aortic valves (and the consequent lack of an
Figure 39.9  The classically described surface ECG findings of a PVC arising from the commissure between the right (RCC) and left coronary cusps (LCC) of the aortic sinuses of Valsalva are seen in Panel A with an early transition left bundle branch block configuration and left inferior axis. V1 shows the characteristic notching on its initial downslope (arrow). Panel B shows the fluoroscopic appearance of a catheter prolapsed across the aortic valve into the left ventricle. The deflection is released to allow the catheter tip to achieve excellent stability at the LCC/RCC commissure as seen on the intracardiac echocardiogram (ICE) frame in Panel C. Local activation here preceded the surface QRS by 48 ms and focal radiofrequency ablation led to immediate suppression of bigeminal ectopy with no recurrence seen during follow-up. RVOT, right ventricular outflow tract.

infundibulum). Recent work has suggested that the unifying etiology of these VTs is a site of origin located somewhere on the so-called LV ostium\(^1 \) with varying preferential conduction to various contiguous structures. Care must be undertaken to delineate the coronary anatomy and avoid coronary injury when ablating in the aortic cusps and the epicardium or epicardial coronary venous system (Figure 39.10).

Non-Outflow Tract Focal Ventricular Tachycardia

Idiopathic focal VT not arising from the outflow tracts may arise from the mitral or tricuspid papillary muscles,\(^107,134,135\) the posterior mitral or tricuspid annuli,\(^136,137\) the apex,\(^138\) and the epicardial crux of the heart.\(^139\) The general strategy to map and ablate these arrhythmias relies heavily once again on the accurate interpretation of the surface ECG which is characterized in all these foci by the absence of an inferiorly directed QRS axis and either frequent PVCs or bursts of nonsustained tachycardia suggesting a triggered mechanism.

Real-time imaging with ICE, sometimes integrated into the EAM system, is very useful for ablation of these foci, particularly those associated with endoluminal papillary muscle origins where no other modality currently allows for navigation to precise sites on these structures.

Fascicular Ventricular Tachycardia

Also known as left septal VT or verapamil-sensitive VT, this is the only idiopathic VT that is due to a reentrant rather than focal mechanism.\(^140\) The QRS is usually quite narrow and mostly of a RBBB configuration with superior axis. It is thought that a diseased Purkinje fiber forms the antegrade limb of the reentry circuit with the left posterior (or more rarely anterior) fascicle comprising the retrograde limb. While verapamil may acutely terminate this VT (often with the mistaken presumption that SVT is being treated), long-term oral verapamil has limited suppressive activity and catheter ablation targeting the abnormal Purkinje tissue on the septum is curative.
SCAR-RELATED VENTRICULAR TACHYCARDIA

Postinfarct Ventricular Tachycardia and Ischemic Cardiomyopathy

Monomorphic VT in the presence of prior infarction almost always results from reentry through ventricular scar. Surviving bundles of myocardial fibers that course through regions of dense, confluent scar can form protected diastolic conduction channels during VT, with the location of exit from the scar border zone determining the QRS morphology. The infarcts able to sustain VT are generally extensive, often with aneurysm formation, and this advanced structural disease generally means that most patients with postinfarct VT either have a primary prevention ICD in situ, or are candidates for a secondary prevention ICD after presentation. Frequent ICD therapies refractory to antiarrhythmic drugs remain the commonest indication for catheter ablation and in this setting the procedure may be dramatically life changing and associated with significant quality-of-life gains.

The ventricular scars of patients with postinfarct VT can generally support more than one reentrant circuit and most patients have several morphologies. In the presence of poor systolic function, the majority of induced VTs are not tolerated and conventional activation and entrainment mapping are not possible for those VTs. The development of substrate mapping and ablation techniques, based largely on the surgical paradigm, has underpinned modern VT catheter ablation. A detailed characterization of the scar geometry using the EAM system is vital before devising an ablation strategy for both the mappable and unmappable VTs. During substrate mapping, isolated late potentials, sites of slow conduction, and zones of good pacemaps are defined, as well as regions of electrically unexcitable scar. Proven or putative targets for all induced VTs are then ablated, generally using open-irrigated RF ablation catheters to allow for greater power delivery in scar, thereby increasing lesion depth and size. The currently accepted endpoint for the procedure is noninducibility of VT although this has limitations. Contemporary multicenter data show that clinical VT can be eliminated in 81% of patients, with a marked decrease in the frequency of recurrence during medium-term follow-up. A recent randomized trial examined the role of prophylactic substrate-based VT ablation at the time of ICD implantation in postinfarct patients and found a two-thirds reduction in the frequency of appropriate ICD therapies in the ablation group.
Nonischemic Idiopathic Dilated Cardiomyopathy

Monomorphic VT is relatively uncommon in the setting of DCM but when it occurs, scar-related reentry is again the main mechanism. The characteristic pattern of scarring seen in DCM affects perinuclear regions, usually involving the basolateral LV.

This results in an LBBB QRS configuration that may mimic that noted in sinus rhythm if present. Frequently incomplete LBBB is present in sinus rhythm. Interfascicular reentry involving the left anterior and posterior fascicles is also seen in patients with DCM and other substrates causing distal His-Purkinje conduction disease. These tachycardias are amenable to curative catheter ablation, generally with focal RF ablation of the right bundle branch if a larger macroreentrant circuit is identified or of the retrograde limb of a left fascicular reentrant circuit. Patients with BBR VT are at risk for other myocardial VTs or VF however, and hence ICD implantation is usually still required.

Bundle Branch Reentry

Particularly important not to overlook in DCM patients is the possibility of bundle branch reentry (BBR) VT. These are generally very rapid tachycardias of LBBB configuration and are due to diffuse His-Purkinje conduction disease. The commonest form of BBR is characterized by wavefront propagation antegrade down the RBBB and retrograde up the LBBB.

Recently, the role of a structural substrate for VF located on the RV infundibular epicardium has been described by Nademanee et al. in the context of Brugada syndrome. Ablation here not only normalized the signature ECG pattern of the syndrome but also eliminated VF recurrence over a mean 20-month follow-up.

Other Nonischemic Cardiomyopathies

Various other nonischemic cardiomyopathies can underlie the development of monomorphic VT, and catheter ablation has been reported as a management strategy in all these contexts.

In the setting of arrhythmogenic right ventricular dysplasia (ARVD), it has become clear that extensive targeting of the epicardial and endocardial substrate is essential for clinical success. When this is done, around 80% of patients can remain free of VT during medium-term follow-up. This requirement for epicardial ablation is a function of the pathologic process and is also recognized with VT ablation in the context of hypertrophic cardiomyopathy and Chagas disease.

Recent reports have also described catheter ablation in the context of congenital heart disease, particularly repaired tetralogy of Fallot where there are clear isthmus targets defined between the ventriculotomy and/or septal patch and the adjacent valve structures. Consequently, a high 91% success rate was seen during follow-up by Zeppenfeld et al. By comparison, the diffuse, progressive, and often intramural substrate of sarcoidosis is much more challenging in terms of ablation targets and catheter ablation has more limited long-term success in this context although acute control of VT storm can usually be accomplished. More limited experience with catheter ablation for VT observed after valve surgery or reconstructive ventricular surgery can also be effective.

Patients who are candidates for ablation of polymorphic ventricular arrhythmias (either idiopathic or associated with structural heart disease) are generally identified by the presence of constant triggering PVCs, usually of quite sharp and narrow morphology to suggest an origin within the Purkinje network. The basic strategy in these cases centers around activation mapping of the earliest Purkinje-like potentials preceding the PVCs, up to 10 to 150 ms pre-QRS. Elimination of the PVCs is an endpoint of the procedure and is associated with excellent long-term freedom from recurrence. These Purkinje-associated triggering foci may be of left or right ventricular origin, including from the border zone of any associated infarct scar or from the RV infundibulum. Recently, the role of a structural substrate for VF located on the RV infundibular epicardium has been described by Nademanee et al. in the context of Brugada syndrome. Ablation here not only normalized the signature ECG pattern of the syndrome but also eliminated VF recurrence over a mean 20-month follow-up.

CONCLUSION

Interventional cardiac EP has developed into a comprehensive diagnostic and therapeutic subspecialty, with a substantial suite of interventional and device-based solutions for clinical arrhythmia problems. Rapid progress is being made in the field and new arrhythmia mechanisms and targets constantly identified. It is expected that ongoing improvements to the safety and efficacy of complex ablations for AF and VT in structural heart disease will occur, and that their success rates will approach those of SVT and idiopathic VT ablation in the near future.

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in accessory AV pathways and improves localization for catheter ablation. 


Chapter 39: Interventions for Cardiac Arrhythmias


147. Lopera G, Stevenson WG, Soejima K, et al. Identification and ablation of three types of ventricular tachycardia involving the


The cardiac valves function to maintain unidirectional flow, thus ensuring that the energy released during myocardial contraction is utilized efficiently for the circulation of blood around the body. When the valves become diseased (either by restriction [stenosis] or insufficiency [regurgitation]), efficient unidirectional flow is compromised and various compensatory mechanisms are brought into play to maintain adequate blood flow to support the metabolic needs of the body. These mechanisms—chiefly dilatation and hypertrophy—have their own clinical costs, which are responsible for the major manifestations of valvular heart disease.

Valvular heart disease imposes two different types of stress on the cardiac chamber proximal to the lesion: either pressure overload (increased afterload) or volume overload (increased preload). The former is generally the result of valvular stenosis, and the latter, of valvular insufficiency. Both pressure overload and volume overload serve as stimuli for compensatory mechanisms, chiefly hypertrophy (which allows the generation of greater systolic force and at the same time tends to normalize wall stress by increasing wall thickness) and dilatation (which enables increased strength and extent of shortening by the Frank-Starling mechanism). These mechanisms preserve the circulation at the cost of increased myocardial oxygen needs and elevated ventricular filling pressures, leading to clinical evidence of ischemia and congestive heart failure.

This chapter will illustrate the hemodynamic and angiographic findings seen in patients with valvular heart disease. Application of the general physiologic principles discussed above in the interpretation of catheterization data will enable the physician to unravel even the most complicated problems.

**MITRAL STENOSIS**

The orifice area of the normal mitral valve is about 4.5 cm². Most often, as a result of chronic rheumatic heart disease, the orifice becomes progressively smaller, and this leads to at least two distinct and important circulatory changes. The first is the development of a pressure gradient across the mitral valve, the left ventricular mean diastolic pressure remaining at its normal level of about 5 mmHg and the left atrial mean pressure rising progressively, reaching about 15 to 25 mmHg when the orifice of the mitral valve is reduced to approximately 1.0 cm² (Figure 40.1). The second major circulatory change is reduction of blood flow across the mitral valve, that is, reduction of cardiac output. The normal resting cardiac output of 3.0 L/minute per m² usually
falls to about 2.5 L/minute per m² when the valve size is 1.0 cm². A rise in left atrial pressure necessitates a similar rise in pressure in pulmonary veins and capillaries, and pulmonary edema occurs when the pulmonary capillary pressure exceeds the oncotic pressure of normal plasma, which is about 25 mmHg.

Reactive pulmonary hypertension practically never occurs in mitral stenosis until the mitral valve area approaches 1.0 cm², that is, when the resting left atrial pressure approaches 25 mmHg. After this point, reactive changes in the pulmonary arteriolar bed develop frequently, resulting in progressive obstruction to blood flow through the lungs.

As pulmonary vascular obstruction becomes increasingly severe, the pulmonary arterial pressure rises and occasionally may exceed the systemic arterial pressure. In the extreme case, the pulmonary vascular resistance can rise to 25 or 30 times the normal. Despite substantial hypertrophy, the right ventricle cannot cope with the enormous pressure load imposed on it, and it dilates and fails.

The Second Stenosis

Thus, in mitral stenosis, two stenoses eventuate—the first at the mitral valve and the second in the arterioles of the lung. The hemodynamic findings in patients with tight mitral stenoses with and without major pulmonary vascular disease are illustrated in Figure 40.2. As can be seen, the second stenosis (Figure 40.2, bottom) has resulted in a 70-mmHg mean pressure gradient across the lungs, giving rise to a pulmonary vascular resistance of 1,866 dyn-second cm⁻⁵. Workup of the patient with mitral stenosis should include an assessment of both these obstructions.

Catheterization Protocol

The usual indication for cardiac catheterization in patients with mitral stenosis is that the patient is being considered for either balloon mitral valvuloplasty or corrective surgery. Catheterization should be a combined right and left heart procedure in which the following measurements and calculations are made:

1. Simultaneous left ventricular diastolic pressure, left atrial (or pulmonary capillary wedge) diastolic pressure, heart rate, diastolic filling period, and cardiac output. From these, the size of the mitral valve orifice may be calculated (see Chapter 13 for details of orifice area calculation).
2. If the transmitral pressure gradient is <5 mmHg, the error in calculation of the mitral valve orifice area is appreciable. The circulatory measurements should be repeated under circumstances of stress (exercise, reversible increase in preload resulting from passive elevation of the patient's legs, tachycardia induced by pacing) to increase the pressure gradient across the mitral valve.
3. Simultaneously, or in close succession, pulmonary arterial mean pressure, left atrial (or pulmonary capillary wedge) mean pressure, and cardiac output for the calculation of pulmonary vascular resistance.
4. Right ventricular systolic and diastolic pressures for assessment of right ventricular function.
5. If other lesions are suspected (e.g., mitral regurgitation, associated rheumatic tricuspid stenosis, aortic valve disease, and left atrial myxoma), they too must be evaluated. In this regard, it should be pointed out that certain lesions tend to occur in combination with mitral stenosis.
Many (if not most) patients with severe mitral stenosis have some degree of aortic regurgitation. Also, although it is very rare, tricuspid stenosis should always be looked for in the patient with severe mitral stenosis, because the former is seen only in association with the latter condition. Another condition that may be associated with mitral stenosis is atrial septal defect with left-to-right shunt. The combination of mitral stenosis and atrial septal defect is known as the Lutembacher syndrome. Thus, as with standard right heart catheterization, the operator should obtain screening blood samples from the superior vena cava and pulmonary artery for oximetry determination. This has taken on added importance in the present era when balloon mitral valvuloplasty (see Chapter 33) has become a standard treatment for mitral stenosis. Balloon mitral valvuloplasty generally requires trans-septal catheterization and involves limited dilatation of the interatrial septum; thus the procedure may create an atrial septal defect, thereby producing iatrogenic Lutembacher syndrome. A few patients who present with recurrent mitral stenosis after prior valvuloplasty will have such a persistent iatrogenic atrial septal defect.

The following case studies illustrate the different clinical and hemodynamic syndromes seen in patients with mitral stenosis. The first is a typical example of a symptomatic patient with severe mitral stenosis, normal pulmonary vascular resistance, and a normal-sized heart (stage II, Figure 40.3). The second is an example of a relatively asymptomatic patient with more severe mitral stenosis, a fivefold to tenfold increase of pulmonary vascular resistance, and an enlarged heart caused principally by enlargement of the right ventricle (stage III, Figure 40.3). The third represents terminal mitral stenosis with an extreme degree of pulmonary vascular resistance, pulmonary hypertension, and right ventricular failure (stage IV, Figure 40.3).

Figure 40.2 Diagrammatic representation of the circulation in patients with normal hemodynamics (top), tight mitral stenosis (center), and tight mitral stenosis with pulmonary vascular disease and the development of a second stenosis at the pulmonary arteriolar level (bottom). See text for discussion.

Figure 40.3 Stages in the natural history of mitral stenosis. As the mitral orifice progressively narrows, pulmonary vascular resistance increases. This increase is slow at first, but when the mitral valve area becomes “critical” (<1 cm²), the increase is rapid, reflecting the development of a second stenosis at the level of the precapillary pulmonary arterioles. Clinical correlations are discussed in the text.
**CASE 40.1**  Mitral Stenosis with Normal Pulmonary Vascular Resistance.  A.R., a 35-year-old woman, had chorea as a child and was asymptomatic thereafter until age 33, when she noted the onset of exertional dyspnea. This progressed to the point of her having to stop after climbing one flight of stairs slowly. She had had one recent episode of hemoptysis. Her most troublesome symptom at the time of presentation was paroxysmal atrial fibrillation over a period of several months. She had had orthopnea and one episode of paroxysmal nocturnal dyspnea.

On physical examination, she was in no apparent distress. Blood pressure was 130/70 mmHg, and pulse rate was 80 beats per minute and regular. There was no jugular venous distension, lungs were normal, and the point of maximal impulse was in the fifth interspace in the midclavicular line. S1 was accentuated. At the apex, there was a grade 1/6 holosystolic murmur, an opening snap, and a grade 2 diastolic rumble with presystolic accentuation. The liver edge was at the costal margin, and there was no edema. The ECG was within normal limits. Chest roentgenogram showed a normal-sized heart, an enlarged left atrium, a mild degree of pulmonary venous redistribution, and no calcification in the region of the mitral valve, and was otherwise normal.

Cardiac catheterization revealed the following:

<table>
<thead>
<tr>
<th>Body surface area, m²</th>
<th>1.78</th>
</tr>
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<tbody>
<tr>
<td>O₂ consumption, ml/min</td>
<td>180</td>
</tr>
<tr>
<td>A–V O₂ difference, mL/L</td>
<td>40</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>4.5</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>76, NSR</td>
</tr>
<tr>
<td>Pressures, mmHg</td>
<td></td>
</tr>
<tr>
<td>Brachial artery</td>
<td>130/70, 90</td>
</tr>
<tr>
<td>Left ventricle</td>
<td>130/8</td>
</tr>
<tr>
<td>Diastolic mean</td>
<td>6</td>
</tr>
<tr>
<td>Diastolic filling period, s/beat</td>
<td>0.42</td>
</tr>
<tr>
<td>Pulmonary capillary wedge</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>24</td>
</tr>
<tr>
<td>Diastolic mean</td>
<td>20</td>
</tr>
<tr>
<td>Pulmonary artery</td>
<td>40/22, 28</td>
</tr>
<tr>
<td>Right ventricle</td>
<td>40/6</td>
</tr>
<tr>
<td>Right atrium, mean</td>
<td>4</td>
</tr>
<tr>
<td>Pulmonary vascular resistance, dyn·s·cm⁻⁵</td>
<td>71</td>
</tr>
<tr>
<td>Calculated mitral valve area, cm²</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Both cineangiography of the left ventricle and prior Doppler echocardiogram revealed no mitral regurgitation.

**Interpretation.** This patient was symptomatic because of her increased left atrial pressure and atrial arrhythmia. She had not yet developed the second stenosis, discussed previously, at the precapillary pulmonary arteriolar level. Thus her pulmonary artery pressure elevation was purely a consequence of the increased left atrial and pulmonary venous pressures, and the pulmonary vascular resistance was normal (<120 dyn-second·cm⁻⁵). In the spectrum of patients with mitral stenosis, she would fall into stage II of Figure 40.3.

Appropriate therapy might be balloon mitral valvuloplasty or surgical valve replacement, depending on the degree of valve deformity seen on echocardiography. Without relief of the mitral stenosis, her paroxysmal atrial fibrillation will likely become persistent.

**CASE 40.2**  Severe Mitral Stenosis, Moderately Elevated Pulmonary Vascular Resistance, Few Symptoms, Fatigue Syndrome.  E.C., a 42-year-old woman, had no history of acute rheumatic fever. She was asymptomatic until she was 19 years old, when during the last month of her first pregnancy, at which time she was quite anemic, she developed pulmonary congestion. She responded well to medical therapy and remained asymptomatic thereafter, even during three subsequent pregnancies. However, during her fifth pregnancy at age 37, dyspnea, orthopnea, paroxysmal nocturnal dyspnea, and one episode of hemoptysis of red blood occurred at the seventh month, necessitating hospitalization through term. Thereafter she improved, but became progressively tired with loss of energy and drive. She became less thorough in her housework and in her attention to the children’s clothes and lost her previous meticulousness. If she pushed herself, she would become somewhat short of breath on a flight of stairs, but it was fatigue more than breathlessness that bothered her.

On examination, she was well nourished and had a malar flush. Her blood pressure was 115/70 mmHg, and her pulse, 90 beats per minute and irregularly irregular. Respirations were 15 per minute. There was no pulmonary or peripheral congestion. The neck veins were just visible at the clavicles with the patient sitting upright. The point of maximal impulse was in the fifth interspace just outside the midclavicular line. The impulse was normal. A prominent parasternal heave was present. S₁ was accentuated. No apical systolic murmur was present. There was an opening snap and a grade 2 apical diastolic rumble. The ECG showed right ventricular hypertrophy and atrial fibrillation. Chest radiographs showed the heart to be moderately enlarged because of enlargement of the left atrium and right ventricle. The pulmonary arteries were prominent, and there was a moderate degree of pulmonary vascular redistribution.
The findings at cardiac catheterization were as follows:

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Body surface area, m²</td>
<td>1.41</td>
</tr>
<tr>
<td>O₂ consumption, mL/min</td>
<td>188</td>
</tr>
<tr>
<td>A-V O₂ difference, mL/L</td>
<td>51</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>3.7</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>85, AF</td>
</tr>
<tr>
<td>Pressures, mmHg</td>
<td></td>
</tr>
<tr>
<td>Brachial artery</td>
<td>120/62, 84</td>
</tr>
<tr>
<td>Left ventricle</td>
<td>120/7</td>
</tr>
<tr>
<td>Diastolic mean</td>
<td>5</td>
</tr>
<tr>
<td>Diastolic filling period, s/beat</td>
<td>0.38</td>
</tr>
<tr>
<td>Pulmonary capillary wedge</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>27</td>
</tr>
<tr>
<td>Diastolic mean</td>
<td>23</td>
</tr>
<tr>
<td>Pulmonary artery</td>
<td>82/32, 51</td>
</tr>
<tr>
<td>Right ventricle</td>
<td>82/10</td>
</tr>
<tr>
<td>Right atrium, mean</td>
<td>8</td>
</tr>
<tr>
<td>Pulmonary vascular resistance, dyn-s-cm⁻⁵</td>
<td>520</td>
</tr>
<tr>
<td>Calculated mitral valve area, cm²</td>
<td>0.7</td>
</tr>
</tbody>
</table>

**Interpretation.** This patient's symptoms were initially caused by elevated left atrial pressure when, during her fifth pregnancy, she developed hemoptysis, orthopnea, and paroxysmal nocturnal dyspnea. Subsequently, however, her major symptom was fatigue, associated with a reduced cardiac output and an increased arteriovenous O₂ difference. The orthopnea and paroxysmal dyspnea had receded somewhat despite the fact that her pulmonary capillary pressure was at the pulmonary edema level. This is a common, although poorly understood, phenomenon in patients with mitral stenosis when pulmonary vascular disease begins to occur. Thus, this patient was beginning to develop the second stenosis discussed previously, and this is apparent from the elevated pulmonary vascular resistance (520 dyn-second-cm⁻³). In the spectrum of patients with mitral stenosis, she would be representative of stage III of Figure 40.3. As was true for the patient just discussed (case 1), appropriate therapy would be either balloon mitral valvuloplasty or surgical valve replacement.

**CASE 40.3 Terminal Mitral Stenosis with Severe Pulmonary Hypertension.** C.A., a 47-year-old woman, had had acute rheumatic fever at 8 years of age and a murmur ever since. She did well thereafter until age 42, when she noticed exertional dyspnea and paroxysmal nocturnal dyspnea. At age 43, these symptoms worsened. Orthopnea and ankle edema appeared. Her symptoms then improved for nearly 2 years, only to return 2 months prior to admission. Since then, despite a good cardiac regimen, she had had a bed-chair-bathroom existence.

On examination, she was cachectic, dyspneic, and orthopneic. Acrocyanosis was evident. Blood pressure was 96/72 mmHg; pulse rate was 90 beats per minute and irregularly irregular; respirations were 32 per minute. Neck veins were distended to the angle of the jaw, v waves were prominent, and there were bibasilar rales over the lung fields. The point of maximal impulse was in the anterior axillary line. The apex impulse was normal, but a parasternal heave was present. S₁ was loud. Systole was silent. An opening snap was present, and there was a barely audible mitral diastolic murmur with appreciable presystolic accentuation. The pulmonary component of S₂ was loud and palpable. The liver was two fingerbreadths below the right costal margin and was tender. There was considerable pitting edema up to the knees. The ECG showed atrial fibrillation, right-axis deviation, and right ventricular hypertrophy. Chest roentgenogram showed a large heart with prominent left atrium, right ventricle, pulmonary arteries, pulmonary vasculature, and Kerley B lines.

Cardiac catheterization revealed the following:

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Body surface area, m²</td>
<td>1.4</td>
</tr>
<tr>
<td>O₂ consumption, mL/min</td>
<td>201</td>
</tr>
<tr>
<td>A-V O₂ difference, mL/L</td>
<td>110</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>1.8</td>
</tr>
<tr>
<td>Pulse rate, beats/min</td>
<td>92, AF</td>
</tr>
<tr>
<td>Pressures, mmHg</td>
<td></td>
</tr>
<tr>
<td>Brachial artery</td>
<td>108/70</td>
</tr>
<tr>
<td>Left ventricle</td>
<td>108/12</td>
</tr>
<tr>
<td>Diastolic mean</td>
<td>10</td>
</tr>
<tr>
<td>Diastolic filling period, s/beat</td>
<td>0.36</td>
</tr>
<tr>
<td>Pulmonary capillary wedge</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>33</td>
</tr>
<tr>
<td>Diastolic mean</td>
<td>31</td>
</tr>
<tr>
<td>Pulmonary artery</td>
<td>125/65, 75</td>
</tr>
<tr>
<td>Right ventricle</td>
<td>125/20</td>
</tr>
<tr>
<td>Right atrium, mean</td>
<td>19</td>
</tr>
<tr>
<td>Pulmonary vascular resistance, dyn-s-cm⁻⁵</td>
<td>1,838</td>
</tr>
<tr>
<td>Calculated mitral valve area, cm²</td>
<td>0.3</td>
</tr>
</tbody>
</table>

**Interpretation.** This patient had symptoms of left atrial hypertension 5 years before her catheterization, suggesting that she was in stage II (see Figure 40.3) of mitral stenosis at that
time. At the time of presentation to us, she showed evidence of advanced right heart failure and pulmonary hypertension. This woman has two stenoses, and both are severe: The mitral orifice area is less than one-tenth the normal at 0.3 cm², and the pulmonary vascular resistance is approximately 18 times normal at 1,838 dyn-second·cm⁻⁵. She is in late stage IV of mitral stenosis, as diagrammatically illustrated in Figure 40.3. Even at this stage in their course, patients can respond dramatically to correction of their mitral stenosis. As pointed out in Chapter 11, pulmonary vascular resistance gradually returns toward normal in patients with advanced mitral stenosis (stage III or IV, Figure 40.3) after successful balloon valvuloplasty or surgical commissurotomy/valve replacement.

### MITRAL REGURGITATION

Mitral incompetence, that is, failure of the valve to prevent regurgitation of blood from the left ventricle to the left atrium during ventricular systole, may be caused by functional or anatomic inadequacy of any one of the components of the mitral valve apparatus, which consists of two valve leaflets, two papillary muscles with their chordae tendineae, and the valve ring or annulus.

Mitral regurgitation may occur when there is destruction or deformation of the valve leaflets as a result of rheumatic fever or bacterial endocarditis. In patients with mitral regurgitation resulting from either of these conditions, mitral regurgitation begins during “isometric” ventricular contraction and continues throughout systole, thus giving rise to a holosystolic murmur. A fibromyxomatous process in the mitral valve leaflets and chordae tendineae may give rise to mitral prolapse and the floppy valve syndrome. In such patients, regurgitation usually does not begin until ventricular ejection has led to a reduction in left ventricular chamber size, so that the regurgitation and accompanying murmur occur in middle or late systole. There may or may not be evidence of Marfan syndrome in these patients. The papillary muscles are usually normal, but there is a marked redundancy of the valve leaflets and chordae with resulting prolapse into the left atrium during systole and accompanying regurgitation.

The papillary muscles are particularly vulnerable to ischemia from coronary artery disease as well as to damage from viral myocarditis. The posterior papillary muscle derives its blood supply from the right coronary and left circumflex arteries. Ischemic dysfunction of this muscle may occur in association with either an inferior or a posterolateral myocardial infarction. Less frequently, ischemic involvement of the anterior papillary muscle in an anterior or anterolateral infarction produces mitral regurgitation. Papillary–chordal integrity is maintained to the point when the left ventricle dilates. The common occurrence of a mitral regurgitant murmur in patients with large left ventricles, however, may reflect a simple anatomic loss of this integrity, an involvement of the papillary muscle with the same disease that causes the left ventricle to dilate, or an abnormality of contraction of the mitral annulus.

### Physiology

Mitral regurgitation from whatever cause implies a double outlet to the left ventricle: During systole, blood exits the left ventricle through both aortic and mitral valves. Although total left ventricular output rises, forward output into the aorta may fall. The left ventricular “output” or regurgitant volume through the mitral valve depends on at least five factors: size of the regurgitant orifice, left atrial compliance, systolic mean pressure difference between the left ventricle and the left atrium, duration of systole, and resistance to forward ejection of blood through the aortic valve and into the aorta (e.g., aortic stenosis or peripheral vasoconstriction exacerbates mitral regurgitation). Although hypertension aggravates and lowering of systemic blood pressure lessens mitral regurgitation, the most important factor is probably the size of the regurgitant orifice. In normal subjects and in most other valve lesions, the left ventricular mass-to-volume ratio is >1.0. There is proportionately less left ventricular mass in mitral regurgitation with a mass-to-volume ratio of <1.0. Thus, the radius-to-thickness ratio is high and, despite the usual assumption that the left ventricle is unloaded into the left atrium, systolic wall stress and thus afterload are actually higher than normal.

In patients with mitral regurgitation, cardiac catheterization is important to provide a complete hemodynamic and angiographic assessment of the severity of the valvular lesion.

### Hemodynamic Assessment

First, it is important to assess the hemodynamic consequences of the mitral regurgitation by measuring cardiac output and right and left heart pressures.18

### Interpretation of v Waves in the Pulmonary Capillary Wedge Tracing

With acute mitral regurgitation (e.g., ruptured chordae tendineae), giant v waves will be seen in the left atrial or pulmonary artery pressure tracing (Figure 40.4). In this regard, our fellows and residents have often asked, “How large must a v wave be to be diagnostic of severe mitral regurgitation?” In our experience, v waves up to twice the mean left atrial pressure can be seen in the absence of any mitral regurgitation.9 The patient with left ventricular failure from any cause may have a distended, noncompliant left atrium, and the normal v wave (which is owing to left atrial filling from the pulmonary veins during left ventricular systole) will be prominent in such a setting.7 When pulmonary blood flow is increased, the normal v wave increases in prominence correspondingly; this is particularly striking in acute ventricular septal defect complicating myocardial infarction, wherein enormous v waves (>50 mmHg) can be seen in the absence of any mitral regurgitation.9
With sodium nitroprusside (right), the LV systolic pressure nary capillary wedge (PCW) tracing are insensitive to and also, the level of after load, as determined by systemic vascular resistance, may affect to a great extent the height of the v wave. The giant v wave results from regurgitation of blood into a relatively small and noncompliant left atrium. Electrocardiogram (ECG) illustrates the timing of the PCW v wave, the peak of which follows ventricular repolarization, as manifested by the T wave of the ECG.

A v wave larger than twice the mean left atrial (or pulmonary capillary wedge) pressure is suggestive of severe mitral regurgitation, and when the height of the v wave is three times the mean pulmonary capillary wedge or left atrial pressure, a diagnosis of severe mitral regurgitation is virtually certain (see Figure 40.4). We hasten to point out, however, that the absence of a prominent v wave by no means rules out severe mitral regurgitation. Slowly developing chronic mitral regurgitation commonly leads to marked left atrial enlargement, and the dilated left atrium can accept an enormous regurgitant volume per beat without any increase in mean pressure or height of the v wave. Also, the level of afterload, as determined by systemic vascular resistance, may affect to a great extent the height of the regurgitant wave, or v wave, in patients with mitral regurgitation. As seen in Figure 40.5A, a patient with severe mitral regurgitation had a v wave of 48 mmHg when left ventricular (LV) systolic pressure was approximately 140 mmHg. With sodium nitroprusside (right), the LV systolic pressure came down to 120 mmHg, and the v wave was essentially abolished. Although this patient’s regurgitant fraction was reduced with sodium nitroprusside (from 80% to 64%), it still remained in the range of severe mitral regurgitation (see below). As summarized in a study by Snyder et al., prominent v waves in the pulmonary capillary wedge (PCW) tracing are insensitive to and have a poor positive predictive value in identifying moderate or severe mitral regurgitation.

Exercise Hemodynamics
Another important hemodynamic parameter in the assessment of mitral regurgitation is the forward cardiac output. Low cardiac output is common in advanced mitral regurgitation and may account for much of the clinical picture. If resting cardiac output is near normal, and if the patient’s primary symptoms are related to exertion (i.e., easy fatigueability and dyspnea on exertion), dynamic exercise during cardiac catheterization may be revealing. If the symptoms are cardiac in origin, the patient usually fails to increase cardiac output appropriately with exercise; that is, the increase in cardiac output will be <80% of predicted increase (see the formula for prediction of cardiac output increase with exercise in Chapter 20). In addition, pulmonary capillary wedge or left atrial mean pressure will rise with exercise, commonly reaching levels of >35 mmHg by 4 to 5 minutes of supine bicycle exercise, even if the control value was nearly normal.

Angiographic Assessment
The second objective of cardiac catheterization in patients with mitral regurgitation is the angiographic assessment of the severity of the regurgitation by left ventriculography. The assessment is qualitative, by noting the degree of opacification of the left atrium owing to regurgitation back through the incompetent valve, using a scale of 1+ (mild), 2+ (moderate), 3+ (moderately severe), and 4+ (severe) regurgitation. Although these grades are subjective, certain criteria can be used to enhance consistency of their usage. Regurgitation classified as 1+ clears with each beat and never opacifies the entire left atrium. When regurgitation is 2+ (moderate), it does not clear with one beat and generally does opacify the entire left atrium (albeit faintly) after several beats; however, opacification of the left atrium does not equal that of the left ventricle. In 3+ regurgitation (moderately severe), the left atrium is completely opacified and achieves the same level of opacification as that of the left ventricle. In 4+ regurgitation (severe), opacification of the entire left atrium occurs within one beat, the opacification becomes progressively more dense with each beat, and contrast material can be seen refluxing into the pulmonary veins during left ventricular systole.

Regurgitant Fraction
Angiographic assessment of the severity of mitral regurgitation may be made more quantitative by calculation of the regurgitant fraction. This entails measurement of the total left ventricular stroke volume (TSV) from the left ventriculogram and the amount that goes forward by way of the aorta to the body (the forward stroke volume, FSV) by the Fick method or by the indicator-dilution technique. TSV is calculated as the difference between end-diastolic and end-systolic left ventricular volumes (EDV – ESV = TSV), as described in Chapter 21. Regurgitant stroke volume (RSV, regurgitant
Figure 40.5  
A. Left ventricular and pulmonary capillary wedge pressures before (left) and during (right) an infusion of sodium nitroprusside in a patient with severe mitral regurgitation and atrial fibrillation. This illustrates the sensitivity of the v wave height to LV afterload in patients with mitral regurgitation. See text for discussion. (From Harshaw CW, et al. Reduced systemic vascular resistance as therapy for severe mitral regurgitation of valvular origin. Ann Intern Med 1975;83:312.)  
B. Simultaneous left ventricular (LV) and left atrial (LA) pressures before (left) and after (after) percutaneous mitral repair. Prerrepair, there is 4+ mitral regurgitation, but the peak of the v wave exceeds 40 mmHg, which is less than twice the mean LA pressure. Following repair, the LA waveform has normalized with a dramatic change in the v wave morphology.
volume per beat) is then calculated as \( RSV = TSV - FSV \), and regurgitant fraction (RF) as \( RF = RSV/TSV \).

The accuracy of these calculations depends on many factors. Because FSV is calculated by dividing cardiac output by heart rate at the time of the Fick (or other) cardiac output determination, it is an average stroke volume. The particular beat chosen from the left ventriculogram for volume determination must therefore be an average or representative beat; alternatively, volumes from multiple beats may be calculated and averaged. Thus, in patients with atrial fibrillation or extrasystoles during ventriculography, the regurgitant stroke volume and regurgitant fraction may be highly inaccurate and should not be calculated. It should also be obvious that the accuracy of the regurgitant fraction depends on a similar physiologic state prevailing between the cardiac output and the angiographic phases of the catheterization procedure. An increase in arterial blood pressure may substantially increase mitral regurgitation and decrease forward output. Therefore, if blood pressure or other hemodynamic variables change significantly between the time of cardiac output determination and that of left ventriculography, it is pointless to calculate regurgitant fraction. Finally, regurgitant fraction quantifies, at best, the total amount of regurgitation. Thus, if a patient has both mitral and aortic regurgitation, the regurgitant fraction gives an assessment of the regurgitation owing to both lesions combined.

A study from the Mayo Clinic used left ventricular cineangiography to calibrate Doppler echocardiographic techniques for quantification of mitral regurgitation in 180 patients with isolated, pure mitral regurgitation.\(^6\) Patients underwent left ventricular cineangiography to quantify mitral regurgitation, using a grading scale of I to IV, much the same as just described above. They found that grade I angiographic mitral regurgitation corresponded to a Doppler measured regurgitant fraction of 28 ± 9%, grade II to 38 ± 9%, grade III to 44 ± 10%, and grade IV to 59 ± 12%. The finding that grade I angiographic mitral regurgitation corresponded to a regurgitant fraction of 28 ± 9% is surprising, and probably reflects the sensitivity of the Doppler technique in detecting mitral regurgitation. Using angiographic methods for quantifying left ventricular volumes and regurgitant fraction, grade I (mild) angiographic mitral regurgitation probably corresponds to a regurgitant fraction of <20%, grade II (moderate) to 21% to 40%, grade III (moderately severe) to 41% to 60%, and grade IV (severe) to >60%, although greater precision is limited by contrast injection technique, arrhythmia, and variations in left atrial size\(^1\) (see Chapter 17).

A third objective of cardiac catheterization in patients with mitral regurgitation is the assessment of left ventricular function by measuring the left ventricular diastolic pressure and, more importantly, by measuring the left ventricular ejection fraction and end-systolic volume. As others have emphasized, the nearer the preoperative ejection fraction is to normal, the higher is the degree of postoperative restoration to full activity. Specific parameters of left ventricular function are discussed in Chapters 21 and 22.

### Catheterization Protocol

1. Right heart catheterization for evaluation of right atrial pressure (to detect possible tricuspid valve disease or right ventricular failure), pulmonary artery pressure (degree of pulmonary hypertension), and wedge pressure (v wave height). In severe, acute mitral regurgitation, a v wave may actually be seen as a second or late systolic hump in the pulmonary artery pressure waveform.\(^8\)

2. Left heart catheterization for measurement of left ventricular end-diastolic pressure (LVEDP) and assessment of gradients (if any) across the mitral or aortic valve. A characteristic of severe mitral regurgitation is that the LVEDP is usually much lower than the left atrial (LA) or PCW mean pressure. In contrast, in LV failure owing to cardiomyopathy or coronary artery disease, LVEDP is usually close or equal to the PCW mean pressure, whereas in aortic regurgitation or LV aneurysm, LVEDP is usually much higher than PCW mean pressure.

3. Cardiac output by the Fick or indicator-dilution technique. This measures the fraction of blood going out by way of the aorta to the body and by itself yields no information about regurgitant flow. However, the response of forward cardiac output to dynamic exercise may provide useful information, because patients with severe mitral regurgitation are generally incapable of increasing forward output commensurate with the needs of the body, as estimated by the increased oxygen consumption (see Chapter 20).

4. Left ventriculography is the definitive method for evaluating mitral regurgitation. By this procedure, it is possible to measure left ventricular volumes and regurgitant fraction, as discussed previously. Coronary angiography usually is carried out as well, to assess the need for revascularization at the time of valve repair/replacement surgery, should that prove necessary.

5. Pharmacologic intervention. Bolus injections of nitroglycerin or an infusion of sodium nitroprusside (see Figure 40.5A) often has a dramatic and salutary effect on the hemodynamic abnormalities in mitral regurgitation and may have both diagnostic and therapeutic value. Although TSV may not change, RSV decreases and FSV increases, leading to increased cardiac output.

### CASE 40.4 Mitral Regurgitation

G.A. was a 59-year-old woman with no history of rheumatic fever in childhood. She was healthy and active until 6 months before admission, when she noticed both dyspnea and lower chest discomfort on mild exertion but no other symptoms of heart failure. There was no past history of bacterial endocarditis.

On physical examination, she had normal body habitus. Blood pressure was 130/70 mmHg; pulse was 80 beats per minute and regular. The jugular veins were not distended; the carotid pulsations were normal; and the lungs were clear. The apical impulse was diffuse; \( S_1 \) was diminished. There was a grade 3/6 apical pansystolic murmur transmitted to the axilla.
No opening snap, S₁, or diastolic murmurs were heard. There were no aortic murmurs. The ECG showed normal sinus rhythm, complete right bundle branch block, and left-axis deviation. Chest roentgenogram showed enlargement of the left ventricle and left atrium. No valvular calcification was seen.

Cardiac catheterization, left ventriculography, and coronary angiography were performed, yielding the following findings:

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Body surface area, m²</td>
<td>1.95</td>
</tr>
<tr>
<td>(O_2) consumption, mL/min</td>
<td>200</td>
</tr>
<tr>
<td>A–V (O_2) difference, mL/L</td>
<td>52</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td></td>
</tr>
<tr>
<td>Total left ventricular output (angiographic)</td>
<td>10.4</td>
</tr>
<tr>
<td>Forward flow (Fick)</td>
<td>3.9</td>
</tr>
<tr>
<td>Regurgitant flow</td>
<td>6.5</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>67</td>
</tr>
<tr>
<td>Stroke volume, mL/beat</td>
<td></td>
</tr>
<tr>
<td>End-diastolic LV volume, mL</td>
<td>197</td>
</tr>
<tr>
<td>End-systolic LV volume, mL</td>
<td>42</td>
</tr>
<tr>
<td>Total LV stroke volume, mL</td>
<td>155</td>
</tr>
<tr>
<td>Forward stroke volume, mL (Fick)</td>
<td>58</td>
</tr>
<tr>
<td>Regurgitant stroke volume, mL</td>
<td>97</td>
</tr>
<tr>
<td>Ejection fraction (155 ÷ 197)</td>
<td>0.79</td>
</tr>
<tr>
<td>Regurgitant fraction (97 ÷ 155)</td>
<td>0.63</td>
</tr>
<tr>
<td>Pressures, mmHg</td>
<td></td>
</tr>
<tr>
<td>Brachial artery</td>
<td>140/84, 105</td>
</tr>
<tr>
<td>Left ventricle</td>
<td>140/14</td>
</tr>
<tr>
<td>Systolic mean</td>
<td>112</td>
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<tr>
<td>Systolic ejection period, s/beat</td>
<td>0.28</td>
</tr>
<tr>
<td>Pulmonary capillary wedge, mean</td>
<td>12</td>
</tr>
<tr>
<td>V wave</td>
<td>24</td>
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<tr>
<td>Pulmonary artery</td>
<td>30/14, 19</td>
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<tr>
<td>Right ventricle</td>
<td>30/6</td>
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<tr>
<td>Right atrium, mean</td>
<td>4</td>
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<tr>
<td>Pulmonary vascular resistance, dyn·s·cm⁻²</td>
<td>143</td>
</tr>
<tr>
<td>Systemic vascular resistance, dyn·s·cm⁻²</td>
<td>2,071</td>
</tr>
</tbody>
</table>

Left ventriculography showed excellent and uniform contraction of the left ventricle and a large regurgitant jet into the left atrium, which was filled completely within one beat.

The mitral valve did not prolapse into the left atrium. Coronary angiography revealed normal epicardial vasculature, no irregularities or narrowings, and normal runoff.

**Interpretation.** Mitral regurgitation was identified and quantified. There were no other valvular lesions. Although the left ventricular end-diastolic pressure and volume were above normal, the left ventricle contracted uniformly and vigorously, as judged by cineangiography. The ejection fraction of 0.79 and the end-systolic volume were normal. The slight elevation of pulmonary vascular resistance was mainly related to the low pulmonary blood flow (forward cardiac output) of 3.9 L/minute (cardiac index = 2.0 L/minute per m²).

Systemic vascular resistance was substantially increased, perhaps representing excessive vasoconstriction in response to the decreased forward cardiac output. The increased systemic vascular resistance presented an augmented afterload to the left ventricle, thereby worsening this patient’s mitral regurgitation. Reduced systemic vascular resistance, induced by vasodilator therapy with a converting-enzyme inhibitor, an angiotensin receptor antagonist, an \(\alpha\)-adrenergic blocker, or hydralazine, would probably improve this patient’s cardiac output and her symptoms of dyspnea on exertion.

**CASE 40.5 Mitral Regurgitation with Degenerative Etiology, Amenable to Percutaneous Repair.** H.M., an 84-year-old woman with a long-standing history of chronic obstructive pulmonary disease, was hospitalized 2 months prior to diagnostic catheterization with worsening dyspnea on exertion and orthopnea. Both chest radiograph and computed tomography (CT) scan showed bilateral pleural effusions. The brain natriuretic peptide (BNP) was elevated at 605. No evidence of myocardial infarction was noted.

An echocardiogram demonstrated left ventricular systolic function at the lower limits of normal with an estimated ejection fraction of 50%. There were no regional wall motion abnormalities. There was mild concentric left ventricular hypertrophy. The left atrium was moderately enlarged. Doppler examination across the mitral valve showed laterally and posteriorly directed mitral regurgitant jets reaching all the way to the posterior left atrial wall. Transesophageal echo exam showed moderate left atrial enlargement and Doppler findings of a posterolaterally directed mitral regurgitant jet reaching in the left upper pulmonary vein. Systolic flow reversal was noted in the pulmonary vein.

Her symptoms had been progressively worsening over the 6 months prior to hospitalization. At the time of presentation, she could not walk half a block without stopping several times to catch her breath and was incapable of ascending stairs. She was able to perform light household chores.

Coronary arteriography showed no significant coronary disease in the left main, right coronary, or circumflex arteries. A 60% stenosis proximal to the first diagonal was noted in the left anterior descending, and 50% to 60% stenosis was noted in the left anterior descending distal to the first diagonal. An
adenosine/thallium myocardial perfusion scan did not reveal any evidence of ischemia.

More detailed review of the transesophageal echo study showed significant mitral valve prolapse with prominent prolapse of the posterior leaflet and evidence of a small flail segment, consistent with fibroelastic deficiency. The regurgitant jet originated from the central portion of the line of coaptation of the mitral leaflets, despite its eccentric course over the leaflets into the left atrium. Since she was considered high risk for surgery, it was felt that percutaneous mitral valve repair would be a likely successful strategy for management of the mitral regurgitation.

A second procedure was planned 2 weeks following the diagnostic study to perform percutaneous mitral leaflet repair. Under general anesthesia, and using transesophageal echocardiographic guidance, trans-septal puncture was performed and hemodynamic assessments repeated, which revealed the following:

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Repair</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body surface area, m²</td>
<td>1.71</td>
<td>1.71</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>4.02</td>
<td>5.72</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>91</td>
<td>83</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>65%</td>
<td>63%</td>
</tr>
<tr>
<td>Mitral regurgitation</td>
<td>4+</td>
<td>1+</td>
</tr>
<tr>
<td>Pressures, mmHg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aorta, sys/dias/mean</td>
<td>147/63/96</td>
<td>97/36/59</td>
</tr>
<tr>
<td>Left ventricle, sys/dias/ED</td>
<td>140/7/13</td>
<td>98/9/9</td>
</tr>
<tr>
<td>Left atrium, a/v/mean</td>
<td>7/11/7</td>
<td>14/13/9</td>
</tr>
<tr>
<td>Pulmonary artery, sys/dias/mean</td>
<td>59/21/36</td>
<td>55/22/33</td>
</tr>
<tr>
<td>Right atrium, mean</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Pulmonary vascular resistance, dyn-s-cm⁻⁵</td>
<td>576</td>
<td>335</td>
</tr>
<tr>
<td>Systemic vascular resistance, dyn-s-cm⁻⁵</td>
<td>1,829</td>
<td>756</td>
</tr>
</tbody>
</table>

A 24F guide catheter was exchanged for the Mullins sheath into the left atrium through the echocardiographically guided trans-septal puncture site. The guide catheter was positioned above the mitral valve. An Evalve clip delivery system was used to place a mitral repair clip into the left atrium. The clip was manipulated into the center of the valve orifice, and the orientation of the clip arms was adjusted to be perpendicular to the line of mitral valve coaptation.

The clip arms were opened to about 180° and advanced across the mitral valve into the left ventricle. A slow withdrawal of the clip device from the left ventricular cavity back toward the left atrium resulted in grasping of the anterior and posterior mitral leaflets. The gripping arms were lowered and the clip closed. Mitral regurgitation was reassessed and noted to be dramatically attenuated. After further evaluation, complete normalization of pulmonary vein flow was seen using Doppler exam. The clip was released and mitral regurgitation assessed finally with Doppler echocardiography and left ventriculography. Hemodynamic tracings showing simultaneous left atrial and left ventricular pressures are shown in Figure 40.5B. Prerepair there is an elevated mean LA pressure and a prominent v wave. It is notable that the v wave height is not more than twice the mean LA wave height, despite the clear presence of severe mitral regurgitation.

The 24F trans-septal guide catheter was removed using temporary subcutaneous figure-of-eight suture closure, adopting a preclosure approach with a 10F suture closure device. The left femoral arterial and venous cannulae were removed using manual compression. After recovery from general anesthesia, the patient was discharged on the first morning postprocedure, with clearly dramatically improved symptoms.

Interpretation. A number of observations can be made regarding the changes in hemodynamics before and after percutaneous mitral valve repair. Cardiac output has risen substantially. Although this may reflect a diminished mitral regurgitant volume and an increase in forward stroke volume, it could as easily be owing to shunting across the atrial septum from the passage of a 24F catheter after trans-septal puncture, and also possibly owing to diminished systemic resistance associated with general anesthesia necessary for the procedure. It is noted that the systemic vascular resistance has declined from almost 2,000 dyn-second-cm⁻⁵ to 750 dyn-second-cm⁻⁵. The ejection fraction has not changed significantly. A decrease in EF may result from loss of the retrograde afterload reduction, which is eliminated by improvement in the mitral regurgitation, the degree of which has diminished dramatically.

**AORTIC STENOSIS**

Aortic stenosis may be valvular, subvalvular, or supravalvular. Valvular aortic stenosis is most often of the acquired calcific type, which develops on the substrate of a congenitally deformed (e.g., bicuspid) aortic valve. Valvular aortic stenosis also may be present from birth (congenital aortic stenosis) or may develop as a consequence of rheumatic fever. Subaortic stenosis is of various types. Supravalvular stenosis is rare. All types of aortic stenosis can result in a significant systolic pressure difference between the left ventricle and the aorta. In subaortic stenosis, the gradient is between the main portion of the left ventricle and its outflow tract, although in tunnel subaortic stenosis there may be no discrete subvalvular chamber. In supravalvular stenosis, the gradient is between the initial segment of the proximal aorta (just beyond the aortic
valve) and the main segment of the ascending aorta. To facilitate surgical intervention, it is important to identify the site and nature of the obstruction in each instance. This is determined by both hemodynamics and angiography. In addition, left ventricular function and the presence or absence of aortic and mitral regurgitation should be evaluated. The left ventricle becomes progressively hypertrophied in aortic stenosis. Cardiac output is well maintained until the left ventricle dilates and fails; it then decreases progressively. The following discussion will focus on valvular aortic stenosis in the adult.

The cardinal indications for cardiac catheterization in anticipation of surgery for all three types of aortic stenosis are left ventricular failure, angina pectoris, or syncope. Coronary angiography should be performed in essentially all adults being studied for evaluation of hemodynamically significant aortic stenosis.

**Hemodynamic Assessment**

In hemodynamic assessment of valvular aortic stenosis, primary importance should be placed on obtaining simultaneous measurements of pressure and flow across the aortic valve. As discussed in Chapter 13, this permits calculation of the aortic orifice or valve area (AVA). In the typical adult with symptomatic aortic stenosis, AVA is reduced to ≤0.7 cm². Occasionally, a valve of 0.8 to 0.9 cm² results in a symptomatic presentation, especially when there is concomitant coronary artery disease or hypertension or when the absolute value of cardiac output is high (e.g., a large patient, anemia, fever, and thyrotoxicosis). When AVA is ≤0.5 cm², severe aortic stenosis is present and cardiac reserve is minimal or absent.

For the typical adult patient with acquired aortic stenosis, correlation between clinical severity and aortic valve area calculated by the Gorlin equation (see Chapter 13) is summarized in Table 40.1. If other cardiac disease is present (e.g., coronary disease, other valve disease, cardiomyopathy), the correlations listed in Table 40.1 will not be applicable.

Most patients with aortic stenosis, particularly those with the clinical presentation of angina and/or syncope, have a normal cardiac output/index, normal right heart and PCW mean pressures, and normal LV ejection fraction. The LVEDP is usually elevated, reflecting a stiff LV chamber, and there is a prominent A wave in PCW, LA, and LV pressure tracings (Figure 40.6). In more advanced cases, LV ejection fraction and cardiac output are depressed, and right heart and PCW mean pressures are elevated. Severe pulmonary hypertension with right heart failure, ascites, and edema may eventually dominate the picture. In these patients, the low-output state may lead to a reduction in the intensity of the characteristic systolic murmur, obscuring the diagnosis. Recently, as transcatheter aortic valve replacement has become common and large numbers of very elderly patients are undergoing catheterization, we are seeing many patients with low cardiac output, pulmonary hypertension, and generally more distorted hemodynamics. As described in Chapter 20, evaluation of contractile reserve with dobutamine challenge should be included in the evaluation of patients with severely reduced ejection fraction and with low-flow, low-gradient aortic stenosis. This assessment can provide important prognostic information and can aid in the appropriate triage of patients toward medical therapy or toward surgical or percutaneous aortic valve replacement.

**The Carabello Sign**

An interesting hemodynamic finding, described by Carabello and coworkers, is a rise in arterial blood pressure during left heart catheter pullback in patients with severe aortic stenosis (Figure 40.7). Catheter pullback (withdrawal from the LV to the central aorta of a catheter that had been placed in the LV by retrograde technique) showed increases in peripheral arterial pressure of 5 mmHg in 15 of 42 patients. Fifteen of the 20 patients (75%) with AVA of 0.6 cm² demonstrated this phenomenon, but none of the 22 patients with AVA of 0.7 cm² showed such an increase. It was concluded that a rise in peak arterial pressure during LV catheter withdrawal is an ancillary hemodynamic finding of critical aortic stenosis (see Figure 40.7). The mechanism of this phenomenon is most likely related to partial obstruction of the already narrowed aortic orifice by the retrograde catheter and relief of this obstruction when the catheter is withdrawn.

**Angiographic Assessment**

In patients with aortic stenosis, left ventriculography can yield important information, and we believe that it generally should be part of the catheterization procedure, particularly when echocardiographic evaluation of the left ventricle is suboptimal. It must be emphasized, however, that patients with LV failure and high PCW pressures owing to aortic stenosis may not tolerate the radiographic contrast load of

**Table 40.1**

<table>
<thead>
<tr>
<th>Aortic Valve Area (cm²)</th>
<th>Clinical Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1.0</td>
<td>Mild: symptoms rare in absence of other heart disease (coronary disease, other valve lesions)</td>
</tr>
<tr>
<td>0.7–1.0</td>
<td>Moderate: symptoms with unusual stress, such as vigorous exercise, rapid atrial fibrillation, influenza</td>
</tr>
<tr>
<td>0.5–0.7</td>
<td>Moderately severe: symptoms with ordinary activities of daily living</td>
</tr>
<tr>
<td>≤0.5</td>
<td>Severe: symptoms at rest or minimal exertion, biventricular failure</td>
</tr>
</tbody>
</table>
left ventriculography. Furthermore, abnormal renal function may also limit the use of contrast. Adequate preparation (e.g., intravenous furosemide, morphine, and oxygen) before ventriculography and use of iso-osmolar or low-osmolar contrast agents are mandatory in such patients, and ventriculography should not be done without careful consideration of risk versus benefit. The value to be derived from left ventriculography includes assessment of the mitral valve (is there significant mitral regurgitation?), detection of regional wall motion abnormalities or LV aneurysm indicative of major coronary disease, and overall assessment of LV function. In addition, wall thickness and LV mass may

**Figure 40.6** Pressure recordings in a patient with aortic stenosis. A. Left ventricular (LV) and central aortic (Ao) pressures recorded simultaneously. B. LV and femoral arterial (FA) pressures. The FA pressure is out of phase and exhibits distortion (a higher systolic peak and lower end-diastolic pressure) characteristic of peripheral arterial pressures. (From Blitz LR, Kolansky DM, Hirshfeld JW Jr. Valve function, stenosis and insufficiency. In: Pepine CJ, Hill JA, Lambert CR, eds. Diagnostic and Therapeutic Cardiac Catheterization, 3rd ed. Baltimore: Williams & Wilkins, 1998.)

**Figure 40.7** Left ventricular (LV) and femoral artery (FA) pressure tracings in a patient with severe aortic stenosis (aortic valve area 0.4 cm²). During pullback of the retrograde catheter from LV to ascending aorta, the peak systolic femoral artery pressure can be seen to increase (∆P) by approximately 20 mmHg. This sign is seen only in patients with aortic valve areas of <0.6 cm². The mechanism of this phenomenon is believed to be partial obstruction of an already narrowed aortic orifice by the retrograde catheter and relief of this obstruction with catheter withdrawal. (From Carabello BA, et al. Changes in arterial pressure during left heart pullback in patients with aortic stenosis. Am J Cardiol 1979;44:424.)
be measured from the ventriculogram. Often this information can be obtained from echocardiography, and contrast left ventriculography can be avoided.

Aortography is generally not required in the patient with aortic stenosis, unless the gradient is small and the aortic pulse pressure is wide and significant aortic insufficiency is suspected. When transcatheter aortic valve replacement is being considered, hand injection in the aortic root may be used to help define an optimal working view or implant angle for the TAVR procedure. Selective coronary arteriography should be done in most patients with acquired calcific aortic stenosis, especially if chest pain is present.

Catheterization Protocol

1. Right heart catheterization for measurement of right heart pressures and cardiac output.
2. Left heart catheterization for measurement of pressure gradient across aortic valve and LVEDP, and assessment of the presence or absence of a transmitral gradient (concomitant mitral stenosis). Retrograde crossing of a tight aortic valve may be difficult. From the brachial or radial approach, many operators have been successful in crossing a stenosed aortic valve using a 5F AL1 or a multipurpose catheter. A guidewire is almost always required, and a 0.35-inch-diameter straight or angled glide wire passes easily through the catheter and can help in crossing the aortic valve.

With a femoral approach, a pigtail catheter together with a straight guidewire protruding a short distance beyond the catheter tip has been supplanted by the AL1 catheter as the first approach to retrograde catheterization of the left ventricle in the patient with aortic stenosis; this method is illustrated in Chapter 6. The Amplatzer catheter can be used to direct the guidewire toward the blood flow jet and to successfully cross the stenotic valve. The catheter can then be exchanged for a standard dual-lumen pigtail catheter over an exchange guidewire. On occasion, a right or left Judkins coronary catheter used together with a straight guidewire is successful in crossing a tight aortic valve in the patient with aortic stenosis. An improved catheter design for crossing stenosed aortic valves has been developed by Feldman and coworkers. They found that using this catheter (Cook, Inc., Feldman A1 catheter), the median time taken to cross the aortic retrograde was 30 to 40 seconds in a group of 17 patients with a mean aortic valve area of 0.75 cm². The use of the Amplatz or the Feldman A1 catheter is the preferred initial approach by most operators. If these approaches are not successful (or are not desirable in a particular patient), a trans-septal approach may be used. In some laboratories, the trans-septal approach is the primary technique for patients with aortic stenosis. Retrograde crossing of the aortic valve results in clinically silent cerebral embolic lesions in some patients. The trans-septal approach presumably decreases this risk.

In patients with aortic stenosis, it is highly desirable to measure transvalvular gradients as close as possible to the site of obstruction. Thus, as seen in Figure 40.6, the transaortic gradient measured with a catheter in the left ventricle and another catheter in the central aorta may differ from that obtained when arterial pressure is measured in the femoral artery. This problem is discussed in greater detail in Chapter 13. Dual-lumen pigtail catheters (e.g., Langston catheter, Vascular Solutions Inc., Minneapolis, MN) make it possible to measure left ventricular and central aortic pressures with a single catheter, avoiding the need for a separate arterial entry site. The central aortic pressure may also be compared with the left ventricular cavity pressure by passing a diagnostic catheter into the left ventricle, and then placing a 0.014-inch pressure wire (St. Jude, Minneapolis, MN) through the diagnostic catheter. The diagnostic catheter may then be withdrawn into the aortic root just above the valve, yielding simultaneous measurement of the central aortic and left ventricular pressures. This method produces tracings of sufficient quality to mimic high-fidelity micromanometer pressure recordings.

Another potentially important source of error in pressure measurement in patients with aortic stenosis can result from incomplete entry of a multiple-side-hole catheter into the left ventricular chamber. Some of the holes are in the aorta and some in the left ventricle, resulting in a hybrid recording. Figure 40.8 illustrates this problem, with a pigtail catheter placed partially (Figure 40.8B left) or completely (Figure 40.8B right) within the left ventricular chamber. The partial-entry pressures lead to a gross underestimation of the severity of the aortic stenosis. Additional pitfalls in the measurement of transvalvular pressure gradients are illustrated in Chapters 13 and 14.

3. Angiography following the guidelines just discussed.

Left ventriculography displays the stenotic orifice of the valve during systole as outlined by a jet of contrast material ejected into the aorta. The valve cusps may appear irregular, their mobility may be reduced, and often the number of cusps can be identified. In congenital aortic stenosis, the valve may form a funnel during systole. The ascending aorta is dilated (poststenotic dilatation), but the subvalvular area is widely patent. A subaortic membrane, with a small central orifice, or a subvalvular muscular ring may be seen. The characteristic changes of idiopathic hypertrophic subaortic stenosis may be observed. In supravalvular stenosis, narrowing of the proximal aorta can be seen.

Aortography also can be helpful in evaluation of the patient with aortic stenosis. In “pure” aortic stenosis (no concomitant aortic regurgitation), aortography often demonstrates a negative jet of radiolucent blood exiting focally from the left ventricle. In congenital aortic stenosis, there may be upward doming of the aortic valve leaflets, which together with the central negative jet gives the so-called Prussian helmet sign (Figure 40.8). In the patient with aortic stenosis who also has some aortic regurgitation, aortography permits a rough quantitation of the severity of the regurgitation. If interventional catheter techniques (e.g., balloon aortic valvuloplasty) are under consideration, determination of the extent of associated aortic regurgitation may become important in clinical decision making.
dyspnea and decreased effort tolerance. She had had dizziness but no syncope or angina.

Physical examination was normal except for the heart. There was a forceful apex impulse in the midclavicular line in the fifth interspace. Rhythm was regular. \( S_1 \) and \( S_2 \) were normal. The only murmur was a grade 2/6 ejection-type systolic murmur, maximal along the left sternal border and transmitted to the apex and into the carotids. No thrill was detected. Carotid pulsations exhibited a slow upstroke but were of normal amplitude. ECG revealed left ventricular hypertrophy and strain. Chest radiographs showed a heart of normal overall size. There was a little rounding in the region of the left ventricle. The other cardiac chambers appeared normal, as did the lungs. As observed by fluoroscopy, there was calcification in the region of the aortic valve.

The findings at cardiac catheterization were as follows:

| Body surface area, \( \text{m}^2 \) | 1.87 |
| \( \text{O}_2 \) consumption, \( \text{mL/min} \) | 225 |
| \( \text{A-V} \, \text{O}_2 \) difference, \( \text{mL/L} \) | 40 |
| Cardiac output, \( \text{L/min} \) | 5.6 |
| Heart rate, beats/min | 70 |
| Pressures, mmHg |
| Brachial artery | 100/66 |
| Systolic mean | 84 |
| Left ventricle | 176/16 |
| Systolic mean | 140 |
| Systolic ejection period, s/beat | 0.35 |
| Pulmonary capillary wedge, mean | 10 |
| Pulmonary artery | 25/11, 15 |
| Right ventricle | 25/5 |
| Right atrium, mean | 5 |
| Pulmonary vascular resistance, dyne-s-cm\(^{-5}\) | 72 |
| Calculated aortic valve area, \( \text{cm}^2 \) | 0.7 |
| Ejection fraction | 0.69 |

Hemodynamic assessment often can detect the presence of mixed significant aortic stenosis and regurgitation, as illustrated by the patient whose pressure tracings are shown in Figure 40.9A. This 78-year-old man had the unusual combination of hemodynamically significant aortic stenosis (70 mmHg gradient) and significant aortic regurgitation (3+, regurgitant fraction 48%).

**CASE 40.6 Aortic Stenosis Without Appreciable Cardiomegaly.** L.C. was a 48-year-old married woman with a history of rheumatic fever in childhood. Six months before admission, she noted increasing exertional dyspnea and decreased effort tolerance. She had had dizziness but no syncope or angina.

Left ventriculography showed a vigorously contracting normal-sized left ventricle and a calcified aortic valve with three cusps. The valve leaflets were almost immobile. A jet was seen passing through the valve that almost immediately became obscured by the radiopacity of the aorta. There was a rather discrete poststenotic dilation of the ascending aorta just above the aortic valve.

**Interpretation.** The moderately severe calcific aortic stenosis in this woman was probably rheumatic in origin. The left ventricle contracted well, as indicated by an ejection fraction of 0.69 and a normal cardiac output. The elevated
LVEDP at rest was compatible with a decreased chamber distensibility from hypertrophy.

**CASE 40.7** Aortic Stenosis with Appreicable Cardiomegaly. A.H., a 77-year-old man, was well until 3 years before admission, when exertional dyspnea, orthopnea, fatigue, and peripheral edema appeared. Despite therapy, these symptoms increased progressively to the point of invalidism. He had mild angina and had had two syncopal episodes.

On physical examination, the blood pressure was 110/80 mmHg; the pulse was 78 beats per minute and regular; respirations were 24 per minute. The carotids were of small volume with slow upstroke. Neck veins were moderately distended. There were basilar rales audible over both lungs. The point of maximal impulse was in the sixth interspace 2 cm within the anterior axillary line, diffuse and forceful. There was no parasternal heave. A grade 2/6 aortic systolic ejection murmur was heard all along the left sternal border and over both carotid arteries. The liver was two palpable fingerbreadths below the right costal margin. There was slight pitting edema of both lower legs. The ECG showed left ventricular hypertrophy and strain pattern. Chest roentgenogram showed enlargement of the left ventricle, calcification in the

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**Figure 40.9**

A. Left ventricular (LV) and femoral artery (FA) pressure tracings in a 78-year-old man with increasing dyspnea on exertion and one episode of pulmonary edema. In this case, femoral artery and central aortic pressures were nearly superimposable. There is a 70-mmHg peak-to-peak systolic gradient, but there is also an unusually rapid aortic diastolic runoff with equilibration (diastasis) of end-diastolic LV and FA pressures. This latter finding suggested significant aortic regurgitation, which was confirmed by aortography. B. (Case 40.8) Simultaneous recordings of LV and aortic (Ao) pressures. The prevalluloplasty transaortic valve pressure gradient is shaded in black (left). After valvuloplasty, there is a marked reduction in the transvalvular gradient (right). It is notable that the left ventricular peak systolic pressure has decreased and the aortic peak systolic pressure has increased as a result of the relief of valve stenosis. C. Percutaneous heart valve prosthesis for the aortic valve position (Edwards Lifesciences, Irvine, CA). Equine pericardial leaflet tissue is mounted on a specially designed stainless steel stent. The stent is robust, with thick struts and reinforcement at the commissural lines.
region of the aortic valve, moderate redistribution of vascular markings to the upper lobes of the lungs, and a small amount of pleural fluid on the right.

Cardiac catheterization yielded the following results:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body surface area, m²</td>
<td>1.76</td>
</tr>
<tr>
<td>O₂ consumption, mL/min</td>
<td>218</td>
</tr>
<tr>
<td>A–V O₂ difference, mL/L</td>
<td>81</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>2.7</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>90</td>
</tr>
<tr>
<td>Pressures, mmHg</td>
<td></td>
</tr>
<tr>
<td>Brachial artery</td>
<td>135/78</td>
</tr>
<tr>
<td>Systolic mean</td>
<td>100</td>
</tr>
<tr>
<td>Left ventricle</td>
<td>184/35</td>
</tr>
<tr>
<td>Systolic mean</td>
<td>140</td>
</tr>
<tr>
<td>Systolic ejection period, s/beat</td>
<td>0.27</td>
</tr>
<tr>
<td>Pulmonary capillary wedge, mean</td>
<td>29</td>
</tr>
<tr>
<td>Pulmonary artery</td>
<td>75/40, 52</td>
</tr>
<tr>
<td>Right ventricle</td>
<td>75/12</td>
</tr>
<tr>
<td>Right atrium, mean</td>
<td>10</td>
</tr>
<tr>
<td>Pulmonary vascular resistance, dyn s cm⁻⁵</td>
<td>683</td>
</tr>
<tr>
<td>Aortic valve area, cm²</td>
<td>0.4</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>0.30</td>
</tr>
</tbody>
</table>

Left ventriculography was performed only after pretreatment with intravenous furosemide and showed a large dilated left ventricle with uniformly poor contractions in systole. There was no mitral or aortic regurgitation. The aortic valve had two leaflets that appeared ragged and were heavily calcified. There was considerable dilation of the ascending aorta. Left ventriculography was tolerated well, and coronary angiography (two injections of the left coronary artery and one injection of the right coronary artery) revealed the absence of significant coronary artery obstruction.

**Interpretation.** There was severe calcific aortic stenosis, as indicated by a calculated valve area of 0.4 cm². Severe left ventricular failure was present, as indicated by left ventricular dilatation, high left ventricular end-diastolic pressure (35 mmHg), uniformly poor contraction by cineangiocardiography, an ejection fraction of only 0.30, and a very low cardiac output. The aortic obstruction was severe, and the left ventricle was so compensated that it generated a peak systolic pressure of only 184 mmHg (instead of 250 to 300 mmHg, as would be expected with a normal cardiac output), and the mean transaortic pressure gradient was only 40 mmHg. It is notable that left ventricular dilatation is more common in men than in women with aortic stenosis.²³

The pulmonary capillary wedge pressure of 29 mmHg explained the rales heard at both lung bases as well as the patient’s shortness of breath. The pulmonary hypertension was owing in part to the elevated left ventricular diastolic pressure (passive rise) and in part to reactive pulmonary hypertension, as revealed by the finding of a pulmonary vascular resistance of 683 dyn·second·cm⁻⁵, more than five times the normal.

The pressure load on the right ventricle resulted in its decompensation, as indicated by a mild elevation of the right ventricular diastolic and right atrial pressures. Its clinical counterparts were slight distension of the neck veins, an enlarged liver, and peripheral edema.

**CASE 40.8 Symptomatic Aortic Stenosis in a Poor Candidate for Aortic Valve Replacement.**

FH, an 87-year-old man with a history of coronary artery disease and prior bypass surgery, was admitted to the hospital with worsening heart failure and aortic stenosis. He had undergone coronary bypass graft surgery 6 years prior to admission and was not noted to have aortic stenosis at the time.

Over the previous year, he had had increasingly frequent hospitalizations for congestive heart failure. His clinical picture was complicated by chronic obstructive pulmonary disease requiring home oxygen and chronic renal failure with a creatinine level that has been stable for over 6 months at 2.6 mg/dL. The STS risk score was 12.7%.

Echocardiographic examination demonstrated a poor left ventricle with an estimated ejection fraction of 35% and an estimated aortic valve area of 0.7 cm², with a mean gradient of 27 mmHg. In addition to heart failure, he complained of postprandial chest pain that responds to sublingual...
nitroglycerin, usually after breakfast and occurring a few times each week.

Diagnostic catheterization demonstrated a patent left mammary graft to the LAD, but no other angiographic images were obtained to conserve contrast. The aortic valve area was estimated to be 0.8 cm² with a 30-mm transaortic valve mean pressure gradient. He was referred for evaluation for aortic valvuloplasty owing to his high risk for reoperation in the face of multiple comorbidities.

After bilateral local femoral anesthesia, a 6F sheath was placed in the right femoral artery. Iliofemoral angiography was performed on the right side, which demonstrated moderate diffuse disease in the femoral artery, but adequate for insertion of a 11F sheath for retrograde valvuloplasty. “Stacked” right femoral 5F and 8F venous access was obtained as well. A balloon-tipped catheter via the 8F venous access was used for measurement of right heart pressure and cardiac output. A temporary pacemaker was placed via the 5F venous access. The aortic valve was crossed with a 5F aortic stenosis catheter (Cook, Inc., Bloomington, IN) and a straight movable core guidewire.20 The central aortic and femoral arterial sheath pressures were verified to match and recorded.

After initial catheterization, the following hemodynamic values were obtained:

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Post BAV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body surface area, m²</td>
<td>2.09</td>
<td></td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>5.59</td>
<td>5.63</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>79</td>
<td>88</td>
</tr>
<tr>
<td>Pressures, mmHg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aorta, sys/dias/mean</td>
<td>211/95/140</td>
<td>207/95/136</td>
</tr>
<tr>
<td>Left ventricle, sys/dias/ED</td>
<td>264/11/28</td>
<td>214/16/22</td>
</tr>
<tr>
<td>Left atrium, a/v/mean</td>
<td>32/15/21</td>
<td></td>
</tr>
<tr>
<td>Pulmonary artery, sys/dias/mean</td>
<td>45/29/35</td>
<td>46/32/36</td>
</tr>
<tr>
<td>Right atrium, mean</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>Transaortic valve gradient, mean</td>
<td>46</td>
<td>18</td>
</tr>
<tr>
<td>Aortic valve area, cm²</td>
<td>0.8</td>
<td>1.3</td>
</tr>
<tr>
<td>Systemic vascular resistance, dyn·s·cm⁻⁵</td>
<td>1,731</td>
<td>1,903</td>
</tr>
</tbody>
</table>

After pressure measurements were made, a 260-cm extra-stiff guidewire was exchanged through the 5F catheter into the left ventricle and the catheter removed. A 20-mm-diameter, 6-cm-long balloon was passed retrograde across the aortic valve and inflated three times, with simultaneous rapid RV pacing at a rate of 180 beats per minute. The balloon never locked into the valve, and despite rapid RV pacing, it “watermelon seeded” back and forth, indicating that it was not sized adequately to achieve expansion of the aortic valve leaflets. Since the femoral arterial disease precluded insertion of a 14F arterial sheath for a larger retrograde balloon, the procedure was converted to an antegrade valvuloplasty approach.

The right femoral venous access was upsized to 14F, and trans-septal puncture performed using a standard Mullins sheath and trans-septal needle. A 7F single-lumen balloon catheter was passed through the Mullins sheath into the left atrium and then into the left ventricle. The balloon catheter was then passed antegrade across the stenotic aortic valve into the arch and then into the descending aorta. A 0.032-inch stiff guidewire was passed through the balloon-tipped catheter and snared with a 10-mm gooseneck snare from the left femoral artery in the descending aorta. The snare and wire were left in the descending aorta. The Mullins sheath was removed, and a 14F rigid dilator was passed across the atrial septum and removed. An Inoue 26-mm-diameter balloon catheter was passed via the left atrium and positioned in the aortic valve. The balloon was inflated first to 24 mm and then to 26 mm diameter to accomplish aortic valve dilatation. Hemodynamic measurements were repeated (Figure 40.9B). The catheters were ultimately withdrawn and the femoral sheaths removed using a preplaced suture closure device.

Interpretation. The hemodynamic results of balloon valvuloplasty are illustrated in Figure 40.9B. The mean transvalvular pressure gradient has been reduced from 46 to 18 mmHg. It is important to note that the peak left ventricular systolic pressure has declined, and the peak aortic systolic pressure has risen with the relief of aortic valve obstruction. The rise in peak aortic systolic pressure is an excellent indicator of the hemodynamic success of balloon valvuloplasty. It is also notable that the aortic diastolic pressure has not decreased following dilatation of the valve, indicating that if aortic regurgitation has been caused, it is not hemodynamically important. Similarly, the left ventricular end-diastolic pressure has declined from nearly 30 to 22 mmHg, indicating relief of obstruction with acute improvement in the filling pressures.

Another approach that would also be suitable for a patient like this, with advanced age, prior sternotomy, and multiple comorbid factors causing increased surgical risk, would be percutaneous aortic valve replacement.24-26 Stent-mounted pericardial tissue valves are in use for percutaneous delivery into the aortic valve (Figure 40.9C; see Chapter 33 for a detailed discussion). After obtaining either antegrade or retrograde access, balloon valvuloplasty is performed to predilate the valve. Using a large-caliber sheath for delivery, the stent-mounted prosthetic (percutaneous heart valve) is cramped on a noncompliant 23- or 26-mm balloon catheter and delivered into the aortic valve. Right ventricular pacing at 180 to 220 beats per minute is used to effectively stop left ventricular ejection so that the prosthesis may be positioned carefully in the aortic annulus. The balloon is inflated, expanding the stent. Aortography is used to document free
flow into the coronary arteries, since coronary obstruction is one of the greatest risks of placing a prosthesis in the aortic annulus in this manner. Extensive experience has recently become available with this approach, and it shows excellent hemodynamic results with no residual transaortic valve pressure gradients and valve areas typically about 1.7 cm² (see Chapter 33).

AORTIC REGURGITATION

The dynamic effects of aortic regurgitation are caused by regurgitation of blood from the aorta to the left ventricle in diastole. The magnitude of regurgitation depends on the size of the regurgitant orifice, the pressure difference between the aorta and the left ventricle in diastole, and the duration of diastole. The regurgitant aperture may be as large as 1.0 cm², but regurgitation is generally severe when the aperture is >0.5 cm². The total left ventricular stroke volume increases and equals that which supplies the body (forward flow) plus that which is regurgitated. The amount of blood regurgitated may be as much as 60% of the systolic discharge. Regurgitation usually occurs in early diastole.

Hemodynamic Assessment

The large stroke volume entering the aorta with systole produces an elevated systolic pressure, whereas regurgitation produces a lowered aortic diastolic pressure (Figure 40.10). Left ventricular workload increases progressively with the magnitude of regurgitation. This is owing not only to the raised stroke volume and to the rise of systolic pressure but also to the high left ventricular wall stress that develops when a dilated left ventricle contracts to produce a given pressure (Laplace's law). Dilatation and hypertrophy of the left ventricle are invariable consequences of aortic regurgitation. The heart may become the largest encountered in cardiac pathology—the so-called cor bovinum. Up to a point, the forward cardiac output is well maintained. The addition of blood regurgitated to the normal inflow from the left atrium increases the diastolic volume of the left ventricle, leading to a more forceful contraction (Starling's law). With time, the fraction of end-diastolic volume ejected per beat (ejection fraction) diminishes, reflecting impaired myocardial function. Furthermore, the left ventricle may operate with an excessive end-systolic volume—another index of left ventricular dysfunction. A method to quantify the severity of aortic regurgitation is calculation of the aortic regurgitation index (ARI). ARI is calculated as the ratio of the gradient between diastolic blood pressure (DBP) and left ventricular end-diastolic pressure (LVEDP) to systolic blood pressure (SBP), that is, ARI = [(DBP – LVEDP)/SBP] × 100. As ARI approaches 0, the severity of aortic regurgitation increases, whereas higher values of ARI reflect less severe aortic regurgitation.

Premature Mitral Valve Closure

The reflux of blood from the aorta into the left ventricle in diastole added to the blood streaming through the mitral valve from the left atrium results in a rapid rise in left ventricular pressure early in diastole. The mitral valve may close prematurely because the regurgitating blood may raise the left ventricular diastolic pressure to exceed that in the left atrium. This is particularly common in acute aortic regurgitation, where the sudden onset of severe regurgitation into a normal-sized left ventricle leads to striking elevations in LV diastolic pressure (Figure 40.11). In the case illustrated in Figure 40.11, LVEDP approaches 50 mmHg, and LV diastolic pressure exceeds left atrial (or wedge) pressure for nearly half of the diastole. This reversal of pressures is associated with premature mitral valve closure, which may be seen on the echocardiogram.

Another example of premature closure of the mitral valve in association with severe aortic regurgitation is shown in Figure 40.12. These tracings were recorded during cardiac catheterization of a 71-year-old man who had previously undergone aortic valve replacement for aortic stenosis. After doing extremely well for more than 5 years, he suddenly developed marked shortness of breath and a new murmur of aortic regurgitation. Pressure recordings (see Figure 40.12) show that left ventricular diastolic pressure exceeds left atrial (pulmonary capillary wedge) pressure by the end of the first third of the diastolic filling period. Also, complete diastasis of aortic and left ventricular pressures occurs by mid-diastole, at which point aortic regurgitation...
Acute versus Chronic Aortic Regurgitation

The typical hemodynamic findings in acute versus chronic aortic regurgitation have been reported by Mann et al. and are presented in Table 40.2. As can be seen, widened pulse pressure is characteristic only of chronic aortic regurgitation, reflecting both the enormous stroke volume associated with this condition and the tachycardia commonly seen in patients with acute aortic regurgitation. This may give rise to a situation in which there exists a high end-diastolic pressure in the noncompliant left ventricle in the presence of little, if any, elevation of the mean pressure in the left atrium. With time and with the severity of the leak, the mean diastolic pressure of the left ventricle rises, and when this happens, left atrial and pulmonary capillary wedge pressures rise.

Another hemodynamic finding in aortic regurgitation is the amplification of peak systolic pressure in peripheral arteries (especially the femoral and popliteal) so that peak systolic femoral artery pressure may exceed central aortic pressure by 20 to 50 mmHg. This is essentially an exaggeration of a normal phenomenon (see Chapter 10) but emphasizes the importance of central aortic pressure measurement in aortic regurgitation.

Angiographic Assessment

Aortic cineangiography (aortography) yields a graphic demonstration of the severity and dynamics of aortic regurgitation. Qualitative assessment is subjective, as for mitral regurgitation. A scale of 1+ to 4+ may be used, with the following definitions, to aid discrimination of these four degrees of regurgitation. In 1+ regurgitation (mild), a small amount of contrast material enters the left ventricle in diastole; it is essentially cleared with each beat and never fills the ventricular chamber. More contrast material enters with each diastole in 2+ (moderate) regurgitation, and faint opacification of the entire chamber occurs. With moderately severe (3+) regurgitation, the LV chamber is well opacified, with a density of opacification equal to that of the ascending aorta. Severe (4+) aortic regurgitation is characterized by complete, dense opacification of the LV chamber in one beat, and the left ventricle appears more densely opacified than the ascending aorta.

Quantitative assessment of aortic regurgitation involves calculation of regurgitant fraction (RF), as described in Chapter 21. The same scale of interpretation holds as for mitral regurgitation, with RF <20% corresponding to mild regurgitation; 20% to 40%, moderate; 40% to 60%, moderately severe; and >60%, severe aortic regurgitation.

Part of the angiographic assessment of aortic regurgitation involves assessment of the aortic valve leaflets (mobility, calcification, number of leaflets), the ascending aorta (extent and type of dilatation), and possible associated abnormalities (e.g., coronary lesions, sinus of Valsalva aneurysm, dissecting aneurysm of the aorta, and ventricular septal defect). All these aspects are best evaluated in the LAO view.
Table 40.2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Acute AR</th>
<th>Chronic AR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>33 ± 14</td>
<td>40 ± 15</td>
<td>NS</td>
</tr>
<tr>
<td>Regurgitant fraction</td>
<td>0.6 ± 0.1</td>
<td>0.7 ± 0.1</td>
<td>NS</td>
</tr>
<tr>
<td>LVEDP (mmHg)</td>
<td>41 ± 12</td>
<td>36 ± 13</td>
<td>NS</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>0.6 ± 0.1</td>
<td>0.6 ± 0.1</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>108 ± 15</td>
<td>71 ± 14</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LV volumes (mL/m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDV</td>
<td>146 ± 28</td>
<td>264 ± 64</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ESV</td>
<td>57 ± 23</td>
<td>101 ± 42</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>TSV</td>
<td>89 ± 22</td>
<td>163 ± 57</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Systolic pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic pressure</td>
<td>110 ± 14</td>
<td>155 ± 26</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mean</td>
<td>56 ± 11</td>
<td>50 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td>Pulse pressure (mmHg)</td>
<td>78 ± 12</td>
<td>90 ± 8</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Systemic vascular resistance</td>
<td>55 ± 7</td>
<td>105 ± 22</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>1,326 ± 372</td>
<td>1,341 ± 461</td>
<td>NS</td>
</tr>
</tbody>
</table>

EDV, end-diastolic volume; ESV, end-systolic volume; TSV, total stroke volume; AR, aortic regurgitation; LVEDP, left ventricular end-diastolic pressure; NS, not significant.

**Catheterization Protocol**

1. Right heart catheterization for measurement of right heart pressures and cardiac output.
2. Left heart catheterization for measurement of central aortic pulse pressure and LVEDP; detection of transvalvular gradients (if any) and diastasis between LV and aorta, if it is present (see Figure 40.12); and determination of the relative height of LVEDP as compared with PCW or LA mean pressure.
3. Angiography, including left ventriculography, aortography, and possibly coronary angiography (if indicated clinically).
4. If resting hemodynamics are normal, consider stress intervention, such as dynamic exercise.

**TRICUSPID REGURGITATION**

Tricuspid regurgitation can be functional or organic. Functional tricuspid regurgitation is thought to be owing to right ventricular dilatation and failure as a result of excessive right ventricular afterload. Most commonly, this is caused by pulmonary hypertension from mitral stenosis, cardiomyopathy, primary pulmonary hypertension, cor pulmonale, or pulmonary embolism.

Organic tricuspid regurgitation implies disease of the tricuspid valve or its supporting apparatus and is seen most commonly with bacterial endocarditis, rheumatic heart disease, or right ventricular infarction.

**Hemodynamic Assessment**

In tricuspid regurgitation, either organic or functional, the primary hemodynamic finding is a large systolic wave in the right atrial pressure tracing. Tracings of jugular venous pulsations show a, c, and v waves in the normal subject; in the patient with moderate tricuspid regurgitation, there is a fourth pulsation, the s wave. This systolic wave precedes and blends with the normal venous filling (v) wave, and in severe tricuspid regurgitation, the s and v waves form a single regurgitant systolic wave (Figure 40.13). As can be seen in
Figure 40.13, the right atrial pressure tracing in severe tricuspid regurgitation resembles the right ventricular pressure tracing. In the most extreme cases, the right atrial and ventricular pressure tracings are virtually superimposable, which is to be expected because the right atrium and ventricle are physiologically a common chamber in such cases.

Hemodynamic distinction between organic and functional tricuspid regurgitation is difficult. Generally, if the patient with severe tricuspid regurgitation has a right ventricular systolic pressure of >60 mmHg, the tricuspid regurgitation is functional, whereas if the right ventricular systolic pressure is 40 mmHg, there is a substantial organic component. This distinction is of practical importance in terms of surgical correction, because functional tricuspid regurgitation will improve substantially with correction of the right ventricular hypertension (e.g., following balloon valvuloplasty or corrective surgery for mitral stenosis), whereas the patient with major organic tricuspid regurgitation may not survive cardiac surgery unless the operation includes tricuspid valve replacement or tricuspid annuloplasty.

Angiographic Assessment

Angiographic demonstration of tricuspid regurgitation is generally accomplished by right ventricular cineangiography in the right anterior oblique (RAO) projection, as discussed in Chapter 17. Some artificial tricuspid regurgitation is seen because of the presence of the catheter across the tricuspid valve, but this is usually minor. It is important to choose a catheter type, position, and an injection rate that will avoid extrasystoles because a run of ventricular tachycardia makes it impossible to evaluate the degree of tricuspid regurgitation. There has been considerable experience with the Grollman, pigtail, and Eppendorf catheters positioned mid-RV or in the RV outflow tract, with injection rates of 12 to 18 mL/second depending on RV size and irritability. A scale of 1+ to ++ is used to grade severity of tricuspid regurgitation, using criteria of definition similar to those described for mitral regurgitation. In certain circumstances, a right atrial cineangiogram in RAO projection can be used for assessment of tricuspid regurgitation; in this instance, a negative jet (unopacified blood) from RV to RA shows the regurgitation.

Cardiac catheterization protocol depends on the associated conditions.

TRICUSPID STENOSIS

Previously, this rare condition was seen only in patients with rheumatic heart disease and mitral stenosis. Today, however, stenosis of a prosthetic tricuspid valve (placed originally as treatment for tricuspid regurgitation) accounts for most of the cases seen in most major medical centers. Clinical diagnosis may be difficult, especially if the patient is in atrial fibrillation. Diagnosis is aided by the characteristic finding of an increased jugular venous pressure with blunting or absence of the y descent. One patient had severe stenosis of her native mitral, aortic, and tricuspid valves. This was a 43-year-old woman with a history of repeated bouts of rheumatic fever in childhood, whose major complaints were fatigue and “blackouts.”

Hemodynamic Assessment

The sine qua non of tricuspid stenosis is a pandiastolic gradient across the tricuspid valve. The gradient is usually small (4 to 8 mmHg) and may be missed unless a careful assessment is made. Two catheters (or a single catheter with a double lumen) for simultaneous measurement of RA and RV pressures should be used if there is any doubt about the presence of this condition. A careful RV to RA pullback using a standard catheter, however, will serve to confirm or eliminate this diagnosis with reliability in most cases. The tricuspid valve area is calculated using the formula given in Chapter 13. Tricuspid stenosis is usually of clinical and hemodynamic significance when the tricuspid valve area is <1.3 cm².

Angiographic Assessment

The valve is usually calcified and shows decreased mobility. There may be associated right atrial dilatation and some tricuspid regurgitation.

Cardiac catheterization protocol depends on associated lesions.
PULMONIC STENOSIS AND REGURGITATION

Pulmonic stenosis is essentially a congenital condition. Pulmonic regurgitation is usually functional and a consequence of severe pulmonary hypertension. When the pulmonary artery pressure exceeds 100 mmHg systolic, there is usually some pulmonic regurgitation. This may lead to widening of the pulmonary artery pulse pressure and an increase in right ventricular end-diastolic pressure (RVEDP). Angiographic assessment of pulmonic regurgitation is difficult because the angiographic catheter lying across the pulmonic valve may cause artifactual regurgitation. Echocardiography is far superior to angiography in assessing pulmonic regurgitation.

Cardiac catheterization protocol depends on associated conditions.

EVALUATION OF PROSTHETIC VALVES

Evaluation of mechanical heart valves can be at times challenging. It requires knowledge of the baseline hemodynamic profile and effective orifice area of each valve, as well as additional skills in trans-septal cardiac catheterization and, in rare cases, in the performance of direct apical puncture (see also Chapter 6).

Relative Stenosis of Prosthetic Valves

An unusual case of relative tricuspid stenosis, mitral stenosis, and aortic stenosis in a 60-year-old man is shown in Figure 40.14 which illustrates an important point concerning function of prosthetic cardiac valves. This man had mitral valve replacement with a Harken disc valve in 1969 for rheumatic mitral regurgitation. He did well until 1980, when he presented with left and right heart failure and was found at cardiac catheterization to have severe aortic and tricuspid regurgitation but normal function of the mitral prosthetic valve. Aortic valve replacement (Starr–Edwards prosthesis) and tricuspid valve replacement (porcine prosthesis) led to improvement, but over the following years he required large amounts of diuretic therapy to remain free of edema and pulmonary congestion. Echocardiographic assessment of his prosthetic valves demonstrated apparently normal function, and left ventricular contraction was vigorous.

Because of persistent left and right heart failure, cardiac catheterization was undertaken in 1985. The porcine tricuspid valve was crossed antegrade with a Swan-Ganz catheter, and the Starr-Edwards aortic prosthesis was crossed retrograde with a Sones catheter to obtain the pressure measurements shown in Figure 40.14. As can be seen, significant pressure gradients were present across tricuspid, mitral, and aortic prostheses. A surprising finding, however, was an elevated cardiac output, measured by both Fick and thermodilution methods. Oxygen consumption index was 148 mL/minute per m² and arteriovenous oxygen difference was 29 mL O₂/L, giving a Fick cardiac index of 5 L/minute per m² and a cardiac output of 10 L/minute. Using the Gorlin formula (Chapter 13), the calculated aortic valve area was 1.3 cm², mitral valve area was 1.6 cm², and tricuspid valve area was 2.4 cm²; these values were all consistent with the known effective orifice areas of the particular prosthetic valves implanted and did not signify prosthetic valve dysfunction or stenosis. Thus, a high cardiac output state caused substantial pressure gradients to occur across the patient's three

Figure 40.14 Pressure tracings in a 60-year-old man with high cardiac output and significant pressure gradients across normally functioning tricuspid, mitral, and aortic valve prostheses (A) from the right ventricle (RV) and right atrium (RA); (B) from the left ventricle (LV), femoral artery (FA), and pulmonary capillary wedge (PCW) positions.
Catheter Passage across Prosthetic Valves

As illustrated in the case just described, it has become routine to cross prosthetic valves with catheters in an attempt to assess their function or the function of other valves. Published reports have documented the safety of this procedure in many patients with a variety of prosthetic valves. Based on our own experience and anecdotal experience reported to us by many others, we offer the following guidelines: First, porcine valves may be crossed retrograde or antegrade safely with a variety of catheters. For retrograde crossing of a porcine prosthetic valve in the aortic position, a pigtail catheter is generally highly effective. The pigtail catheter tip is rested on top of the valve's leaflets as they protrude into the aorta high above the sewing ring and is gently rotated and advanced until it prolapses into the left ventricular chamber. Antegrade crossing of a porcine tricuspid valve is accomplished easily using a balloon-flotation catheter, as described in the preceding section.

Retrograde crossing of a ball-valve (e.g., Starr-Edwards) prosthesis in the aortic position may be accomplished easily using a 6F Sones catheter with or without guidewire assistance. The pigtail catheter also may be advanced into the left ventricle over a guidewire across a ball-valve prosthesis, but the wire should be reinserted for catheter withdrawal to avoid hooking the pigtail on the metal cage of the valve. Although some operators have crossed low-profile tilting-disc valve prostheses (e.g., Bjork-Shiley, St. Jude, Medtronic-Hall valve) retrograde without complications, instances where catheter entrapment occurred with retrograde crossing of such valves have been reported. Also, Dr. Viking Bjork has specifically that the Bjork-Shiley valve must not be crossed retrograde, based on his own vast experience. Accordingly, one should not attempt to cross a Bjork-Shiley valve or any low-profile disc valve prosthesis retrograde and when a restudy is required, the trans-septal approach should be used. More recently some operators have been able to leave 0.014-inch angioplasty catheters or 0.035-inch glide wires across tilting disc valves, but this cannot be recommended as a routine practice.

Patients with dual tilt disc or bileaflet mechanical valves in aortic and mitral positions present additional challenges. In these patients, as illustrated in the following case, a combined trans-septal and direct apical puncture approach has been used successfully when a less invasive assessment has been inadequate or uncertain for clinical decision making (see also Chapter 6).

CASE 40.9 Evaluation of Prosthetic Aortic Valve Stenosis in a Patient at High Risk for Re-Do Valve Replacement. A 47-year-old female presented with complaints of fatigue, dyspnea, and dependent edema. Her past medical history was significant for rheumatic heart disease. At the age of 12 she had undergone mitral commissurotomy. At the age of 35 she had presented with severe aortic stenosis and had undergone aortic valve replacement with a St. Jude valve in aortic position (St. Jude Medical, Minneapolis, MN), and 8 years later she had undergone mitral valve replacement with a St. Jude valve in mitral position. The patient was evaluated with transthoracic and transesophageal echocardiograms, which were suggestive of possible stenosis of the aortic valve prosthesis. There was moderate global hypokinesis with an estimated ejection fraction of 35%. The right ventricular systolic pressure was 32 mmHg. The peak velocity \((V_{max})\) across the aortic valve was 3.5 m/s, with a peak gradient of 53.6 mmHg and a mean gradient of 28 mmHg. The aortic valve area was estimated as 0.74 cm². The mean gradient across the mitral valve was 5.0 mmHg. The patient was referred for evaluation for possible re-do aortic valve replacement. Given the high surgical risk, it was decided to proceed with further evaluation.

Cinefluoroscopy revealed normally functioning St. Jude prosthetic valves in mitral and aortic position, with normal opening and closing angles (Figures 40.15 and 40.16). Right heart catheterization and left heart catheterization through a direct apical puncture approach were then performed. The left ventricular apex was identified with transthoracic echocardiographic imaging and marked. Under local anesthesia with 2% lidocaine, a 5F micropuncture sheath was advanced into the left ventricular cavity via the apical approach (Figure 40.17). A 6F pigtail catheter was advanced into the ascending aorta using the right femoral artery percutaneous approach, and a pulmonary wedge catheter was advanced to the pulmonary wedge position using the right femoral vein percutaneous approach. Given an excellent wedge position and no evidence of any significant gradient across the mitral valve, a previously planned trans-septal catheterization was not performed. Hemodynamic measurements were as follows:

<table>
<thead>
<tr>
<th>Body Surface area, m²</th>
<th>1.56</th>
</tr>
</thead>
<tbody>
<tr>
<td>(O_2) Consumption, mL/min</td>
<td>154.9</td>
</tr>
<tr>
<td>A–V (O_2) difference, mL/L</td>
<td>39.4</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>3.9</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>59</td>
</tr>
<tr>
<td>Pressures, mmHg</td>
<td></td>
</tr>
<tr>
<td>Right atrium, a/v/mean</td>
<td>13/9/11</td>
</tr>
<tr>
<td>Right ventricle, sys/dias</td>
<td>42/13</td>
</tr>
</tbody>
</table>
Coronary angiography did not reveal any evidence of obstructive coronary artery disease. At the end of the procedure, the transapical catheter was removed in the cardiac catheterization lab and hemostasis was achieved with manual compression. An echocardiogram obtained prior to transfer to the coronary care unit for observation did not show any effusion, and there were no complications.

<table>
<thead>
<tr>
<th>Pulmonary artery, sys/dias/mean</th>
<th>42/21/28</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCWP, a/v/mean</td>
<td>15/22/15</td>
</tr>
<tr>
<td>Left ventricle:</td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>125</td>
</tr>
<tr>
<td>LVEDP</td>
<td>17</td>
</tr>
<tr>
<td>Aortic valve gradient, mmHg</td>
<td>15</td>
</tr>
<tr>
<td>Mitral valve gradient, mmHg</td>
<td>4</td>
</tr>
<tr>
<td>Aortic valve area, cm²</td>
<td>1.2</td>
</tr>
<tr>
<td>Mitral valve area, cm²</td>
<td>2.4</td>
</tr>
</tbody>
</table>

**Interpretation.** The gradients and valve areas obtained during cardiac catheterization are consistent with those of normally functioning mechanical valves. Additional information needed for clinical decision making includes the type and size of prosthesis implanted. In this case, the aortic valve was a St. Jude valve 17 AHPJ-505 (St. Jude Medical® Masters Series) with a leaflet opening angle of 85° and an effective orifice area of 1.16 cm², while the mitral valve was a St. Jude # 27 MJ501 with a leaflet opening angle of 85° and an effective orifice area of 3.08 cm². Based on the fluoroscopic and hemodynamic data, it was felt that there was no indication for high-risk re-do aortic valve replacement. The patient was managed medically, and at 1-year follow-up, she was in stable NYHA functional class II with no further hospitalizations.

In general, cinefluoroscopy can provide important initial information on the function of tilt disc valves and, in our opinion, it should be one of the initial diagnostic tests when acute valve thrombosis is suspected. In the setting of mechanical valves both in mitral and in aortic positions, we revert to invasive hemodynamic assessment with a direct apical puncture only in those extremely rare cases where the information is critical for the clinical decision regarding medical therapy versus re-do valve surgery.
REFERENCES


Atherosclerotic coronary artery disease (CAD) continues to be the most frequent cause of death in the United States and other developed nations.1-3 Besides mortality, coronary artery disease accounts for substantial morbidity and disability. Diagnostic and therapeutic procedures for coronary disease have evolved rapidly over the last 40 years, and in parallel with advancements in medical therapy, have resulted in a significant decrease in both morbidity and mortality.4 The medical and procedural progress in the treatment of CAD represents one of the major accomplishments of modern medicine.

Cardiologists play a crucial role in identifying clinical CAD and developing a cogent treatment plan for an individual patient. The cardiovascular physician is charged with applying evidence and guideline-based diagnostic and treatment regimens that are individualized around anatomic and clinical characteristics. Though technical in basis, these approaches must also consider patient and family preference, and thus incorporate cultural, emotional, and value-based considerations on a background of clinical science.

This chapter is designed to provide examples of patient-centered therapy of CAD based on individual clinical and angiographic profiles. These case-based examples have been selected to demonstrate the application of clinical evidence and guideline recommendations of percutaneous coronary intervention (PCI) in the contemporary management of CAD.5

STABLE CORONARY ARTERY DISEASE

In patients with symptoms of stable angina, it is critical to establish a diagnosis of coronary artery insufficiency. While this may be based solely on functional noninvasive testing, coronary angiography using cardiac catheterization6 and, in selected cases, coronary computed tomographic angiography (CTA)? are indicated in patients with high-risk functional testing, or in whom diagnostic certainty is critical.6 The objective of therapy for stable CAD is to reduce not only mortality, but also prevent further progression, anginal pain, and disability.

For the majority of patients with clinically stable, symptomatic CAD, guideline-directed medical therapy (GDMT),9 including aspirin, beta blockade, hypertension control, and HMG-CoA reductase inhibitors (statin) if tolerated, and lifestyle modification constitute the primary proven treatment modality at this time,9,10 In advanced CAD, significant left main CAD, and three-vessel CAD with diminished left ventricular systolic function, surgical revascularization with coronary artery bypass graft surgery (CABG) has demonstrated survival benefit over historic (limited) medical therapy.

The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial randomized patients with stable coronary artery disease (single-vessel and low-risk multivessel) to GDMT versus GDMT and PCI.11 This trial demonstrated no significant reduction in cardiac mortality, myocardial infarction, need for revascularization, or long-term angina symptoms in those patients treated with PCI. These trial findings have remained controversial, but pending more contemporary trials that utilize advanced imaging techniques and drug-eluting stents (DESs), an initial therapeutic approach of guideline-directed medical therapy (GDMT) has been deemed appropriate.9,10 More recently, the Fractional Flow Reserve–Guided PCI versus Medical Therapy in Stable Coronary Disease (FAME 2) trial suggested that in patients with stable CAD, FFR-guided PCI of lesions (FFR < 0.80) in addition to optimal medical therapy can reduce the incidence of urgent revascularization.12 Whether this approach will be adopted in clinical guidelines or practice remains to be determined.

For those patients who continue to experience lifestyle limiting angina despite guideline-directed medical therapy, coronary revascularization is an option. For patients with single-vessel CAD, PCI is an option and class I indication8 when GDMT fails in relieving symptoms. For patients with...
multivessel CAD, PCI and bypass surgery have been shown to have similar 5-year rates of myocardial infarction and death.13 However, the need for repeat revascularization is higher in patients undergoing PCI. Stratification of multivessel CAD patients for PCI on the basis of angiographic complexity can, however, select patients in whom this risk is minimal.16 In addition, a note of caution should be applied regarding the choice of revascularization for the subgroup of patients with diabetes mellitus. The Bypass Angioplasty Revascularization Investigation (BARI) trial suggested a survival benefit of CABG when compared to PCI in patients with multivessel disease and diabetes mellitus, thus raising an initial concern in this patient population.15 This concern has been confirmed by several subsequent clinical trials and registry analyses and by a meta-analysis summarizing 10 randomized clinical trials.16 More recently, in the Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial, patients with diabetes mellitus and multivessel coronary artery disease were randomized to revascularization with CABG or with contemporary PCI utilizing drug-eluting stents.17 The primary outcome was a combined endpoint including death from any cause, nonfatal myocardial infarction, and nonfatal stroke at 5 years. At 5-year follow-up, the primary endpoint occurred more frequently in patients undergoing PCI when compared to patients undergoing CABG. The difference between PCI and CABG was driven by a higher rate of death from any cause and nonfatal myocardial infarction in the PCI group when compared to the CABG group.17 Thus, when considering revascularization for patients with multivessel CAD, the revascularization modality should be established on the basis of patient preference, clinical and angiographic characteristics that are determinant of acute and long-term success, and the presence of diabetes mellitus. As such, for patients with multivessel CAD requiring revascularization, collaborative, evidence-driven decision-making by cardiologists and cardiac surgeons, based on clinical and angiographic determinants of acute and long-term benefit, is essential.9

Invasive, as well as CT based, coronary angiography is effective in identifying fixed stenosis of coronary arteries. While important in establishing a diagnosis of CAD with attendant need for secondary prevention, it is the functional significance of individual coronary stenosis that is critical in developing a patient-centered therapeutic strategy. Physiologic stress testing, both exercise and pharmacologic, provides the physiologic basis for CAD treatment, especially revascularization. Similarly, fractional flow reserve (FFR) can provide critical functional information in the cardiac catheterization lab. This invasive technique (see Chapter 24) provides the opportunity to further assess the functional significance of specific coronary stenoses in order to direct therapy at the time of angiography. FFR has been shown to be similar to perfusion stress testing in predicting clinical events associated with a given stenosis. Conversely, FFR has been shown to be effective in identifying coronary stenoses that do not require revascularization in order to prevent CAD-related events.12,18 Like all procedures, FFR should be used judiciously. For those patients with a severe stenosis that corresponds to a territory of ischemia identified with functional testing, there is no need to perform FFR. However, in the case of intermediate stenoses, or stenoses that do not appear to be related to ischemia by functional testing, FFR should be performed in order to assess functional significance.

## CASE STUDIES

### CASE 41.1

A 45-year-old man with a history of hypertension, hyperlipidemia, and cigarette smoking presented to his physician with exertional dyspnea and vague chest discomfort. He was being treated with a statin, beta blockers, and an ACE inhibitor. Exercise stress testing with sestamibi scintigraphy, to 9 METS, demonstrated severe reversible perfusion defects of the inferior, inferoapical, anterior, and anteroapical segments. Rest ejection fraction was 52%, but declined to 33% during stress. There was transient left ventricular dilation. Nitrates and aspirin were added to his medical regimen. The patient was referred for coronary angiography (Figure 41.1). This demonstrated severe three-vessel CAD, with discrete lesions in the proximal right coronary and proximal to mid left anterior descending arteries. There was a more diffuse lesion in the small mid circumflex artery. Stress testing was consistent with a high risk of future events and the patient was symptomatic, despite medical therapy, necessitating revascularization. The angiographic complexity of the coronary arteries' stenoses was limited, suggesting a successful outcome with percutaneous revascularization. A 3.0 × 20 mm drug-eluting stent was deployed in the left anterior descending artery, with excellent angiographic result. Subsequently, a 3.0 × 12 mm drug eluting stent was deployed in the right coronary artery, also with excellent result. Given the limited distribution of the left circumflex artery, and the absence of detectable ischemia in that distribution, revascularization of this artery was deferred. The patient had an uncomplicated clinical course and was discharged with dual antiplatelet therapy for 1 year.

**Commentary:** This case was selected to demonstrate clinical decision-making in stable coronary artery disease. The patient’s left ventricular compromise and ongoing symptoms despite medical therapy were the indications for revascularization. While the patient had multivessel coronary artery disease, the angiographic complexity was limited. This suggested a favorable outcome with a percutaneous approach utilizing drug-eluting stents.
Figure 41.1
Stable coronary artery disease. A. Angiography of the right coronary artery in the left anterior oblique view demonstrates a severe stenosis of the proximal segment (arrow). B. Right anterior oblique with cranial angulation demonstrates severe stenosis of the proximal and mid left anterior descending artery (arrow). C. Right anterior oblique with caudal angulation demonstrates severe stenosis of the circumflex artery (arrow), as well as of the proximal and mid left anterior descending artery. D. Deployment of a $3.0 \times 20$ mm drug-eluting stent in the left anterior descending artery (arrow). E. Postdilation with a $3.5 \times 15$ mm balloon in the left anterior descending artery stent (arrow). F. Excellent angiographic appearance of the left anterior descending artery (arrow). G. Deployment of a $3.0 \times 12$ mm drug-eluting stent in the right coronary artery (arrow). H. Excellent angiographic appearance of the right coronary artery stent (arrow).
Indications for Angiography and Percutaneous Coronary Intervention

It has been estimated that annually 610,000 Americans will have a new myocardial infarction (MI) and 325,000 will have a recurrent MI.3 While the incidence of ST segment elevation myocardial infarction (STEMI) has been declining, the incidence of non-ST segment elevation myocardial infarction (NSTEMI) has increased.20 It has been suggested that the increase in the incidence of NSTEMI might be related to improved detection with the use of more sensitive biomarkers. Over the past six decades, the annual death rate for coronary artery disease has declined progressively,5,21 and it is today >50% lower than it was in 1950. This reduction is owing to a combination of factors including the institution of ICU care and EMS services, the decline in the rate of STEMI,3,20 improved primary and secondary prevention through GDMT20 and, more recently, by further evolution of reperfusion therapy for STEMI. Reperfusion therapy, by which coronary blood flow is reestablished through pharmacologic (thrombolytic) or mechanical (primary PCI) means, is the hallmark of therapy for STEMI. Primary PCI, when available in a timely fashion, is more effective than thrombolytic therapy for the treatment of STEMI (see Chapter 30), and it is associated with a significant reduction in mortality, reinfarction, and stroke. Despite these differences, the key to STEMI management depends on the timely establishment of reperfusion. Current ACC/AHA Guidelines place primary PCI as a Class I indication, when performed within 12 hours of symptom onset, when it can be performed in a timely fashion (goal within 90 minutes of medical contact), in patients ineligible for thrombolytic therapy, and in patients presenting with heart failure and/or cardiogenic shock.8,22 Thrombolytic therapy remains a viable and Class I indication for those patients who are unable to receive primary PCI within 120 minutes from first medical contact (FMC).21

Technical Considerations

Angiography and PCI should be performed expeditiously, with the goal to minimize the time to successful reperfusion. To this end, as described in Chapter 30, most operators routinely perform a diagnostic angiography of the “non-culprit” vessel initially, based upon ECG localization, and then perform angiography of the culprit vessel with a guide catheter. In vessels in which thrombotic obstruction persists, initial wiring attempts with a soft, hydrophobic wire are advisable, as most lesions are soft and easily crossed. Upon crossing the lesion, confirmation of intraluminal position, either based on angiography or in the event of persistent occlusion, by Dottering with a balloon to allow some distal flow, is advised. In patients with persistent obstruction, the balloon may be advanced distal to the obstruction and the wire removed, and careful, manual injection of contrast through the wire lumen can confirm intraluminal position. Thereafter balloon inflation of the thrombotic occlusion can proceed. In patients with large visible thrombi, or proximal occlusions, many operators will proceed initially with aspiration thrombectomy. The TAPAS trial demonstrated an acute improvement in coronary blood flow and a reduced incidence at 1 year of cardiac death and the composite of death and nonfatal reinfarction with aspiration thrombectomy.23 This approach carries a level IIa indication in current guidelines.24 Stent implantation can then follow. Both bare-metal and drug-eluting stents have been shown to be effective. Decisions about stent type remain operator dependent and should be based on vessel size and other angiographic factors, as well as clinical variables, including likelihood of patient compliance with dual antiplatelet therapy. In all cases, proper vessel sizing is critical in order to ensure adequate stent expansion and strut apposition, thereby reducing the risk of stent thrombosis.

STEMI often occurs in patients with multivessel CAD, with significant lesions in “non-culprit” vessels. Current guidelines argue against immediate treatment of “non-culprit” lesions at the time of primary PCI (Class III indication). The guidelines are supported by several registry analyses and randomized clinical trials, as well as by recent large meta-analysis showing that in the setting of primary PCI for acute myocardial infarction, staged PCI is associated with lower short- and long-term mortality when compared with simultaneous culprit vessel PCI and multivessel PCI.24

**CASE 41.2**

A 45-year-old man with no prior cardiac history and risk factors limited to cigarette smoking presented to a rural hospital emergency room with 3 hours of worsening substernal chest discomfort. Initial EKG was consistent with acute anterior wall myocardial infarction (Figure 41.2). The patient was administered aspirin, prasugrel, and unfractionated heparin per protocol.

Expeditied transfer to a nearby primary PCI center was arranged with a transport time of 20 minutes. Coronary angiography was performed (Figure 41.3). This demonstrated a culprit lesion in the mid segment of the left anterior descending artery, highly suggestive of a large intraluminal thrombus. The lesion was crossed with a soft wire and aspiration thrombectomy was performed with evident thrombus aspiration (Figure 41.4). Subsequently a drug-eluting stent was deployed in “direct” fashion.

The patient had a stable postprocedural course. Medical therapy at discharge included indefinite aspirin therapy, prasugrel for 12 months, an ACE inhibitor, and a beta blocker. Smoking cessation was initiated in the hospital and continued in cardiac rehabilitation.
Commentary: This case was selected to demonstrate the importance of rapid reperfusion therapy in management of ST segment elevation myocardial infarction. Primary PCI was selected given its rapid availability owing to a coordinated system of care in this rural region. Had this been lacking, or had transport time to a PCI-capable facility been longer, initial treatment with thrombolytic therapy would have been appropriate, as would have been had the patient’s presentation been closer to symptom onset, despite the availability of PCI. The significant thrombus burden favored the initial employment of aspiration thrombectomy prior to stent deployment.

NON-ST SEGMENT ELEVATION ACUTE CORONARY SYNDROME

Indications for Angiography and Percutaneous Coronary Intervention

Coronary angiography, with an intent of revascularization (surgical or percutaneous), is a Class I recommendation for patients presenting with non-ST segment elevation acute coronary syndrome, unstable angina, or myocardial infarction. Patients with refractory ischemia—including angina, or hemodynamic or electrical instability—or more stable patients at higher risk for future clinical events should undergo early angiography, and if indicated PCI. Large randomized clinical trials utilizing a background of contemporary antithrombic therapy demonstrated that an initial strategy of angiography followed by appropriate revascularization reduced the incidence of death and recurrent myocardial infarction, as compared to a more conservative initial approach of medical therapy and noninvasive risk stratification. Early angiography and subsequent revascularization (6 to 24 hours), as compared to “cooling off,” with later angiography and revascularization, reduce clinical events (composite of death, myocardial infarction, or CVA in high-risk Acute Coronary Syndrome (ACS) patients).

In ACS patients undergoing coronary angiography, the determination of revascularization strategy (PCI versus CABG) should be similar to that for patients with stable CAD. The patient’s angiographic profile, likelihood of success, clinical variables, and patient preference should all be considered.

Management

For patients with non-ST elevation ACS, appropriate medical management including aspirin, ADP receptor blockers, and anticoagulation with either unfractionated or low molecular weight heparin is mandatory (see Chapter 5). Additional
medical therapy including beta-blockers and blood pressure control in conjunction with aggressive lipid lowering therapy with statins is also indicated.\(^{28,29}\)

Approaches to PCI should be based on anatomic and clinical factors. Both bare-metal and drug-eluting stents can be utilized. As in the setting of STEMI, stent choice should be predicated on risk of restenosis, stent thrombosis, patient compliance, and other technical and clinical considerations. With fourth-generation drug-eluting stents being widely employed, stent delivery is rarely a consideration in determining if a bare or coated stent is to be employed. In patients with multivessel CAD undergoing PCI, multivessel intervention in a single setting is commonplace. That said, consideration of contrast burden and risk of contrast-induced nephropathy (CIN), radiation dose, initial lesion result, the extent of myocardium at risk, and other patient-specific factors should guide whether staging of secondary lesions should be considered.

**CASE 41.3** An 82-year-old man with a history of coronary artery disease presented with severe chest pain and diaphoresis. Electrocardiography demonstrated dynamic anterolateral T-wave inversions, and cardiac markers (troponin) were borderline. The patient was stabilized with aspirin, unfractionated heparin, beta blocker, and nitrates. The patient had undergone coronary angiography and placement...
of bare-metal stents in the proximal and middle left anterior descending artery 2 years earlier. Shortly after stent placement the patient developed recurrent episodes of both gastrointestinal and genitourinary bleeding requiring transfusion. Clopidogrel had been stopped at that time and was not restarted during the current admission. Prior to angiography the patient expressed that he was adamantly opposed to coronary artery bypass surgery owing to the need for prolonged recovery and risk of stroke, both of which would prevent his wife from living independently.

The patient underwent coronary angiography (Figure 41.5), which demonstrated a culprit lesion in the middle left anterior descending artery at the site of the earlier stent. In addition, there were high-grade stenosis in the right and circumflex arteries. The limited angiographic complexity (low SYNTAX score) and preserved systolic function, suggested that PCI would afford a good outcome and meet the patient's desire to avoid surgery. However, the patient's poor candidacy for long-term dual antiplatelet therapy precluded multiple drug-eluting stents. Fractional flow reserve was performed on the right coronary (FFR = 0.84) and circumflex (FFR = 0.91) arteries. Accordingly, revascularization of these lesions was deferred. Given the discreet segmental nature of the in-stent restenosis of the middle left anterior descending lesion and the patient's bleeding risk, conventional balloon angioplasty with a 2.5 x 12 mm balloon was

Figure 41.5 Non-ST segment elevation acute coronary syndrome. A. Angiography of the right coronary artery in the left anterior oblique angle demonstrates a severe stenosis of the proximal segment (arrow). B. Right anterior oblique view with cranial angulation demonstrates severe stenosis of the mid left anterior descending artery, at the site of a previous stent (arrow). C. Left anterior oblique view with cranial angulation demonstrates moderate to severe stenosis of the proximal circumflex artery (arrow). D. Balloon angioplasty of mid left anterior descending in-stent restenosis with a 2.5 x 12 mm balloon (arrow). E. Excellent angiographic result of mid left anterior descending artery in-stent restenosis (arrow).
performed. This resulted in an excellent angiographic result. The patient was discharged with a limited course of dual antiplatelet therapy and optimal medical therapy for his residual coronary disease. He had an excellent long-term outcome.

Commentary: This case was selected to show complex, patient-centered decision-making in a patient with acute coronary syndrome. An early invasive stratification strategy was employed. Consideration of the patient's preferences and hemorrhagic risk was central in choosing the revascularization approach. Fractional flow reserve provided physiologic insight into lesions that angiographically appeared severe, thereby mitigating the need for multivessel revascularization and playing a key role in evidence-based revascularization that met the patient's personal and clinical needs.

CASE 41.4

The patient is a 79-year-old female with a history of hypertension and diabetes mellitus. In addition, she has had angina for many years, which has been stable and is controlled with beta blocker, amlopidine, long-acting nitrates, a statin, and aspirin. She presented to the emergency room with the acute onset of severe left-sided chest pain and left arm numbness at rest. Initial EKG was unremarkable; however, the initial troponin was elevated. She was treated with intravenous nitrates, clopidogrel, and low molecular weight heparin. Her chest pain abated upon initiation of her therapy, and she remained pain free; however, her troponin peaked at 12. She was referred for coronary angiography and further therapy.

Coronary angiography demonstrated severe three-vessel coronary artery disease with bifurcation stenosis of the mid left anterior descending artery involving the ostium of the diagonal branch (Figure 41.6), a stenosis of the proximal segment of a large-branching obtuse marginal branch of the circumflex artery, and a subsequent bifurcation lesion of the vessel involving both the ostia of both terminal vessel branches. The angiogram also demonstrated moderate to severe stenosis of the distal segment of the right coronary artery. Left ventriculography demonstrated markedly reduced systolic function, with an ejection fraction of approximately 30% and with anterior and inferior hypokinesis and apical dyskinesis. The study was completed and revascularization options were considered in a collaborative heart team meeting of the clinical and interventional cardiologists and a cardiac surgeon. The diminished left ventricular function, as well as the angiographic complexity of the coronary artery disease (numerous lesions including multiple, complex bifurcation stenosis, with the resultant need for many stents), led the group to favor CABG. The patient's high functional status and lack of other major morbidities were felt to support this choice clinically. After consultation with the patient and her family, CABG (with five grafts including an internal mammary artery graft) was performed. The patient had an uneventful postoperative course.

Commentary: In this case, while percutaneous coronary intervention was technically possible, the complexity of the patient's coronary anatomy, as well as the significant reduction in left ventricular function, favored surgical revascularization, which was chosen.

Figure 41.6

Non-ST segment elevation acute coronary syndrome. A. Left anterior oblique view with caudal angulation demonstrates a bifurcation lesion of the middle left anterior descending artery involving the ostium of the diagonal branch (arrow). B. Right anterior oblique view with caudal angulation demonstrates severe stenosis of the proximal segment of the large branching obtuse marginal branch. There is additional stenosis of the distal vessel as it bifurcates into terminal branches, involving the ostia of both branches (arrow). C. Angiography of the right coronary artery in the left anterior oblique view demonstrates a moderate to severe stenosis of the distal segment (arrow).
**UNPROTECTED LEFT MAIN CORONARY ARTERY DISEASE**

**CASE 41.5** A 70-year-old man with known severe occlusive peripheral vascular disease and chronic obstructive pulmonary disease (forced expiratory volume = 700 mL) developed pulmonary edema requiring intubation and ventilatory support. During an episode of atrial fibrillation with a rapid ventricular response, the patient developed deep precordial ST-segment depression and hypotension. Owing to ongoing ischemia despite maximal medical therapy and ongoing ventilator dependence, coronary arteriography was performed from the right radial approach. Diagnostic angiography demonstrated an 80% ostial left main stenosis. Surgical consultation recommended that he was not a candidate for CABG owing to his severe pulmonary disease, and the left main lesion was corrected by balloon predilatation and implantation of a drug-eluting stent.

**CASE 41.6** A 62-year-old woman with severe iliofemoral vascular disease underwent CABG for 80% ostial left main stenosis and 95% stenosis of the second marginal. The mammary artery was not suitable for CABG, and she received vein grafts to the left anterior descending and the marginal branch. Five months later she developed recurrent angina. Angiography demonstrated preserved left ventricular function and occlusion of the bypass grafts, an 80% ostial left main stenosis, and an occluded marginal (Figure 41.7A). Her surgeon referred her for percutaneous revascularization. Hemodynamic support was initiated using an Impella device, which was successfully advanced through an iliac stent (Figure 41.7B). The marginal artery was recanalized and stented, and the ostial left main was also stented (Figure 41.8).

**CASE 41.7** An 85-year-old man with severe pulmonary fibrosis on home oxygen presented with atrial fibrillation with rapid ventricular response, pulmonary edema, and non-ST elevation myocardial infarction. Coronary angiography demonstrated critical distal left main disease involving the ostium of the LAD, LCX, and ramus intermedius (Figure 41.9). The ejection fraction was 20%. After being declined for CABG, he was referred for consideration of high-risk coronary intervention. Given the complexity of the stenosis and the severely reduced left ventricular systolic performance, prior to the intervention hemodynamic support with TandemHeart was initiated. The trifurcation lesion was managed successfully by stent implantation and the patient was symptom-free at 2-year follow-up (Figure 41.10).

**Commentary:** Diagnostic coronary angiography uncovers significant unprotected left main coronary artery (ULMCA) stenosis in 5% to 7% of cases. Coronary artery bypass graft (CABG) surgery has historically reigned as the standard of care for these high-risk patients based on the improved survival as compared to medical therapy observed in the Veterans Administration Cooperative Study and in the Collaborative Study in Coronary Artery Surgery. With improved pharmacologic therapy and the dramatic reduction in restenosis afforded by DES, enthusiasm for tackling ULMCA lesions with interventional techniques has mounted. Important data from clinical trials are now available to help guide decision-making for such high-risk interventions.

The multicenter, nonrandomized Revascularization for Unprotected LM Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty versus Surgical Revascularization (MAIN-COMPARE) registry examined long-term outcomes after PCI (DES = 784; BMS = 318) or CABG (n = 1,138) for ULMCA stenosis. After propensity matching, there was no difference in death or the composite of death, MI, and stroke. However, repeat revascularization was
significantly higher after PCI with a hazard ratio of 4.76 at 3 years ($P < 0.001$)

The Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease (PRECOMBAT) trial randomized 600 patients with ULMCA stenosis to CABG versus PCI with a sirolimus DES in a noninferiority trial. Surveillance angiography was performed at 8 to 10 months after PCI or for symptoms. At 1 year the primary endpoint of death, MI, stroke, or ischemia-driven target vessel revascularization was reached in 8.7% of PCI and 6.7% of CABG patients, meeting the wide noninferiority margin set for this study. The composite event rates at 2 years were not statistically different (12.2% PCI versus 8.1% CABG), but there was a significant increase in ischemia-driven target lesion revascularization after PCI as compared to CABG (9.0% versus 4.2%). Outcomes favored PCI in isolated left main or left main plus single-vessel disease, whereas more complex anatomy favored CABG. The overall low event rates in this study are notable, and it is unclear if surveillance angiography drove higher repeat revascularization rates in the PCI group.

The Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) study randomized 1,800 patients with multivessel or left main CAD to PCI with a paclitaxel-eluting stent versus CABG. As the overall study failed to demonstrate noninferiority of PCI, subgroup analyses from this trial are considered hypothesis generating. In the ULMCA subgroup (705 patients), similar 1 year major adverse cardiac and cerebrovascular events were found (15.8% versus 12.7%; $P = 0.44$).

The incidence of stroke was significantly higher after CABG (0.3% versus 2.7%; $P = 0.009$), whereas repeat revascularization was higher with PCI (11.8% versus 6.5%; $P = 0.02$). Outcomes with the two strategies appeared to depend in part on the SYNTAX score, a measure that incorporates lesion location, lesion complexity, and number of lesions. Composite outcomes were similar for PCI and CABG in patients with low or intermediate SYNTAX scores. However, patients with high (>32) scores had a significantly higher rate of the primary outcome with PCI (25.3% versus 12.9%).

Recent
A. Left anterior oblique caudal angiogram showing critical distal LM stenosis (arrow) involving the origin of the LAD, ramus, and LCX. B. Through an 8F guide, the LAD, ramus, and LCX are wired (arrows). Cardiac support with TandemHeart is initiated. Left atrial cannula of the TandemHeart is seen in the left atrium (double arrow).

5-year outcome data on the ULMCA cohort from SYNTAX show similar outcomes for PCI and CABG (MACCE of 36.9% versus 31%; \( p = 0.12 \)). The outcomes were again best in low and intermediate SYNTAX score patients, and in those with single- or double-vessel CAD. In those with three-vessel CAD and high SYNTAX scores, the outcomes appear to continue to favor CABG.

The Evaluation of Xience Prime or Xience V versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) trial is currently enrolling patients with left main disease and a SYNTAX score of \( \leq 32 \) to evaluate patients with less complex coronary artery disease than found in those enrolled in SYNTAX.\(^{38}\) This will allow an assessment of second-generation DES for the treatment of ULMCA.

**Technical Considerations**

Mechanical support (Intraaortic balloon pump, TandemHeart, Impella, ECMO) is generally not required in hemodynamically stable patients undergoing ULMCA PCI. In unstable patients mechanical support may be considered in advance, and vascular access for these devices should be assessed. Objective lesion assessment with fractional flow reserve (FFR < 0.80) or intravascular ultrasound (IVUS; minimal luminal area <6 mm\(^2\)) may help confirm the functional significance of the lesion.

A. Origin of LCX is “T stented” with a 2.5 × 18 mm Endeavor using a balloon in the left main to ensure that the stent does not protrude back into the left main and impede access to the ramus and LAD for additional intervention. The stent is postdilated to 2.75 mm. B. The LAD and ramus are treated using a 3.0 × 12 mm Endeavor DES (Ramus) and 3.0 × 15 mm Endeavor DES (LAD) deployed in simultaneous kissing stent fashion. Both are postdilated to 3.5 mm. C. Right anterior oblique cranial view of the final result after stenting the LAD, ramus, and LCX.
of a lesion. Heavy endoluminal calcification by IVUS suggests the need for rotational atherectomy to facilitate stent expansion. Speed is of the essence in PCI of ULMCA. Given the large volume of myocardium subtended, balloons and stents are all readied prior to critical steps, inflation durations are minimized, and bailout equipment for side branch occlusion or perforation is on standby. While PCI is generally performed on the most distal lesion first, ULMCA lesions may require treatment first in order to work distally later without inducing global ischemia.

The location of the stenosis within the left main coronary artery will generally determine the complexity of the PCI (see Chapters 28 and 31). About 30% of stenoses involve the ostium or body of the left main.

Focal, ostial/body left main lesions can generally be treated with short, large-diameter stents with a minimum of peri-PCI ischemia. Coaxial guiding catheter support allows positioning of the proximal portion of the stent just 1 to 2 mm within the aorta and fully covering the ostial left main stenosis. A nonaggressive guide (e.g., Judkins left) may facilitate controlled guide disengagement to allow precise positioning of the ostial stent. Short, high-pressure balloon inflations minimize ischemia time and provide full stent expansion.

Left main lesions involving the distal left main bifurcation account for roughly 60% of ULMCA stenoses. These generally require placing the distal portion of the stent within either the left anterior descending (LAD) or the left circumflex coronary artery, or both. One large observational study of LMCA bifurcation stenting found that a one-stent technique was associated with reduced MACE at 2 years as compared to a two-stents technique (propensity-adjusted hazard ratio for the risk of 2-year MACE was 0.53 (95% CI: 0.37 to 0.76). Restenosis rates in left main bifurcation lesions are higher than for isolated ostial/body lesions, with the most common site of restenosis being the circumflex ostium. The distal LMCA bifurcation angle generally dictates the technique employed. Angles of ~90 degrees allow T stenting or one of its variants—techniques that minimize stent overlap. More acute angles are generally treated with single-vessel provisional stenting or other techniques (crush, Culotte, V stenting, T and Protrusion). Completion kissing balloon angioplasty is recommended to optimize stent geometry.

For elective intervention, current U.S. guidelines provide a class Ila recommendation for LMCA PCI when the lesion is ≥50%, the anatomy is consistent with low acute complications and favorable long-term outcome (e.g., SYNTAX score ≤22, ostial or body location), and there is increased surgical mortality risk (e.g., STS mortality prediction of ≥5%). The recommendation is IIb for a similar situation with a low-to-intermediate risk of acute complications and an intermediate-to-high likelihood of favorable long-term outcome (e.g., SYNTAX score ≤33, bifurcation left main lesion). PCI should not be performed in ULMCA for patients with unfavorable anatomy for PCI and low surgical risk. Given the enormous stakes for patients with ULMCA, the importance of a heart team approach to decision-making in stable patients cannot be overemphasized.

### Indications for Coronary Arteriography and Percutaneous Revascularization

Defined as a complete occlusion of ≥3 months duration, CTOs are found in up to 50% of patients with significant obstructive coronary artery disease (≥70%) at catheterization. Despite this prevalence, historically only 8% to 15% of patients with CTO has undergone PCI. In fact, the presence of CTO is a major predictor of advising against PCI in favor of medical therapy or CABG. This practice pattern likely reflects uncertainty regarding the clinical benefit of CTO PCI, as well as the significant technical challenges with this procedure. Fortunately, recent marked advances in equipment and procedural technique have rendered CTOs less daunting in experienced hands. The challenge for interventionalists is to determine when to tackle these complex lesions and how to achieve effective revascularization safely and expeditiously when PCI is attempted.

There are no randomized trials comparing CTO PCI to medical therapy. The Occluded Artery Trial (OAT) compared PCI to medical therapy for total occlusion of the culprit vessel ≥28 days after acute myocardial infarction in stable patients with high-risk features (proximal vessel occlusion or ejection fraction <50%). PCI did not reduce the incidence of death, reinfarction, or Class IV heart failure up to 4 years.
as compared to medical therapy (17.2% versus 15.6%), but the clinical context (recent MI) and the coronary anatomy (recent thrombotic occlusion) in OAT were far different from those of the CTO population. In true CTOs, successful PCI has been associated with improved left ventricular function, reduced angina and need for CABG, and even improved survival when compared to failed procedures. Other observational data have suggested an adverse prognostic effect of untreated CTO. Fractional flow reserve of the collateral circulation to CTOs is reliably <0.80, consistent with ischemia in the CTO territory even in the presence of large collaterals. Following primary PCI, nonrevascularized CTO of a non-infarct related artery at 30 days is associated with increased long-term mortality. Among unselected PCI patients the presence of unattempted CTO in two vessels appears to define the population at highest risk for subsequent death and myocardial infarction.

It is possible that the observed favorable effects of successful CTO PCI in fact reflect the fact that patients with failed or unattempted CTO PCI may represent a sicker population or, more ominously, that failed attempt PCI actually confers harm. Studies in Europe and Asia are currently randomizing CTO patients to PCI versus medical therapy, but at present we are left to make our best clinical judgment. Current guidelines provide a Class IIA recommendation that PCI of the CTO is reasonable in patients with appropriate clinical indications and suitable anatomy when performed by operators with appropriate expertise. A Heart Team approach is emphasized, with specific input from cardiothoracic surgery, as is an individualized risk–benefit analysis encompassing clinical, angiographic, and technical considerations.

**Technical Considerations**

Several consensus documents have attempted to formalize a systematic approach to CTO intervention. Operator experience and commitment to the technique are considered critical to the success of complex CTO intervention. Ad hoc PCI of complex CTOs is discouraged to allow for intensive review of the angiographic and clinical data and to utilize the Heart Team approach. Bilateral simultaneous coronary angiography is recommended with minimal panning in low magnification, injecting the contralateral vessel first, followed by the CTO vessel to optimize vessel assessment. Septal collaterals are best assessed in the RAO cranial and caudal views. Critical angiographic characteristics to review include (i) the proximal cap location and morphology, (ii) lesion length, (iii) size and quality of the target at the distal cap, and (iv) the collateral vessels. A clear entry into the proximal cap and a lesion length >20 mm favor success with a standard antegrade approach. When the proximal cap has no clear entry point, or the distal target is poor, or there are favorable collaterals, a retrograde approach may be preferable. Epicardial collaterals should be avoided in the retrograde approach owing to
Figure 41.12 Recanalization of a total coronary occlusion. 

A. A flush occlusion of the distal continuation of the right coronary artery (arrow). 

B. Initial attempts at crossing the occlusion with a hydrophilic coronary guidewire result in the creation of a false lumen and parallel tract to the right posterolateral branch (arrow). 

C. The Intraluminal Therapeutics SafeSteer coronary guidewire is used to advance the wire into the true lumen using optical coherence reflectometry (arrow). 

D. Using this method, the guidewire is advanced into the distal portion of the right posterolateral branch. 

E. A 2.0 mm balloon is used to dilate the occlusion initially. 

F. This is followed by stent placement in the very distal right coronary artery. 

G. An additional balloon inflation is performed in the distal right posterolateral branch. 

H. The final angiographic result demonstrates no residual stenosis and normal flow into the distal vessel.
perforation risk. Success of retrograde PCI is enhanced if the collaterals have minimal tortuosity and enter the distal vessel far enough beyond the distal cap to allow wire purchase. If the collateral is the sole source of perfusion to the occluded vessel, the risk of acute intraprocedural ischemia increases.

Anticoagulation with unfractionated heparin is favored over bivalirudin for PCI on CTO, as it can be reversed in the case of perforation. Similarly, glycoprotein IIb/IIIa inhibitors are avoided. Equipment for pericardiocentesis, embolization coils, and covered stents should be readily available to manage perforation. An activated clotting time of >350 seconds is recommended during retrograde procedures to minimize the risk of thrombosis in the instrumented collateral vessels.\textsuperscript{53} Routine use of a two-guide technique is advocated—one guide for antegrade injection in the CTO vessel and a second shorter guide (≤90 cm) in the contralateral coronary to facilitate retrograde techniques. Large-caliber guides enhance support and allow exchange of bulky devices or balloon-trapping techniques, while long-access sheaths help overcome peripheral vascular tortuosity that may otherwise hinder guide performance. Techniques to minimize radiation exposure to the patient and the operator (reducing cine and fluoroscopy frame rates, using “store” fluoroscopy rather than cineangiography when appropriate, and using additional protective shielding) should be employed for these potentially long procedures.

Successful CTO intervention requires familiarity with a significant number of niche wires and devices. Hydrophilic 0.014 inch wires with 0.009 inch tapered tips of low stiffness are available to probe the entry cap for microchannels in the antegrade approach. If unsuccessful, and if the pathway to the distal lumen is clear, escalation to increasingly stiff, nontapered wires is appropriate. A wire-directed retrograde through collaterals to the distal cap can provide a target for antegrade approach. Alternatively, an antegrade subintimal dissection approach can be attempted, using a knuckled wire or a blunt-tip metal microcatheter (CrossBoss, BridgePoint Medical, Plymouth, MN). The wire or catheter is advanced parallel to the true lumen up to the distal cap. With a microcatheter in the subintimal space for support, reentry into the distal true lumen is attempted with a stiff wire. The Stingray system (BridgePoint Medical) can be advanced over a wire into the subintimal space. When inflated, the balloon assumes a flat shape with an exit port on either side. A 0.0025 inch wire is then advanced into the appropriate port facing the true lumen to achieve reentry.

Once successful antegrade wiring is achieved, low-profile balloons are used to cross the occlusion to establish a channel for stenting. If balloons cannot cross, guide support can be enhanced with a GuideLiner (Vascular Solutions, Minneapolis, MN) and wire support can be augmented with various balloon-trapping techniques. Finally, a Tornus microcatheter (Asahi Intecc) can be used. This device is counterclocked over the wire to screw through the lesion. Stents are superior to balloon angioplasty for CTO intervention, and DES are superior to BMS.\textsuperscript{55-57}

In the retrograde approaches, access to the distal target vessel via a bypass graft is preferred to a septal collateral, and access via an epicardial collateral is generally avoided due to increased risk of perforation. Generally a low-profile over-the-wire balloon or a microcatheter is used to support a long hydrophilic wire. Once the wire is negotiated into the distal target vessel, retrograde to the distal cap, the septal is dilated with a small balloon (~1.5 mm) at low pressure or using the Corsair septal dilator microcatheter (Abbott Vascular) to avoid equipment entrapment in the collateral. A microcatheter is advanced to the distal cap and the occlusion is traversed using one of multiple techniques, such as antegrade puncture with the retrograde wire as a target, retrograde puncture, or reverse subintimal dissection and reentry. If the lesion is crossed retrograde, subsequent treatment of the lesion is most easily accomplished by crossing this new lumen antegrade and completing the procedure in a standard antegrade fashion. Externalization of the retrograde wire using a snare is also possible. In this approach, maintaining microcatheter position through the septal collaterals is critical to prevent septal injury during the wire manipulations. The externalized rail can then be used to complete the procedure in an antegrade fashion.

In specialized CTO centers, CTO intervention is successful in up to 85% of cases,\textsuperscript{58} with substantially lower success rates in less experienced hands. Similarly, rates of perforation and mortality are <1%,\textsuperscript{51} With DES, target lesion revascularization rates are <10%,\textsuperscript{51} Although a randomized trial of PCI versus CABG or medical therapy for CTO is sorely needed, at this time CTO intervention is a reasonable alternative in appropriately selected patients when performed in experienced centers.

**CASE 41.9** A 60-year-old man with a history of coronary artery disease and prior CABG presented with an acute inferior-wall myocardial infarction. The EKG demonstrated an inferior-wall myocardial infarction, manifest by ST-segment elevation of leads II, III, and AVL (Figure 41.13). Coronary arteriography demonstrated a patent left internal mammary artery (LIMA) to the LAD, patent SVG to the obtuse marginal and diagonal branches, ostial left main and RCA occlusions, and a recently occluded SVG to the posterior descending artery (PDA; Figure 41.14). The occluded SVG to the PDA was crossed with a 0.014 inch BMW wire, and a distal injection demonstrated abundant thrombus and a focal stenosis in the midportion of the SVG. A 0.014 inch FilterWire EZ (Boston Scientific, Natick, MA) was placed across the stenosis, and the FilterWire was deployed in a smooth portion of the SVG. A 5F AngioJet XVG catheter was used to remove the residual thrombus. Following this, two 3.5 x 33 mm CYHER stents were placed in the proximal and mid SVG. The SVG was postdilated with a 4.0 mm postdilatation balloon. The FilterWire was then removed, and normal flow was found in the distal RCA and its branches.
CASE 41.10 A 55-year-old man with prior bypass surgery, including a vein graft to the first marginal, presents with unstable angina. The proximal portion of the graft has been previously stented and angiography demonstrates a severe in-stent restenosis (Figure 41.15A). The in-stent lesion is deemed low-risk for distal embolization and no-reflow at the time of intervention, and stenting of the lesion is performed without distal protection. The lesion is successfully treated, but there is now a distal cutoff in the subtended marginal branch (Figure 41.15B). Balloon angioplasty is performed at the site of distal cutoff with restoration of brisk antegrade flow with no residual obstruction (Figure 41.15B).

Indications for Coronary Arteriography and Percutaneous Revascularization

Even with excellent surgical techniques, SVGs are at risk for deterioration owing to progressive degeneration in the higher-pressure arterial environment. It is thus estimated that >50% of SVGs become diseased or occlude within the first decade after CABG. Repeat CABG for SVG failure, particularly when there is a patent LIMA to the LAD, is associated with lower success rates and less symptomatic benefit than those of the initial procedure.

Technical Considerations

Anticoagulation for percutaneous intervention on SVGs is typically achieved with unfractionated heparin or bivalirudin. Procedural success with current techniques generally exceeds 90% depending in part on the presence of graft degeneration and lesion location. The major risk of SVG intervention is the occurrence of distal embolization. The degree of risk for embolization relates to the extent of SVG degeneration, which includes an estimate of the percentage of graft irregularity and ectasia, friability, presence of thrombus, and number of discrete or diffuse lesions (>50% stenosis) located within the graft. Case selection is therefore critical. Severely diffusely degenerated grafts with poor distal outflow and chronic total SVG occlusions are generally avoided, particularly if an option for revascularization via the native coronary circulation exists. Glycoprotein IIb/IIIa antagonists are not beneficial in this regard and do not improve overall outcomes of SVG intervention. Although atherectomy and thrombectomy have been tried to prevent embolization and its attendant complications, only the use of embolic protection devices has resulted in a reduction of adverse clinical events (see Chapter 29).

Three general classes of embolic protection devices have been approved for clinical use: occlusion systems that use a low-pressure balloon to occlude flow during intervention, embolic entrapment filters that permit flow through the SVG during intervention but capture the debris within the distal filter, and proximal occlusion systems. The PercuSurge Guardwire (Medtronic Vascular, Santa Rosa, CA) device is a low-profile system (0.014 inch guidewire) with a balloon that is inflated at low pressures to occlude flow once it is positioned distal to the target lesion. Any debris liberated by intervention remains trapped in the stagnant column of blood and is subsequently aspirated with a different catheter before the occlusion balloon is deflated to restore antegrade flow. The 801-patient SAFER trial, in which patients undergoing SVG intervention were randomized to stenting using this distal protection device versus a conventional guidewire, demonstrated a substantial reduction in 30-day major adverse clinical events (16.9% to 9.6%) and no-reflow (8.3% to 3.3%) using the device. Subsequent trials with distal filters (e.g., FilterWire, Boston Scientific, Natick, MA; SpiderFX, ev3 Endovascular, Inc., Plymouth, MN) and proximal occlusion...
Figure 41.14  Saphenous vein graft intervention (SVG). A. The left main coronary artery is occluded at its origin. 
B. The right coronary artery is occluded and fills faintly by right-to-right bridging collaterals. C. The SVG to the diagonal branch is patent. D. The SVG to the ramus branch is patent. E. The SVG to an obtuse marginal branch is patent. F. The SVG to the posterior descending branch is acutely occluded (arrow). G. After wire recanalization, a large thrombus is seen in the midsegment of the SVG (large arrow) that extends more distally within the SVG (small arrows). H. An XVG AngioJet catheter (large arrow) is used to remove the thrombus after placement of a distal protection FilterWire (small arrow). I. A 3.5 × 33 mm CYPHER stent is placed in the distal portion of the SVG. J. Another 3.5 × 33 mm CYPHER stent is positioned in the proximal portion of the SVG. K. After removal of the FilterWire, the left anterior oblique projection demonstrates patency of a cascade of posterior descending and posterolateral branches. L. Complete stent expansion is confirmed in the left lateral projection.
devices (Proxis Embolic Protection System, St Jude Medical, Maple Grove, MN) have been noninferiority trials demonstrating similar outcomes. Given our inability to predict which patients will develop an embolic complication, embolic protection devices should be used in all suitable patients undergoing SVG intervention. Despite this Class I recommendation in the 2011 ACC/AHA/SCAI PCI guidelines, embolic protection is used in only ~23% of eligible patients.

Microvascular (arteriolar) spasm and dislodgement of platelet aggregates are also causes of periprocedural myocardial infarction (MI). In addition to appropriate antiplatelet and antithrombotic therapy, agents to treat microvascular
spasm (nitroprusside, adenosine, verapamil, nicardipine) are therefore typically employed when treating vein grafts.66

A meta-analysis of 19 studies demonstrated a 41% relative reduction in target vessel revascularization with DES as compared to BMS for SVG intervention without an increase in the risk of death, MI, or stent thrombosis.67 Two ongoing trials are comparing DES with BMS in SVGs.61

REFERENCES


63. Mauri L, Cox D, Hermiller J, et al. The proximal trial: Proximal protection during saphenous vein graft intervention using the proxi


Pulmonary Hypertension

Pulmonary hypertension (PH) is a broad term used to describe an elevation of pressure in the pulmonary arteries as a consequence of one or more disease processes (Table 42.1). The diagnosis requires a mean pulmonary artery pressure (mPAP) of >25 mmHg by right heart catheterization (RHC), and is suggested by a Doppler trans-thoracic echocardiogram (TTE) revealing a tricuspid regurgitation velocity of >2.3 m/second or a right ventricular systolic pressure (RVSP) of >40 mmHg. Pulmonary arterial hypertension (PAH) is a subset of PH, and results from restricted flow through the pulmonary arterial system. The diagnosis of PAH requires an RHC and fulfillment of a specific set of hemodynamic criteria: mPAP of >25 mmHg, pulmonary capillary wedge of ≤15 mmHg, and pulmonary vascular resistance (PVR) of >3 Wood units. Pulmonary venous hypertension (PVH) refers to the subset of PH resulting from processes affecting the left side of the heart, resulting in an increased pressure in the pulmonary veins, which is transmitted back to the right side of the heart. Left heart disease is by far the most common etiology of PH identified by Doppler echocardiography; in one study, pulmonary arterial hypertension was identified in only 2.7% of patients found to have PH by TTE (Table 42.2). The distinction between PAH and PVH is an important one, as it has a large impact upon prognosis, the need for referral to an expert, and treatment options.

Some of the material in this chapter was contributed by Samuel Z. Goldhaber, Nils Kucher, and Michael J. Landzberg in previous editions.

Pathology of Pulmonary Hypertension

The pulmonary vasculature is a low-pressure system with a normal systolic pulmonary artery pressure (sPAP) range of 15 to 30 mmHg and mPAP of 9 to 18 mmHg. The pulmonary circulatory system functions with one-twelfth the resistance to flow observed in the systemic vascular bed, in part due to the large cross-sectional area of the pulmonary circulation. Moreover, a typical right ventricular systolic pressure of 25 mmHg is one-fifth the typical left ventricular systolic pressure. Increases in pulmonary vascular resistance are not well tolerated by this low-pressure system, and adaptive responses, including right ventricular hypertrophy (RVH), begin to develop within 96 hours of induced pulmonary hypertension in animal models. RVH is often followed by contractile dysfunction and/or RV dilatation as further compensatory responses. Continued remodeling leads to an alteration in RV shape from crescent to concentric, and the septum flattens due to the increased RV pressures. As a result of these processes, RV-LV interventricular dependence is affected, leading to LV diastolic dysfunction, a decrease in LV end-diastolic volume, and a resultant decrease in stroke volume and cardiac output. Progressive right-sided heart failure is both the final common pathway and the primary cause of death in patients with PH.

For non-Group I PH, the mechanism by which a disease process results in an elevated PA pressure is often apparent. For example, occlusion of the pulmonary vasculature owing to pulmonary thromboembolic disease results in elevated right-sided pressures as blood is impeded from flowing freely toward the left atrium. A similar process occurs in patients with obstructive lung disease or sleep disordered
Table 42.1 Dana Point Clinical Classification of Pulmonary Hypertension (2008)

1. Pulmonary Arterial Hypertension (PAH)
   1.1 Idiopathic PAH
   1.2 Heritable
      1.2.1 BMPR2
      1.2.2 ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia)
      1.2.3 Unknown
   1.3 Drug- and toxin-induced
   1.4 Associated with
      1.4.1 Connective tissue diseases
      1.4.2 HIV infection
      1.4.3 Portal hypertension
      1.4.4 Congenital heart disease
      1.4.5 Schistosomiasis
      1.4.6 Chronic hemolytic anemia
   1.5 Persistent pulmonary hypertension of the newborn

1’. Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)

2. Pulmonary hypertension owing to left heart disease
   2.1 Systolic dysfunction
   2.2 Diastolic dysfunction
   2.3 Valvular disease

3. Pulmonary hypertension owing to lung diseases and/or hypoxia
   3.1 Chronic obstructive pulmonary disease
   3.2 Interstitial lung disease
   3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
   3.4 Sleep disordered breathing
   3.5 Alveolar hypoventilation disorders
   3.6 Chronic exposure to high altitude
   3.7 Developmental disorders

4. Chronic thromboembolic pulmonary hypertension (CTEPH)

5. Pulmonary hypertension with unclear multifactorial mechanisms
   5.1 Hematologic disorders: myeloproliferative disorders, splenectomy
   5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
   5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

breathing owing to hypoxic pulmonary vasoconstriction. Left ventricular systolic or diastolic dysfunction or mitral regurgitation results in PH as an inefficient pump hampers antegrade flow.

In PAH, more complex structural changes occur in the pulmonary vascular bed, resulting in pulmonary arterial obstruction owing to vascular proliferation and remodeling. This process involves all layers of the vessel wall and is characterized by intimal hyperplasia, medial hypertrophy, adventitial proliferation, and in situ thrombosis.

MOLECULAR AND CELLULAR MECHANISM OF PAH

The vasculopathy that results in PAH is likely triggered by the accumulation of multiple “hits” that may include a genetic predisposition, systemic disorder, or environmental factors. Once triggered, the pathobiology of PAH is dependent upon contributions from prostanoids, endothelin-1 (ET-1), and nitric oxide (NO), as shown in Figure 42.1. Additional research has implicated the serotonin, vasoactive intestinal peptide (VIP), and BMPR2 pathways in various forms of PAH.

Prostanoids

Prostacyclin (PGI₂) is a potent vasodilator and a strong inhibitor of platelet aggregation and smooth muscle cell proliferation. Thromboxane A₂ is a potent vasoconstrictor and promotes platelet activation. In PAH, a decrease in prostacyclin and an increase in thromboxane A₂ levels contribute to the phenotype.

Endothelin-1

ET-1 is a potent vasoconstrictor and smooth-muscle mitogen that exerts its effects through the receptors ETₐ (located on smooth muscle cells) and ETₐ (located on vascular endothelial cells and smooth muscle cells). Activation of the ETₐ and ETₐ receptors on smooth muscle cells induces vasoconstriction, cellular proliferation, and hypertrophy, whereas stimulation of ETₐ receptors on endothelial cells results in production of vasodilators (NO and PGI₂). Plasma ET-1 levels increase in PAH, and correlate to severity of disease and prognosis. Endothelin receptor antagonists (ERAs) function by selectively (ETₐ) or nonselectively (ETₐ and ETₐ) blocking ET-1 receptors.

Nitric Oxide Pathway

NO is a potent vasodilator and inhibitor of both smooth muscle cell proliferation and platelet activation. NO exerts its effects through cyclic guanosine monophosphate (cGMP), which is ultimately degraded by phosphodiesterase-5 (PDE-5).

PDE-5 inhibitors act by selectively blocking this enzyme, thus promoting the accumulation of intracellular cGMP and enhancing NO-mediated effects.

Serotonin

Serotonin is a vasoconstrictor that promotes smooth muscle cell hypertrophy and hyperplasia. Elevated total plasma serotonin and reduced platelet serotonin have been reported in PAH associated with ingestion of the anorexic agent dexfenfluramine, which increases the release of serotonin from platelets and inhibits its reuptake. Mutations in the serotonin transporter (5-HTT) and its receptor 5-HT₂B have been described in PAH patients. Of note, selective serotonin-reuptake inhibitors (SSRI) are not associated with an increased incidence of pulmonary hypertension, and may be protective against hypoxic PH.

ETIOLOGIES

The earliest classification system (1972) described two categories of PH: primary pulmonary hypertension and secondary pulmonary hypertension, depending upon the presence or absence of an identifiable cause. Groupings in the most recent classification system (Table 42.1) are based upon similar pathophysiological, clinical, and therapeutic characteristics. Familiarity with the system facilitates the generation of a differential diagnosis when considering the etiology of PH. Specialists use the classification when considering treatment options, as the majority of clinical trials involving PH medications have focused on Group 1 diagnoses.

Table 42.2 Prevalence of PH Groups

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAH (Group 1)</td>
<td>2.7%</td>
</tr>
<tr>
<td>Left heart disease</td>
<td>67.9%</td>
</tr>
<tr>
<td>Lung disease and hypoxemia (Group 3)</td>
<td>9.3%</td>
</tr>
<tr>
<td>CTEPH (Group 4)</td>
<td>2%</td>
</tr>
<tr>
<td>Miscellaneous/Unclear diagnosis (Group 5)</td>
<td>18.1%</td>
</tr>
</tbody>
</table>

CTEPH, thromboembolic pulmonary hypertension; PAH, Pulmonary arterial hypertension; PH, pulmonary hypertension.
Three major mechanistic pathways are known to be perturbed in patients with PAH. (1) The NO pathway: NO is created in endothelial cells by type III NO synthase (eNOS), which in turn induces guanylate cyclase (GC) to convert guanosine triphosphate (GTP) to cGMP, a second messenger that constitutively maintains pulmonary artery smooth muscle cell (PASMC) relaxation and inhibition of PASMC proliferation. (2) The endothelin (ET) pathway: Big-ET (or pro-ET) is converted in endothelial cells to ET-1 (21 amino acids) by endothelin-converting enzyme (ECE). ET-1 binds to PASMC ETA and ETB receptors, which ultimately leads to PASMC contraction, proliferation, and hypertrophy. ET-1 also binds to endothelial cell ETB receptors. (3) The prostacyclin pathway: The production of PG12 (prostacyclin) is catalyzed by prostacyclin synthase (PS) in endothelial cells. In PASMCs, PG12 stimulates adenylate cyclase (AC), thus increasing production of cAMP from ATP, another second messenger that maintains PASMC relaxation and inhibition of PASMC proliferation. Importantly, the pathways interact as illustrated, modulating the effect of any single pathway. They also are impacted by transmitters and stimuli that act at cell membrane receptors (Rec). Examples of these include but are not limited to thrombin, bradykinin, arginine vasopressin (AVP), vessel-wall shear stress, angiotensin II (Ang II), cytokines, and reactive oxygen species (ROS). In addition, the effect of a transmitter depends on its specific site of action (such as PASMC ETA or ETB receptors versus endothelial cell ETB receptor). The large white arrows depict aberrations observed in these pathways among patients with PAH. The orange boxes represent agents with reported clinically beneficial effects in patients with PAH. PDE5-inh indicates PDE-5 inhibitor, e.g., sildenafil; ETRA, endothelin receptor antagonist, e.g., bosentan (dual), ambrisentan, and sitaxsentan (receptor A selective). Prostanoids, e.g., epoprostenol, treprostinil, and iloprost, supplement exogenously deficient levels of PG12. Red stop signs signify an inhibitory effect of the depicted agents. Dotted arrows depict pathways with known and unknown intervening steps that are not shown.8 (Reproduced with permission from: McLaughlin VV, McGoon MD. Pulmonary arterial hypertension. Circulation 2006;114:1417–1431.)
At the time of diagnosis, patients with PH typically have experienced progressive dyspnea-on-exertion (DOE) over the course of months to years. Fatigue, light-headedness, chest pain, palpitations, orthopnea, edema, paroxysmal nocturnal dyspnea, and cough are other common presenting symptoms. Syncope in a patient with PH is suggestive of advanced disease with RV failure.

Examination findings suspicious for the presence of PH include a prominent P2, a parasternal lift, a right ventricular S4, a systolic murmur of tricuspid regurgitation, an early systolic click, and a diastolic murmur of pulmonary regurgitation. Clues to the etiology of PH include central ease with RV failure.

If the history, physical examination, ECG, and CXR are suggestive of PH, a carefully selected systematic series of diagnostic studies is indicated. Experts endorse the approach presented in Figure 42.2. Doppler TTE is a left ventricular S3, or mitral and/or aortic valve murmurs as a result of left heart disease; and wheezing or protracted expiration secondary to hypoxic lung disease. Findings in advanced PH with right heart failure may include jugular venous distention, a right ventricular S3, edema, ascites, and hepatomegaly.

The initial evaluation of any patient with suspected PH should begin with a 12-lead ECG and two-view chest X-ray. PH is supported by ECG findings of right axis deviation, right ventricular hypertrophy, right atrial enlargement, and ST and T wave abnormalities in the precordial leads consistent with right ventricular strain. The chest radiograph may show prominent central pulmonary arteries and peripheral hypovascularity or “pruning.” The lateral view may demonstrate RV obliteration of the retrosternal space owing to RV enlargement.

If the history, physical examination, ECG, and CXR are suggestive of PH, a carefully selected systematic series of diagnostic studies is indicated. Experts endorse the approach presented in Figure 42.2. Doppler TTE is...
generally obtained early in the evaluation of patients with suspected PH. The tricuspid regurgitant jet is used to estimate the RVSP, and pressures >40 mmHg are consistent with PH. However, TTE can both under- and overestimate pulmonary artery pressures, as compared to the gold standard of RHC. In addition to the pressure measurements, TTE is useful in identifying elevated right-sided pressures by showing evidence of right atrial or ventricular enlargement, flattening of the interventricular septum, or an underfilled LV.

The following points should be kept in mind when ordering and evaluating tests for PH:

- **Ventilation/perfusion (V/Q) scan**: the test of choice for the initial evaluation of chronic, surgically accessible thromboembolic disease. A PE protocol CT is excellent for identifying acute PE; however, is not sensitive for chronic thromboembolic disease. If indicated, pulmonary angiography can often be scheduled immediately following RHC if chronic thromboembolic disease is highly suspected.
- **Pulmonary function tests (PFTs)**: may show only mild restrictive disease and a mildly decreased diffusing capacity for carbon monoxide (DLCO); scleroderma patients may have a more marked decrease in DLCO.
- **Polysomnogram**: should be performed if a patient endorses symptoms of sleep disordered breathing.
- **Blood tests**: given the association between PH and both connective tissue disorders and chronic liver disease, antinuclear antibody (ANA) tests and liver function tests (LFTs) are routinely performed. HIV testing should be performed if a patient endorses risk factors. A complete blood count is helpful in identifying anemia as a cause of high-output heart failure. Thyroid function studies should be performed in all patients.
- **Six minute hall walk (6MWT)**: commonly used to objectively assess functional capacity; this test is often performed at baseline and repeated periodically to assess response to treatment; it is frequently used as an endpoint in clinical PAH trials.

**Right Atrial Pressure**

Accurate assessment of right atrial pressure is essential, as it has prognostic implications and can help guide therapy. The most common right atrial manifestations of PAH are an attenuated x descent, prominent c–v wave, and deep and rapid y descent caused by tricuspid regurgitation (TR). In cases with severe TR, the RA waveform may be indistinguishable from that of the RV. Presence of RV hypertrophy and/or pressure overload may produce a prominent a wave owing to RV noncompliance.

**Pulmonary Artery and Pulmonary Capillary Wedge Pressures**

PAH is diagnosed by an mPAP of >25 mmHg and a pulmonary capillary wedge pressure of ≤15 mmHg. Careful assessment of the PA and PCWP waveforms is essential, as measurements made using an improperly placed catheter can lead to misdiagnosis. For example, an underwedged catheter can produce a hybrid waveform with a morphology intermediate between PA and PCWP tracings (Figure 42.3). Underwedging results in a falsely elevated PCWP that may lead to a diagnosis of PVH instead of PAH. Overwedging is less common and may result in inaccurate pressure measurements and pulmonary artery rupture. If the accuracy of a PCWP is in doubt, it is recommended that a left heart catheterization be performed to measure left ventricular end-diastolic pressure.

**Cardiac Output and Pulmonary Vascular Resistance**

An accurate cardiac output (CO) is essential, as cardiac index (CI), along with mRAP and mPAP, has been shown to be an important predictor of survival. It should be emphasized that mPAP may actually decrease with advancing PAH as right ventricular function fails. CO is also necessary for the computation of pulmonary vascular resistance [(mPAP – PCWP)/CO]. Patients with PAH generally have a transpulmonary gradient (mPAP – PCWP) >12 mmHg and a PVR >3 Wood units.

**Vasodilator Testing**

Acute vasodilator testing with inhaled NO (most common), intravenous epoprostenol, or intravenous adenosine is useful for identifying patients with a better prognosis who may experience a prolonged and beneficial response to calcium channel blocker (CCB) therapy. Responders exhibit at least a 10-mmHg decrease in mPAP to an absolute mPAP of <40 mmHg without a decrease in cardiac output. Patients who do not meet these criteria should not be treated.
with CCBs. Acute vasodilator testing should be avoided in patients with significantly elevated left heart filling pressures or low cardiac output. Veno-occlusive disease and pulmonary capillary hemangiomatosis should be considered in patients who experience pulmonary edema during vasodilator testing.\footnote{22}

**Other Considerations**

A careful oximetry run to localize step-ups in the right heart should be performed if an intracardiac shunt is suspected. Dynamic exercise during right heart catheterization is used by some centers to unmask exercise-induced PAH (ePAH) in at-risk populations, such as patients with the scleroderma spectrum of diseases.\footnote{23}

**TREATMENT**

General treatment recommendations for PH include sodium restriction, graded aerobic exercise, limited isometric exercise, and consideration of birth control for women. Non-PAH PH is further treated by addressing the underlying cause and by adding supplemental oxygen and diuretics, as needed. As the vast majority of patients with PH have either diastolic or systolic heart failure, treatment of volume status can often alleviate the PH, thus resulting in increased functional capacity. PAH-specific therapies should be utilized under the direction of a PAH specialist. These therapies may include warfarin, diuretics, calcium channel blockers (for those with a positive vasodilator response during RHC), prostacyclin analogues, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors (Table 42.3).

More invasive strategies may be indicated in select patients. Pulmonary thromboendarterectomy is the treatment of choice for surgically accessible chronic thromboembolic pulmonary hypertension, and should be performed at high-volume centers. Creation of a right-to-left interatrial shunt via percutaneous atrial septostomy improves right heart function and left heart filling by decreasing right heart filling pressures. Though the shunt decreases systemic arterial oxygen saturation, the improved cardiac output results in an overall improvement in systemic oxygen delivery. The mortality associated with atrial septostomy is high (15%), and it is reserved for patients with advanced right heart failure despite maximal medical therapy. Lung and heart-lung transplantation are options for patients with intractable disease.
<table>
<thead>
<tr>
<th>Medications</th>
<th>Comments</th>
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<tbody>
<tr>
<td><strong>Supplemental oxygen</strong></td>
<td>■ As needed to treat symptoms (may be needed for air travel)</td>
</tr>
<tr>
<td><strong>Anticoagulation</strong></td>
<td>■ Improved survival in observational studies involving patients with IPAH&lt;br&gt;■ Also recommended in advanced associated PAH&lt;br&gt;■ INR 1.5 to 2.5</td>
</tr>
<tr>
<td>■ warfarin</td>
<td>■ Indicated only in patients with positive vasodilator response during RHC;&lt;br&gt;■ Empiric administration without hemodynamic guidance may result in rapid deterioration&lt;br&gt;■ Avoid verapamil (decreased inotropy)</td>
</tr>
<tr>
<td><strong>Calcium channel blockers</strong></td>
<td>■ Mechanism: replenishes PGI₂, resulting in vasodilation, inhibition of platelet aggregation and inhibition of vascular SMCs&lt;br&gt;■ Indication: WHO class III to IV symptoms (IPAH or scleroderma spectrum of PAH)&lt;br&gt;■ Administration: continuous infusion requires a central venous catheter&lt;br&gt;■ Overdose can result in high-output heart failure</td>
</tr>
<tr>
<td>■ diltiazem</td>
<td></td>
</tr>
<tr>
<td>■ nifedipine</td>
<td></td>
</tr>
<tr>
<td>■ amlopidine</td>
<td></td>
</tr>
<tr>
<td><strong>Endothelin receptor antagonist</strong></td>
<td>■ Mechanism: nonselectively blocks vasoconstrictive and SMC mitogenic effects of endothelin-1 (ETₐ and ET₆) &lt;br&gt;■ Indication: WHO class II to IV symptoms (PAH) &lt;br&gt;■ Administration: oral, 125 mg po BID&lt;br&gt;■ Considerations: must monitor LFTs and hemoglobin; potential teratogen; may reduce sperm count</td>
</tr>
<tr>
<td>■ bosentan (Tracleer)</td>
<td></td>
</tr>
<tr>
<td>■ ambrisentan (Letairis)</td>
<td></td>
</tr>
<tr>
<td>■ sildenafil (Revatio)</td>
<td></td>
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<tr>
<td>■ Tadalafil (Adcirca)</td>
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cGMP, Cyclic guanosine monophosphate; INR, International normalized ratio; IPAH, Idiopathic pulmonary arterial hypertension; PAH, Pulmonary arterial hypertension; RHC, Right heart catheterization; SMC, Smooth muscle cell.
CASE 42.1 A 37-year-old previously healthy woman presented with progressive dyspnea on exertion since the birth of her second child, 14 months previously. Initially, she attributed the dyspnea to weight gain, but it progressed to the point where she was unable to make it up one flight of stairs and had to take frequent breaks while grocery shopping. She suffered a syncopal event while walking up an incline with her older child. She also experienced atypical chest pain, occasional palpitations, and lower extremity edema. On physical examination, her heart rate was 90 beats per minute, blood pressure 130/68, weight 190 pounds, and height 5'4". Her JVP was > 15 cm and her carotid upstrokes were reduced. Her lungs were clear. She had a palpable right ventricular heave, a normal S1, and a loud pulmonic component to her second heart sound. She also had a III/VI holosystolic murmur at the left lower sternal border. She had 2+ lower-extremity edema. Her electrocardiogram demonstrated normal sinus rhythm with a right bundle branch block and right ventricular hypertrophy (Figure 42.4). A chest X-ray demonstrated large pulmonary arteries and clear lungs. There was a reduction in retrosternal air space on the lateral view. Her echocardiogram demonstrated severe RV enlargement and dysfunction with a small left ventricle and septal flattening. Her estimated right ventricular systolic pressure was 75 mmHg. A transesophageal echocardiogram did not demonstrate an intracardiac shunt. Her ventilation perfusion scan was normal. On pulmonary function tests, she had normal volumes and flows and her diffusing capacity of carbon monoxide was 81%. The ANA test was negative. Her baseline 6-minute walk was 222 m.

A right heart catheterization was performed and the following hemodynamics were recorded: RAP 19 mmHg; PAP 93/40 mmHg with a mean of 63 mmHg; LVEDP 10 mmHg; cardiac output 2.5 L/minute with a cardiac index of 1.3 L/minute/m². She was given a vasodilator trial with inhaled nitric oxide and her hemodynamics were unchanged.

Given the severity of her symptoms and pulmonary vascular disease, she was hospitalized immediately after the catheterization. She was given IV diuretics, and intravenous epoprostenol was started for idiopathic pulmonary arterial hypertension. Over the course of her hospitalization, she and her husband learned the techniques of sterile preparation of the medication, operation of the ambulatory infusion pump, and care of the central venous catheter. After losing 20 pounds, she was transitioned to oral diuretics. She was also anticoagulated with warfarin.

Over the ensuing 6 months, her epoprostenol was titrated to a dose of 30 ng/kg/minute and a PDE5 inhibitor was added.

![ECG demonstrating sinus rhythm, right axis deviation, and right ventricular hypertrophy with strain pattern.](image-url)
Her symptoms improved to the point at which she had no dyspnea with her usual activities. A 6-minute hall walk was performed at 6 months during which she walked for 602 m. A right heart catheterization was performed after 1 year of therapy, which demonstrated the following hemodynamics: RAP 4 mmHg; PAP 65/24 mmHg with a mean of 40 mmHg; PCWP 7 mmHg; Cardiac output 4.61 L/minute with a cardiac index of 2.77 L/minute/m². She was maintained on intravenous epoprostenol and a PDE5 inhibitor.

**CASE 42.2**

A 22-year-old, previously healthy woman presented with a 6- to 7-month history of worsening dyspnea on exertion. By the time of her presentation, she had dyspnea after going up one flight of stairs or with heavier housework such as vacuuming. She also complained of exertional light-headedness and chest pain. She denied palpitations and lower extremity edema. On physical examination her blood pressure was 105/60 mmHg with a heart rate of 89 bpm. Her JVP was 8 cm and her carotid upstrokes were normal. Her lungs were clear. She had a palpable right ventricular heave. On cardiac auscultation, she had a normal S₁ and a physiologically split S₂ with a loud pulmonic component. She had a holosystolic murmur at the left lower sternal border. Her abdomen was soft, and she did not have lower extremity edema.

Her electrocardiogram revealed normal sinus rhythm with right axis deviation and right ventricular enlargement with a strain pattern. Her CXR demonstrated large pulmonary arteries and clear lungs. Her PFTs and ventilation perfusion scan were normal. ANA and HIV tests were negative. An echocardiogram demonstrated moderate right atrial and right ventricular enlargement and hypertrophy with mild-to-moderate right ventricular dysfunction. Her left ventricular function was normal, and the estimated RVSP was 75 mmHg. With an injection of agitated saline, there was immediate right-to-left flow. A transesophageal echo was then performed which demonstrated a 1.5-cm sinus venous atrial septal defect with bidirectional shunting. Anomalous pulmonary veins were also identified by cardiac MRI (Figure 42.5).

Right and left heart catheterizations were performed, and the following hemodynamics were measured: RAP 9 mmHg; PAP 74/26 mmHg with a mean of 47 mmHg; PCWP 9 mmHg. The following saturations were also measured: SVC 49.1%, IVC 50.8%, PA 71.3%, PCWP 95.1%, anomalous pulmonary vein 95.0%, left ventricle 90.5%. The following calculations were carried out: Qp 5.48 L/minute, Qs 3.2 L/minute,

![Figure 42.5](image)

**Figure 42.5**

A. CMR showing anomalous return of the right upper lobe (RUL) and right middle lobe (RML) pulmonary veins to the superior vena cava. B. The patient was also found to have an anomalous return of the right lower lobe (RLL) pulmonary vein to the right atrium.
right-to-left shunt 0.32 L/minute, left-to-right shunt 2.6 L/minute, Qp/Qs 1.7, PVR 6.9 Wood Units. Given her high PVR, right-to-left shunting, and RV dysfunction, she was not considered a good candidate for surgical repair of the defect. She was treated with an oral endothelin receptor antagonist and currently has dyspnea only with severe exertion.

**CASE 42.3** A 36-year-old woman without significant past medical history presented with a 6-month history of progressive dyspnea on exertion, presyncopal episodes, and lower extremity edema. Her initial evaluation included a transthoracic echocardiogram, which revealed right atrial enlargement; a dilated, hypertrophic, mildly dysfunctional right ventricle; a RVSP of 83 mmHg; and bowing of the interatrial septum (Figure 42.6). A right heart catheterization with nitric oxide challenge was performed, which revealed an mRAP of 7 mmHg, mPAP of 51 mmHg, and PCWP of 11 mmHg. Her cardiac output was 3.0 L/minute by thermodilution technique and the PVR was 13 Wood Units. She did not respond to nitric oxide challenge. The patient elected to undergo initiation of treprostinil via subcutaneous infusion. Her symptoms persisted despite up-titration of her medication, and a repeat RHC 18 months later showed a PVR of 12 Wood Units. She was transitioned to intravenous epoprostenol therapy, but once again showed no improvement in her intracardiac pressures by RHC 6 months later. Lung transplantation evaluation and combination therapy with an oral endothelin receptor antagonist, along with dual forms of birth control, were initiated. She experienced significant improvement in her symptoms and 6-minute hall-walks over the next 2 years, but then discontinued the endothelin receptor antagonist owing to hepatotoxicity. Repeat RHC performed 4 years following her initial diagnosis showed an RA pressure of 15 mmHg, mPAP of 54 mmHg, and a PCWP of 7 mmHg. Her CI was 1.08 L/minute/m² by the Fick method and 1.54 L/minute/m² by thermodilution technique. An oral phosphodiesterase-5 inhibitor was added. Six months later the patient was admitted with worsening lower extremity edema, hypotension, and hyponatremia. Transthoracic echocardiogram showed marked right atrial and ventricular enlargement, worsening right ventricular dysfunction, an RVSP of 80 mmHg, an underfilled left ventricle with normal function, and reversal of the normal curvature of the interventricular septum consistent with suprasystemic right ventricular pressures.

The patient was listed for lung transplantation and referred for atrial septostomy. RHC showed an mRAP of 17 mmHg, PAP of 83/32 mmHg with a mean of 52 mmHg, a PCWP of 4 mmHg, and systemic pressures of 71/41 mmHg. Systemic arterial saturation was 95%, with a PA saturation of 56%. A trans-septal puncture was performed using a BRK1 trans-septal needle. Inflations were then performed across the interatrial septum with a 10 mm × 20 mm Opta balloon that was inflated to a maximum of 5 atm. The balloon was then deflated and withdrawn into the right atrium. A transthoracic echocardiogram revealed the presence of a moderate-sized atrial septal defect with right-to-left shunting (Figure 42.7). The systemic O₂ saturation was 92% on 2 liters of oxygen nasal cannula and 87% on room air. Post-septostomy mRAP was 15 mmHg.

Over the next month the patient’s blood pressure increased and her lower extremity edema lessened, but her severe dyspnea with minimal exertion persisted. A lung transplant donor was identified, and she underwent successful double lung transplantation with closure of the atrial septal defect. Six months after the transplantation transthoracic echocardiogram showed biatrial enlargement and a slightly enlarged right ventricle, but normal biventricular function and a normal RVSP (Figure 42.8). Six years following her bilateral lung transplantation she continues to do well. She...
denies dyspnea, dizziness, or lower extremity edema, and is working full-time.

**PULMONARY EMBOLISM**

Acute pulmonary embolism (PE) encompasses a wide spectrum of acuity, with varying prognoses and therapies. Most patients with acute PE maintain normal systolic arterial pressure and normal right ventricular function once therapeutic levels of anticoagulation are established. Unfortunately, some PE patients suffer clinical deterioration including death from right ventricular failure or the need for cardiopulmonary resuscitation, mechanical ventilation, pressors, thrombolysis, catheter thrombectomy, or surgical thromboendarterectomy.24

Many patients with chronic thromboembolic pulmonary hypertension (CTEPH) present with worsening dyspnea or fatigue but do not have a clear history of venous thromboembolism or an identifiable thrombophilic disorder. This condition often remains undiagnosed until an echocardiogram or chest computed tomogram (CT) shows right ventricular enlargement. Clinical outcome may improve with pulmonary thromboendarterectomy in combination with placement of a vena cava filter and indefinite-duration anticoagulation.

**Diagnosis**

Maintaining a high degree of clinical suspicion for PE is of paramount importance. The onset of symptoms may be sudden, gradual, or intermittent. The most common symptoms and signs are nonspecific: dyspnea, chest pain, tachypnea, and tachycardia. Usually, pulmonary embolism patients with pleuritic pain or hemoptysis have anatomically small emboli near the periphery of the lung, where nerve innervation is the maximum and where pulmonary infarction is most likely to occur owing to poor collateral circulation. In contrast, patients with life-threatening PE often have a painless presentation characterized by profound dyspnea, syncope, or cyanosis.

PE should be suspected in a hypotensive patient when (i) there is evidence of, or there are predisposing factors for, venous thrombosis; (ii) there is clinical evidence of acute cor pulmonale (acute right ventricular failure) such as distended neck veins, an S3 gallop, a right ventricular heave, tachycardia, or tachypnea; and especially if (iii) there is electrocardiographic evidence of acute cor pulmonale manifested by a new S1-Q3-T3 pattern, new incomplete right bundle branch block, or right ventricular ischemia. Under such circumstances, a bedside echocardiogram is especially helpful.
**Laboratory and Imaging Tests**

*Chest radiograph* abnormalities include focal oligemia (Westermark sign), indicating massive central embolic occlusion, or a peripheral wedge-shaped density above the diaphragm (Hampton hump), indicating pulmonary infarction. An enlarged right descending pulmonary artery (Palla sign) is also a useful clue. Furthermore, the chest radiograph can help identify patients with other diseases such as lobar pneumonia or pneumothorax that can mimic pulmonary embolism.

The *electrocardiogram* helps to exclude acute myocardial infarction and to identify electrocardiographic manifestations of right-heart strain.\(^{25-27}\) The differential diagnosis of new right heart strain includes acute pulmonary embolism, acute asthma, or exacerbation of chronic bronchitis in patients with chronic obstructive pulmonary disease.

Unfortunately, the time-honored screening test of abnormal room air *arterial blood gases* is not helpful in triaging patients suspected of pulmonary embolism. Extensive analyses of the large PIOPED (Prospective Investigation of Pulmonary Embolism Diagnosis) database indicate that even sophisticated calculations of the alveolar-arterial oxygen difference do not differentiate patients with and without PE.\(^{28,29}\) Therefore, arterial blood gases should not be obtained as a screening test in patients suspected of pulmonary embolism.

An abnormally elevated level of enzyme-linked immunosorbent assay (ELISA) plasma *D-dimer* (>500 ng/mL) has a >90% sensitivity for identifying patients with PE proven by lung scan\(^{30}\) or by angiogram.\(^{31}\) Although low plasma concentrations of D-dimers are sensitive for excluding PE, they are not specific. D-dimer levels remain elevated in patients for at least 1 week postoperatively and will also be abnormally high in patients with myocardial infarction, sepsis, or almost any other systemic illness. Therefore, the plasma D-dimer ELISA is best used in patients who present to the office or emergency department without coexisting acute systemic illness.\(^{32,33}\)

*Ventilation-perfusion* (V-Q) lung *scanning* has traditionally served as the principal diagnostic imaging test when the clinical suspicion for pulmonary embolism is high. The V-Q scan is most useful if it is clearly normal or if it demonstrates a pattern suggestive of a high probability for pulmonary embolism.

*Spiral chest CT scanning* with contrast allows image acquisition with 1-mm resolution during a single breath-hold, enabling accurate detection of central, lobar, segmental, and subsegmental thrombi. Sensitivity and specificity for PE are >90%.\(^{34}\) Spiral chest CT is also useful for the rapid detection of alternative diagnoses, such as aortic dissection, pneumothorax, or pericardial tamponade (Chapter 18).

*Gadolinium-enhanced magnetic resonance* (MR) angiography is accurate for PE diagnosis and avoids ionizing radiation or iodinated contrast agents. MR appears to be almost as sensitive and specific for PE as is pulmonary angiography.\(^{35}\) However, in most institutions, MR has limited round-the-clock availability, and there is restricted monitoring, rendering this imaging modality unsuitable for hemodynamically unstable patients.

*Venous ultrasound* is usually accurate in diagnosing proximal leg deep venous thrombosis in *symptomatic outpatients*\(^{36}\) and may serve as a useful surrogate for PE. However, almost two-thirds of PE patients have no venographic\(^{37}\) or ultrasound evidence of leg deep venous thrombosis.\(^{38,39}\) Therefore, if clinical suspicion of pulmonary embolism is high, patients without clinical or imaging evidence of deep venous thrombosis should still be worked up for PE.

*Echocardiography* is indicated to guide the use of thrombolytics and thrombectomy in cases of known acute pulmonary embolism, and may be used to assess changes in RV function and pulmonary artery pressure following such therapies; however, it is not indicated in cases of suspected pulmonary embolism to establish the diagnosis.\(^{40}\) Besides, echocardiography will suggest PE if a constellation of findings indicates right heart failure, especially in the presence of regional right ventricular systolic wall motion abnormalities (the McConnell Sign).\(^{41}\) In a patient with suspected massive PE and severe right ventricular dysfunction on the echocardiogram, initiation of reperfusion therapy, including thrombolysis, catheter fragmentation, or surgical embolectomy, may be considered without performing time-consuming imaging tests.\(^{42}\) Echocardiography in this setting can also help to exclude other life-threatening conditions, such as ventricular septal rupture, aortic dissection, and pericardial tamponade. However, echocardiography is normal in about half of the patients with suspected PE and therefore is not a good screening test in hemodynamically stable patients.

*Pulmonary angiography* is warranted if the clinical suspicion for PE remains high after negative or equivocal noninvasive imaging studies, including contrast-enhanced chest CT, lung scanning, or venous ultrasound. In the case of CTEPH, pulmonary angiography is necessary to determine whether the disease is amenable to surgical thromboendarterectomy (see Chapter 18).

**Risk Stratification**

Contemporary risk stratification focuses on early detection of those patients who are at increased risk for adverse clinical events while the systemic arterial pressure is preserved, prior to the development of cardiogenic shock.\(^{43}\)

On *physical examination*, tachycardia, tachypnea, and arterial hypotension suggest high risk. Clinical signs of right ventricular dysfunction include distended jugular veins, an accentuated pulmonic heart sound, a right ventricular heave, or a tricuspid regurgitation murmur.

The *Geneva Prognostic Index*\(^{44}\) uses an eight-point scoring system and identifies clinical predictors of adverse clinical outcome: two points each for cancer and hypotension, and one point each for heart failure, prior DVT, arterial hypoxemia, and concomitant DVT. As points accumulate, prognosis
Anticoagulation

When PE is diagnosed or strongly suspected, anticoagulation therapy should be initiated immediately unless a contraindication exists. An intravenous bolus of unfractionated heparin (80 U/kg) followed by 18 U/kg per hour is the standard approach to initiate anticoagulation. The activated partial thromboplastin time (aPTT) should be followed at 6-hour intervals until it remains consistently in the therapeutic range of 1.5 to 2.5 times the upper limit of the normal range. Oral anticoagulation with warfarin can be started as soon as the aPTT is within the therapeutic range.

Therapy with low molecular weight heparin (LMWH) is as safe and effective as therapy with unfractionated heparin in hemodynamically stable patients with acute PE. Extended 3-month monotherapy with enoxaparin without warfarin appears to be as effective and safe in the treatment of acute PE as unfractionated heparin bridged to warfarin. The Food and Drug Administration (FDA) has approved enoxaparin for outpatient treatment of symptomatic deep vein thrombosis with or without PE, as a bridge to warfarin.

Pentasaccharides, such as fondaparinux, are anti-Xa agents. They do not cause thrombocytopenia. Fondaparinux, 7.5 mg given subcutaneously once daily, is at least as effective and safe as unfractionated heparin.

In PE patients with transient risk factors, such as surgery or trauma, anticoagulation may be safely discontinued after 6 months. In other patients, indefinite-duration anticoagulation should be strongly considered. The intensity of long-term anticoagulation is controversial but will depend on the risk of both recurrent thromboembolic and bleeding events. In PREVENT, a double-blind randomized controlled trial of patients with idiopathic venous thromboembolism who had completed an average of 6 months of full-intensity warfarin, low-intensity warfarin (target International Normalized Ratio [INR] of 1.5 to 2.0) for an average of 2 years reduced the recurrence rate by two-thirds. In the ELATE study of 739 patients with idiopathic venous thromboembolism, indefinite-duration, full-intensity warfarin therapy (target INR 2 to 3) was more effective than, and as safe as, indefinite-duration, low-intensity warfarin therapy (target INR 1.5 to 1.9).

Thrombolysis, Catheter Intervention, and Surgical Thromboendarterectomy

Systemic thrombolysis is indicated in eligible patients with massive PE. Thrombolysis is effective up to 2 weeks after the onset of symptoms. Streptokinase, urokinase, and alteplase are FDA-approved fibrinolytics that convert circulating plasminogen to the serine protease plasmin (Table 42.4). Plasmin cleaves fibrin, releasing fibrin-split products (including the D-dimer).

A total of 13 placebo-controlled randomized trials of thrombolysis for acute PE have been published, with 480 patients randomized to fibrinolysis and 464 patients to placebo. Pooled analysis reveals that neither recurrent PE nor death was significantly different in the alteplase group versus the placebo group. However, an earlier analysis restricted to trials involving massive PE noted a reduction in recurrent PE or death from 19% with heparin alone to 9.4% with fibrinolysis.

In the largest randomized controlled trial of patients with submassive PE, heparin plus alteplase as a continuous infusion over 2 hours was compared with heparin alone.
Alteplase markedly reduced adverse clinical events from 25% to 11%; these events were defined as in-hospital mortality or the need for cardiopulmonary resuscitation, mechanical ventilation, administration of vasopressors, secondary rescue thrombolysis, or surgical embolectomy. There was no significant increase in major or intracranial bleeding with alteplase among these carefully selected PE patients.

In submassive PE, thrombolysis therapy remains controversial because a reduction in mortality has not been shown. Overall, there is a trend toward reduction of mortality in favor of thrombolysis (relative risk 0.63, 95% CI: 0.32 to 1.23). However, thrombolysis was associated with a twofold increase in the hazard of major hemorrhage (relative risk 1.76, 95% CI: 1.04 to 2.98). Therefore, low-risk PE patients with preserved systemic arterial pressure and normal right ventricular function should not be treated with thrombolysis.

The suggested treatment algorithm for use of fibrinolytics to treat acute pulmonary embolism is presented in Figure 42.9. Absolute and relative contraindications to thrombolysis are included in Tables 42.5 and 42.6, respectively.

**Catheter intervention** is a promising alternative to thrombolysis or surgical embolectomy. Techniques including aspiration thrombectomy, thrombus fragmentation, and rheolytic thrombectomy are all possible using commercially available catheters.

**Surgical pulmonary embolectomy** should be considered in patients with massive PE and cardiogenic shock in the setting of (i) high bleeding risk, (ii) failed thrombolysis, (iii) presence of right atrial or ventricular thrombi, or (iv) need for other cardiac surgery, such as closure of an atrial septal defect or patent foramen ovale in a patient who has suffered a paradoxical embolus. The operation involves a median sternotomy, cardiopulmonary bypass, and deep hypothermia with circulatory arrest periods. Mortality in patients with cardiogenic shock who undergo emergency surgical embolectomy approximates 30%. If surgical embolectomy is performed prior to the onset of cardiogenic shock, the mortality rate may be lowered to about 4% in high-volume centers.

The principal indications for vena caval filter placement include major contraindications to anticoagulation and recurrent venous thromboembolism despite therapeutic levels of anticoagulation. In the United States, a survey of 183 institutions found a high rate (24%) of vena caval filter insertion in patients with newly diagnosed acute deep vein thrombosis. Unfortunately, patients with filters are more than twice as likely as non-filter patients to require rehospitalization for deep vein thrombosis owing to formation of thrombus proximal to or on the proximal tip of the filter. Procedure-related complications are rare and include filter migration or improper filter positioning. Occasionally, the inferior vena cava may be completely obstructed by filter thrombosis. Fracture of the filter struts with distal embolization of fragments has also been reported.

Temporary filters have been used in patients deemed to be at high risk for either thrombotic or bleeding events. Retrievable filters can be removed within several months or can be left in place in case of a persistent contraindication to anticoagulation. Whenever possible, anticoagulation should be administered to prevent filter thrombosis.

**CASE 42.4** A 20-year-old woman experienced a syncopal episode while exerting herself at work, and was transported to her local emergency department. At that time, she described an 18-month history of progressive lower extremity edema and dyspnea on exertion, which began shortly following surgery for repair of an ankle fracture, after which she was relatively immobile for 3 months. Initially, she ascribed the dyspnea to a combination of deconditioning and tobacco use. Twelve months later she experienced a syncopal episode while exerting herself at work, but did not seek medical attention until 2 weeks later when she felt lightheaded and severely tachypneic. A pulmonary embolism protocol computed tomography scan performed at her local emergency department revealed extensive, bilateral filling defects in the main, lobar, and segmental pulmonary arteries consistent with large, bilateral pulmonary emboli (Figure 42.10A). A TTE showed a severely dilated and dysfunctional right ventricle. Tissue plasminogen activator (tPA) was administered, and the patient was discharged on oral warfarin therapy and portable home oxygen. The patient was referred to a...
Section VIII Clinical Profiles

Figure 42.9 Suggested algorithm for the use of thrombolytics in the setting of acute pulmonary embolism.69 (Reproduced with permission from: Jaff MR, McMurtry MS, Archer SL, et al. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. Circulation 2011;123:1788–1830.)

Table 42.5 Absolute Contraindications to Thrombolysis69

<table>
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<tr>
<th>Contraindication</th>
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<tr>
<td>1. Prior intracranial hemorrhage</td>
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<td>2. Known structural intracranial cerebrovascular disease</td>
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<tr>
<td>3. Known malignant intracranial neoplasm</td>
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<tr>
<td>4. Ischemic stroke within 3 mo</td>
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<tr>
<td>5. Suspected aortic dissection</td>
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<tr>
<td>6. Active bleeding or bleeding diathesis</td>
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<tr>
<td>7. Recent significant closed head or facial trauma with radiographic evidence of bony fracture or brain injury</td>
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<tr>
<td>8. Recent surgery encroaching upon the spinal canal or brain</td>
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Table 42.6 Relative Contraindications to Thrombolysis69

<table>
<thead>
<tr>
<th>Contraindication</th>
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<tbody>
<tr>
<td>1. Age &gt;75 y</td>
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<tr>
<td>2. Current use of anticoagulation</td>
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<tr>
<td>3. Pregnancy</td>
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<tr>
<td>4. Noncompressible vascular punctures</td>
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<tr>
<td>5. Traumatic or prolonged CPR (&gt;10 min)</td>
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<td>6. Recent internal bleeding (within 2–4 wk)</td>
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<tr>
<td>7. History of chronic, severe, poorly controlled hypertension (systolic &gt;180 mmHg, diastolic &gt;110 mmHg)</td>
</tr>
<tr>
<td>8. Remote ischemic stroke (&gt;3 mo)</td>
</tr>
<tr>
<td>9. Recent major surgery (within 3 wk)</td>
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Chapter 42 Profiles in Pulmonary Hypertension and Pulmonary Embolism

A. PE protocol helical chest CT showing a clot filling the mid and distal left main pulmonary artery (white arrow). Enlargement of the main pulmonary artery is consistent with pulmonary hypertension. B. Left pulmonary angiogram showing the sharp cutoff of the left descending pulmonary artery (white arrow) with a visible, small segmental branch (black arrow) that has recanalized from the hilum.

pulmonary hypertension center, and pressures measured by RHC included an mRAP of 16 mmHg, mPAP of 37 mmHg, and a PCWP of 12 mmHg. The CI was 1.73 by Fick, and the PVR was 7 Wood Units. She did not respond to inhaled NO. A pulmonary angiogram was performed, which revealed bilateral chronic pulmonary emboli and a sharp cutoff of the left descending pulmonary artery (Figure 42.10B). An infra-renal IVC filter was placed. She was found to be heterozygous for the Factor V Leiden mutation.

Given her severe symptoms and persistent thromboemboli in surgically accessible locations, the patient was referred for thromboendarterectomy. Following cardiopulmonary bypass and cardioplegic arrest, intimal dissection planes were created first in the right interlobar and lower lobe branches and multiple chronic thrombi were removed. Next, the main and left pulmonary arteries were opened and a small amount of fresh thrombus was extracted along with extensive chronic thrombi. The total circulatory arrest time was 37 minutes. She was discharged 7 days later on furosemide, aspirin, and warfarin. Six weeks later she was seen in clinic and she denied dyspnea or near-syncpe at any time, including during her daily exercise at the gym. Her lower extremity edema had resolved, and furosemide was discontinued.

CASE 42.5 A 78-year-old woman presented with marked shortness of breath, persistent hypotension (systemic arterial pressure 78/51 mmHg), and right ventricular dilatation and hypokinesis on echocardiogram. Pulmonary angiogram showed a massive right pulmonary artery embolism as well as a small left lung volume because of a prior thoracoplasty to treat tuberculosis (Figure 42.11A). She received heparin and a filter placed in the IVC. Hypoxemia persisted despite ventilatory support. She developed melena on heparin. Cardiac surgeons felt that she would not survive surgical embolectomy because of the prior left lung thoracoplasty. Because of her hemodynamic compromise, with melena on heparin and surgical inoperability, aspiration thrombectomy was undertaken. Pressures prior to suction catheter embolectomy were as follows: 18 mmHg (mean) in the right atrium, 90/18 mmHg in the right ventricle, and 90/40 mmHg in the pulmonary artery. Systemic hypotension persisted despite removal of both fresh and old clot from the pulmonary artery branches of the upper and lower right lobar arteries. Therefore, 50 mg of rt-PA was administered over 15 minutes through the pulmonary artery catheter. Pulmonary angiography then showed an approximately 30% reduction in the overall clot burden (Figure 42.11B).

The procedure was complicated by a retroperitoneal bleed, which was corrected with 12 units of packed red blood cells. The patient also developed pneumonia and acute respiratory distress syndrome. Nonetheless, her clinical picture gradually improved. She was successfully weaned from the ventilator and was transferred to a rehabilitation facility.
REFERENCES


Heart failure (HF) is a chronic progressive condition that arises when the heart cannot provide adequate cardiac output to meet the systemic metabolic demands or cannot accommodate the venous return without elevation of filling pressure. Thus, HF is a clinical syndrome that can be produced by a number of processes. Examples include any primary insult to the myocardium: infarction, chronic volume or pressure overload, or a frank disorder of the heart muscle itself—a cardiomyopathy. Cardiomyopathies are generally divided into three categories, two of which are morphologic (dilated and hypertrophic); the third one is functional (restrictive). Alternatively, some authorities have divided patients based on whether the clinical syndrome of HF occurs in a patient with reduced ejection fraction (HFrEF or “systolic” HF) or with preserved EF (HFpEF or “diastolic” HF). Other nonmyocardial processes may cause the clinical syndrome of HF, such as valvular stenosis or pericardial disease, and these are reviewed elsewhere.

Heart failure occurs in part owing to the adverse effects of ongoing neurohormonal activation. There is a fairly good correlation between clinical manifestations and the hemodynamic profile. The most recent classification system emphasizes the progression of hemodynamic and neurohormonal stages rather than symptomatic status (which may wax and wane over time) as traditionally embodied by the New York Heart Association (NYHA) classification. Patients thus evolve from being at risk for developing heart failure (stage A), to structural heart disease (stage B), to symptomatic heart failure (stage C), and finally to medically refractory heart failure (stage D). Therapy is driven by both symptoms and the stage of disease and may include diuretic, vasodilator, and inotropic therapies that target the hemodynamic derangements of heart failure (low output, high resistance, elevated filling pressures) and thereby improve symptoms. Antagonism of the adrenergic and renin-angiotensin systems also helps to prevent further injury to the myocardium and thereby slow down the progression of heart failure, at least in the case of HFrEF.

Cardiac catheterization is performed in patients with heart failure for several reasons: (1) to assess etiology, (2) to define both resting and exercise hemodynamic status, and (3) to evaluate therapeutic interventions. In most patients with HF, all three goals can usually be addressed in a single procedure. The hemodynamic profile is generally characterized in the supine state, where resting and exercise conditions can be studied (see Chapter 20), although some centers prefer measurements in the upright state, especially if exercise is being used for diagnostic or prognostic purposes. After the hemodynamic assessment has been completed, angiography should be performed to define the coronary anatomy. Clinical criteria such as the presence or absence of angina are poor predictors of the presence or absence of clinically relevant coronary artery disease. Ventriculography should also be considered to assess systolic function, mitral regurgitation, and ventricular size and shape, although most patients will have had echocardiographic assessment prior to catheterization. If sufficient evidence of coronary artery disease is not present to explain the degree of ventricular dysfunction, an endomyocardial biopsy should be considered to help to define the etiology, especially when a specific diagnosis is suspected on clinical grounds (see Chapter 26).

HEART FAILURE WITH REDUCED EJECTION FRACTION

There are many potential causes of HFrEF, with the most common one in the United States being coronary artery disease (roughly two-thirds of cases), and in most circumstances
this is clinically obvious based upon medical history, electrocardiography, and echocardiogram. Because coronary disease is so common, and because it represents a potentially reversible cause of HF (if viable myocardium is present), cardiac catheterization including coronary angiography is recommended for most patients with new-onset HFrEF. Noninvasive assessment of ischemic heart disease is advocated by some but can be misleading with both false positives and false negatives. Once coronary disease has been excluded, the differential diagnosis includes the various causes of dilated cardiomyopathy (DCM; Table 43.1). The noninvasive clinical assessment may suggest a specific diagnosis such as sarcoidosis or Chagas disease, but in most instances the cause will remain undefined (i.e., idiopathic). Most cases of idiopathic cardiomyopathy likely represent the sequelae of prior myocarditis or genetic mutations. Indeed, a recent study reported that ~25% of patients with “apparent” DCM had mutations within the titin gene. Only a few etiologies of DCM have pathognomonic histologic findings, but endomyocardial biopsy may be helpful in confirming or excluding those diseases. In 1230 patients who underwent endomyocardial biopsy at the Johns Hopkins Hospital (Baltimore, MD) for unexplained HFrEF, a specific cause was eventually determined in 50% of the patients using the results of the endomyocardial biopsy in combination with clinical information, although only 15% had a specific histologic diagnosis, but using the results of the endomyocardial biopsy in combination with clinical information, a specific cause was eventually determined in 50% of the patients. In addition to coronary angiography and biopsy, ventriculography allows assessment of mitral regurgitation and dyskinesis, both of which can be targeted surgically. Ventriculography is used predominantly when other imaging techniques such as echocardiography or MRI are inadequate or inconsistent with the clinical examination.

Invasive hemodynamic assessment is also important, as physical examination may underestimate the degree of congestion and noninvasive methods are limited in accuracy. Many hemodynamic profiles are common to all forms of HF (e.g., elevated right and left heart filling pressure, pulmonary hypertension, low output) and not necessarily unique to particular cardiomyopathies. However, defining the hemodynamic profile in an individual patient can be used to optimize titrate vasodilators and diuretics. In some instances, this tailored management adjusted with an indwelling Swan-Ganz catheter over 48 hours can prolong or even obviate the need for cardiac transplantation. Furthermore, a detailed hemodynamic profile provides prognostic information. In a consecutive series of 152 advanced heart failure patients referred to the University of California, Los Angeles (UCLA) health system for cardiac transplantation, the presenting capillary wedge pressure (mean of 28 mmHg) was not predictive of survival, but the ability to reduce the pulmonary capillary wedge pressure to <16 mmHg by the end of the hospitalization was predictive of outcome with a 1-year survival of 83% (as compared with 38% if the filling pressures could not be so lowered by the end of hospitalization). The effect was independent of the final cardiac index achieved. Finally, while one of the key goals of inpatient management for decompensated HF remains volume removal, registry data have revealed that only ~50% of patients achieve adequate diuresis. Part of this problem may relate to the inability to clinically estimate hemodynamic status. In select patients, catheterization to identify the presence or absence of an optimal volume status after aggressive treatment for decompensated HF may be useful and reduce subsequent risk for rehospitalization owing to inadequate treatment. However, the routine use of an invasive hemodynamic approach for decompensated heart failure does not appear to decrease mortality or rehospitalization.

Responses to exercise, vasodilators, and inotropes are also optimally assessed with invasive hemodynamic measurements, although it should be noted that hemodynamics may improve significantly in the absence of drug therapy over time presumably owing to favorable changes in neurohormonal tone. In 21 patients who had their hemodynamics serially assessed over a 24-hour period, the cardiac index (CI) rose by an average of 0.23 L/minute per m² and the left ventricular filling pressure decreased by 5.9 mmHg. Some patients even had spontaneous improvements that rivaled the effects of oral and intravenous vasodilator therapies. Postprandial improvements were also seen, confirming the importance of studying patients in the fasting state.

### Table 43.1 Causes of Dilated Cardiomyopathies (in the Order of Decreasing Frequency)

<table>
<thead>
<tr>
<th>Idiopathic cardiomyopathy</th>
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<tbody>
<tr>
<td>Familial</td>
</tr>
<tr>
<td>Viral</td>
</tr>
<tr>
<td>Occult Ischemic heart disease</td>
</tr>
<tr>
<td>Myocarditis</td>
</tr>
<tr>
<td>Chagas</td>
</tr>
<tr>
<td>Enteroviruses (e.g., Coxsackie A/B)</td>
</tr>
<tr>
<td>Sarcoid</td>
</tr>
<tr>
<td>HIV</td>
</tr>
<tr>
<td>Drugs e.g., anthracyclines</td>
</tr>
<tr>
<td>Alcohol</td>
</tr>
<tr>
<td>Cocaine</td>
</tr>
<tr>
<td>Peripartum</td>
</tr>
<tr>
<td>Rheumatologic disorders (e.g., lupus)</td>
</tr>
<tr>
<td>Endocrine disorders (e.g., pheochromocytoma, hypothyroidism)</td>
</tr>
</tbody>
</table>
**CASE 43.1** Progressive Dyspnea in a Patient with HFrEF. A 50-year-old man presented with worsening exertional dyspnea, 4 years after presenting with new-onset heart failure. Evaluation at that time had revealed compensated hemodynamics, normal coronary angiography, and an ejection fraction of 10% with an end-diastolic dimension of 7.2 cm plus moderately severe mitral regurgitation. An endomyocardial biopsy had demonstrated myocyte hypertrophy and interstitial fibrosis. With an ACE inhibitor, a beta-blocker, digoxin, and diuretics, his condition had improved to NYHA II, and cardiac transplantation was deferred because of his preserved functional capacity and a maximal oxygen consumption of 17 mL/kg per minute. One year before the current presentation, repeat right heart catheterization demonstrated compensated hemodynamics at baseline but significant increases in wedge and pulmonary pressures with exercise. Biventricular pacing with an implantable cardiac defibrillator improved his symptoms and increased his oxygen consumption to 19 mL/kg per minute.

Over the few weeks prior to the current presentation, however, he developed increasing dyspnea and orthopnea despite an augmented diuretic regimen. Repeat cardiopulmonary exercise testing demonstrated a fall in his oxygen consumption to 15 mL/kg per minute, and he was readmitted for transplant evaluation. Repeat right heart catheterization demonstrated borderline systemic arterial hypotension, pulmonary hypertension, and elevated biventricular filling pressures, which were responsive to acute vasodilator therapy with nitroprusside but were reproduced with oral vasodilators and diuretics (see Table 43.2). His condition returned to NYHA II, and cardiac transplantation was again deferred.

**Illustrative Points.** Ambulatory patients with HFrEF are usually characterized by a relatively normal or mildly depressed resting cardiac output and a modest elevation in both right- and left-sided filling pressures. In advanced heart failure, the systemic vascular resistance rises significantly in response to the reduced cardiac output and neurohormonal response, and may be quite elevated despite a reduced systolic blood pressure of 80 to 100 mmHg. In 1,000 consecutive patients with chronic heart failure electively referred for transplantation (mean ejection fraction [EF] 22%, end-diastolic dimension 7.3 cm, NYHA class 3.4), the initial right atrial pressure was 11 ± 7 mmHg, the pulmonary capillary wedge pressure was 25 ± 9 mmHg, the pulmonary arterial (PA) systolic pressure was 50 ± 16, the cardiac index was 2.1 ± 0.7 L/minute per m², and the systemic vascular resistance was 1,610 ± 610 dynes-second·cm⁻⁵. The right atrial (RA) pressure is typically 50% to 60% of the pulmonary capillary wedge pressure (PCWP) and often correlates with left-side filling pressures regardless of heart failure etiology or tricuspid regurgitation. In the series of patients reported by Drazner, the positive predictive value of an RA pressure of >10 mmHg for a PCWP pressure of >22 mmHg was 88% (Figure 43.1), and more recent studies have confirmed the high correlation between right and left heart filling pressures in HF patients with any EF. The PCWP pressure usually correlates with the PA systolic

<table>
<thead>
<tr>
<th>Year</th>
<th>RAP (mmHg)</th>
<th>PCWP (Mean/ V Wave)</th>
<th>PAP (mmHg)</th>
<th>CO (L/min)</th>
<th>PVR (dyne·sec·cm⁻⁵)</th>
<th>MAP (mmHg)</th>
<th>SVR (dyne·sec·cm⁻⁵)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial diagnosis</td>
<td>10</td>
<td>15</td>
<td>36/13/24</td>
<td>4.5</td>
<td>160</td>
<td>70</td>
<td>1,067</td>
</tr>
<tr>
<td>3 y later</td>
<td>5</td>
<td>15/25</td>
<td>36/13/24</td>
<td>4.4</td>
<td>167</td>
<td>70</td>
<td>1,181</td>
</tr>
<tr>
<td>3 y later, exercise</td>
<td>32/48</td>
<td>73/28/51</td>
<td>9.3</td>
<td>163</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 y later</td>
<td>9</td>
<td>25/35</td>
<td>53/22/37</td>
<td>2.5</td>
<td>234</td>
<td>75</td>
<td>2,112</td>
</tr>
<tr>
<td>4 y later, SNP</td>
<td>5</td>
<td>16/20</td>
<td>30/16/22</td>
<td>4.5</td>
<td>107</td>
<td>60</td>
<td>978</td>
</tr>
</tbody>
</table>

CO, cardiac output; MAP, mean arterial pressure; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SNP, sodium nitroprusside; SVR, systemic vascular resistance.
pressure (usually 50% of the PA systolic) as well as with the PA diastolic pressure (PAD; usually within 1 to 2 mmHg of PCWP) as long as pulmonary vascular resistance is <2 Wood units. Right ventricular pressure can also be used to estimate the PAD, since right ventricular pressure closely approximates pulmonary end-diastolic pressure at the time of pulmonary valve opening (maximal right ventricular dP/dt; Figure 43.2).

Pulmonary hypertension (PH) is also common in HFrEF and is predictive of prognosis. In patients with dilated cardiomyopathy and myocarditis, every 5-mmHg rise in the mean pulmonary artery pressure increased mortality, with a relative hazard ratio of 1.85 (range 1.50 to 2.29). Mean PA pressure is equal to the product of cardiac output and pulmonary vascular resistance summed with PCWP. PH in HFrEF may be
entirely passive (i.e., owing simply to elevated PCWP, often termed “precapillary”) or owing to a combination of passive effects (e.g., elevated PCWP) and high pulmonary vascular resistance (i.e., >2.5 to 3 WU; often termed “reactive” or “postcapillary” PH). Recent data have shown that the presence of any type of PH is associated with increased risk of death or HF hospitalization in HFrEF, but “reactive” PH in particular is associated with a grim prognosis.22 Currently PH in HFrEF is not a specific therapeutic target, but recent studies using phosphodiesterase inhibitors have shown improvement in hemodynamics and quality of life, and multicenter clinical trials of pulmonary-specific vasodilators are underway.23

Advanced HFrEF is characterized by biventricular failure. The right atrial pressure waveform will often demonstrate steep x and y descents indicative of severe volume overload and right ventricular systolic and diastolic dysfunction (Figure 43.3A). Lack of the normal inspiratory fall (or an actual increase) in the right atrial pressure (i.e., the Kussmaul sign) is also common as a result of pericardial constraint in the massively dilated heart, significant tricuspid regurgitation, and right ventricular diastolic dysfunction. The y descent is typically very steep as a result of concomitant tricuspid regurgitation and excessive volume overload leading to rapid, early diastolic inflow. The right ventricular diastolic waveform may also demonstrate a rapid early diastolic filling wave creating a “dip and plateau” configuration, which becomes more prominent during inspiration (Figure 43.3B). This finding reflects abrupt cessation of diastolic inflow as the point of pericardial restraint is reached in the left and right ventricles. The pulmonary capillary wedge pressure may demonstrate a prominent V wave that may exceed twice the magnitude of the post A-wave pressure owing to reduced left atrial compliance, even in the absence of severe mitral regurgitation (Figure 43.3C). The V wave may even be discernible in the pulmonary arterial waveform (Figure 43.3E). The left ventricular pressure tracing is characterized by an elevation in pressure throughout early diastole. The systolic left ventricular waveform may be triangular owing to the reduced + and −dP/dt, and there may be loss of the normal improvement in dP/dt with increasing heart rate (Bowditch treppe effect). In low-output states, the arterial waveform demonstrates a narrow pulse pressure (pulsus parvus), which may be <25% of the systolic pressure when the cardiac index falls below 2.2 L/minute per m². In severe heart failure, there may also be pulsus alternans (Figure 43.3D), owing to oscillations in myocardial contractility with cyclic changes in cytosolic calcium.24,25

A common misconception about HFrEF is that elevated filling pressures are required to maximize preload-sensitive

Figure 43.3 Hemodynamic findings in decompen- sated heart failure from dilated cardiomyopathy. (See text for discussion.)
contractility (Starling’s law). Severe left ventricular dysfunction can be well tolerated with normal or near-normal cardiac filling pressures, concomitant satisfactory functional capacity comparable to that of transplantation, and reasonable long-term survival. In fact, a low ejection fraction alone is not an indication for cardiac transplantation for morbidity or mortality reasons, and many patients with low EF are asymptomatic. In patients with HFrEF, stroke volume, stroke work index, and cardiac output can be maximized at pulmonary capillary wedge pressures as low as 10 mmHg (Figure 43.4). There is no justification for insufficient diuresis and dyspnea resulting from inadequate lowering of filling pressures, although recent data suggest that half of the patients with decompensated HF lose no weight or even gain weight during hospitalization for diuresis. In 754 consecutive patients with chronic heart failure referred electively for cardiac transplantation, tailored doses of vasodilators and diuretics increased the cardiac index from 2.1 ± 0.7 to 2.6 ± 0.6 L/minute per m² despite a fall in the pulmonary capillary wedge pressure from 25 ± 9 to 16 ± 6 mmHg. In part, this improvement in forward cardiac output despite significant reduction of filling pressures is due to a decrease in mitral regurgitation caused by favorable changes in ventricular, atrial, and mitral annular geometry. This change can cause an increased forward stroke volume rather than an increase in total stroke volume. Left ventricular myocardial systolic performance can also improve owing to elimination of right ventricular volume overload with diuretics or nitrates, whereas myocardial diastolic performance can improve owing to reduced myocardial turgor that follows decreased venous congestion.

In general, optimization of hemodynamics is best achieved with intravenous vasodilators and diuretics rather than with inotropic support. Vasodilator therapy takes advantage of the inverse relationship between resistance and output (Figure 43.5) and is especially effective when systemic vascular resistance is > 2,000 dynes-second-cm⁻². Indeed, the failing left ventricle is exquisitely afterload-sensitive. This is reflected in the pressure–volume plane by the shallow end-systolic pressure–volume relationship (ESPVR) in HFrEF. This shallow ESPVR graphically shows how vasodilators produce marked improvements in stroke volume with minimal drop in blood pressure, in contrast to the normal heart or HFpEF, where there tends to be larger arterial pressure drop with less enhancement in stroke volume (Figure 43.6). Once an optimal hemodynamic profile is achieved, the effects of intravenous vasodilators, such as nitroprusside, can be replicated by oral vasodilators like ACE inhibitors, hydralazine, and nitrates, as in the case above, intravenous nitroprusside can be used even in the presence of relative hypotension (systolic blood pressure < 100 mmHg) if the hypotension is the result of low cardiac output and high vascular resistance. If clinically significant ischemia is present, intravenous nitroglycerin is preferred over nitroprusside owing to considerations of coronary steal. Intravenous nitroglycerin and nesiritide can also be used to acutely improve the hemodynamics, especially when pulmonary hypertension and high central venous pressures are present.

The use of inotropic agents to optimize hemodynamics is limited by the inability to replicate the direct inotropic effects with oral vasodilators. Clinical trials have suggested a worsening of mortality with intermittent use of inotropes for the longitudinal management of heart failure, but some patients may still require inotropic support despite attempts...
Effects of nitroprusside (SNP) on ventricular hemodynamics in HFP EF and HFr EF. In HFr EF, contractile function is severely depressed, resulting in a shallow end-systolic pressure-volume relationship (ESPVR, red straight line). The slope of the ESPVR is end systolic elastance ($E_s$). The shallow ESPVR in HFr EF explains how acute vasodilation with SNP (reduction in arterial elastance, $E_t$) results in small drop in blood pressure ($-18$ mmHg) and large enhancement in stroke volume ($+23$ mL). Conversely, HFP EF is characterized by a steep ESPVR (black solid line), and similar dosage and extent of vasodilation with SNP result in much more dramatic drop in blood pressure with less enhancement in stroke volume and cardiac output. (Reproduced with permission from Schwartzenberg, et al. Effects of vasodilation in heart failure with preserved or reduced ejection fraction: Implications of distinct pathophysiologies on response to therapy. J Am Coll Cardiol 2012;59:442–451.)

**HEART TRANSPLANTATION**

Despite the radical nature of replacing a human heart with another, cardiac allograft has emerged as an effective way of restoring essentially normal cardiovascular function in end-stage heart failure. However, the transplanted heart is subject to a number of post-transplant factors that can influence cardiac function including denervation, organ preservation/ ischemic injury, myocardial rejection, donor/recipient size mismatch, allograft coronary artery disease, and hypertension/ ventricular hypertrophy. Initially the transplanted heart also demonstrates a restrictive hemodynamic profile; this resolves over days to weeks, although the less dramatic abnormalities in diastolic function may persist (Table 43.3). Resting contractility and ejection fraction are relatively normal, but total blood volume, cardiac volume, and end-systolic wall.

to tailor their hemodynamics with vasodilators and diuretics. Such patients in general will be bridged to more definitive treatments such as mechanical support or cardiac transplantation. Inotropic agents, such as phosphodiesterase 3 inhibitors (e.g., milrinone) or beta agonists (e.g., dobutamine), will increase contractility ($+\frac{dP}{dt}$) and also decrease early and late diastolic pressures through their lusitropic ($-\frac{dP}{dt}$) effects. Unfortunately these agents also increase myocardial oxygen demand, decrease LV efficiency, and have well-documented proarrhythmic effects.

In chronic heart failure, hemodynamic goals include a right atrial pressure of $<10$ mmHg, pulmonary capillary wedge pressure of $<15$ mmHg, and a systemic vascular resistance of $<1,200$ dynes-second-cm$^5$, maintaining a systolic blood pressure of $>80$ mmHg to avoid light-headedness. Cardiac output can be measured reliably with the thermodilution technique in advanced heart failure, even in the presence of moderate to severe tricuspid regurgitation.

It may even be preferred over the Fick method when oxygen consumption cannot be directly measured, because of the substantial variability in body size–based estimation of resting oxygen consumption. It is rare that hemodynamic monitoring is required for $>72$ hours to tailor hemodynamics in chronic heart failure, but some chronic monitoring is better than relying solely on measurements in the catheterization laboratory. Because hemodynamic goals are tailored and achieved in the supine position, the tolerability of an oral vasodilator regimen should be assessed after 24 hours of ambulation. With careful attention to volume status and vasodilators in follow-up, these hemodynamic profiles can also be maintained for months and years.

Exercise hemodynamic responses can be used to delineate the cause of persistent dyspnea, especially when resting hemodynamics are unremarkable (Figure 43.8), or to assess cardiovascular reserve and prognosis (see Chapter 20). Invasive hemodynamic exercise testing is more frequently utilized in the evaluation of HFP EF and is discussed further in the corresponding section later in this chapter.
The hemodynamic effects of an inotropic agent, milrinone, in dilated cardiomyopathy. Milrinone increases contractility (positive dP/dt), improves lusitropy (negative dP/dt), and lowers preload (decreased left ventricular end-diastolic pressure [LVEDP]). The improvement in systolic and diastolic function occurs without an increase in systolic blood pressure. (Reproduced with permission from Baim DS, et al. Evaluation of a new bipyridine inotropic agent—milrinone—in patients with severe congestive heart failure. *N Engl J Med* 1983; 309:748.)

Although left ventricular responses to hypertension and acute increases in afterload are normal after cardiac transplantation, the denervated heart does not tolerate hypotension well, presumably because of lack of ventricular compliance and reflex sympathetic tone. Denervation also leads to several other clinically relevant hemodynamic abnormalities in addition to the obvious loss of cardiac pain sensation. Efferent parasympathetic denervation of the heart leads to a resting tachycardia of 90 to 110 beats per minute (bpm), lack of heart rate variability, and the ineffectiveness of atropine and digoxin; efferent sympathetic denervation leads to blunted wedge pressure with exercise. This effect was achieved with supine arm exercise (moving bags of saline up and down in supine position) resulting in an almost twofold increase in heart rate (HR). The patient had an ejection fraction of 20%, an end-diastolic dimension of 7 cm, and moderately severe mitral regurgitation at rest. The lack of V waves and normal wedge pressure at rest are indicative of the chronic nature of the regurgitation. BP, blood pressure.
Table 43.3 Resting and Exercise Hemodynamics After Cardiac Transplantation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rest</th>
<th>Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right atrial pressure (mmHg)</td>
<td>6 ± 2</td>
<td>14 ± 7</td>
</tr>
<tr>
<td>Pulmonary artery pressure (mmHg)</td>
<td>18 ± 3</td>
<td>32 ± 9</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure (mmHg)</td>
<td>10 ± 3</td>
<td>20 ± 6</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>5.0 ± 0.9</td>
<td>9.9 ± 1.7</td>
</tr>
<tr>
<td>Stroke volume (mL)</td>
<td>55 ± 9</td>
<td>77 ± 13</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>90 ± 11</td>
<td>122 ± 18</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>91 ± 12</td>
<td>102 ± 14</td>
</tr>
<tr>
<td>Systemic vascular resistance (Wood)</td>
<td>17.7 ± 4.0</td>
<td>9.3 ± 2.4</td>
</tr>
</tbody>
</table>

Hosenpud, JD, Morton, MJ. Physiology and hemodynamic assessment of the transplanted heart. Cardiac Transplant 1986;180.

and delayed increases in heart rate in response to physiologic stress. Afferent denervation results in dysregulation of sodium and water homeostasis as well as in abnormalities in peripheral vascular responses.59

Right ventricular function is critical in the early post-transplant period. The normal right ventricle cannot accommodate significant acute pressure overload,60 and nowhere is this more apparent than in the post–cardiac transplant setting. Acute right heart failure accounts for 50% of all peri- and post-cardiac transplant complications and is a leading cause of early allograft failure and death. Not surprisingly, an elevated preoperative pulmonary vascular resistance predicts early postoperative death from acute right heart failure,61,62 and severe fixed pulmonary hypertension is a contraindication to cardiac transplantation.

**CASE 43.2 Assessing Pulmonary Vascular Resistance Prior to Transplantation.** A 45-year-old woman with a 30-pack-year smoking history is transferred with advanced heart failure for consideration of heart transplantation following an anterior myocardial infarction 2 years earlier. She had three hospitalizations in the past year for heart failure and was readmitted 3 days prior to transfer after stabilization on lisinopril, carvedilol, digoxin, and furosemide. Pulmonary evaluation was remarkable for mild obstructive pulmonary disease. Acute vasodilator testing in the catheterization lab with various agents demonstrated reversible pulmonary hypertension, and she was considered acceptable for transplantation (see Table 43.4).

However, repeat catheterization 3 months later demonstrated recurrent severe pulmonary hypertension. Because of relative hypotension, milrinone was used to assess pulmonary vasoreactivity. Bolus milrinone did lower the pulmonary vascular resistance to an acceptable extent, and she was maintained on continuous intravenous milrinone while awaiting transplantation.

Illustrative Points. Pulmonary hypertension, defined as a pulmonary artery systolic pressure of ≥35 mmHg or mean pulmonary artery pressure of ≥25 mmHg, is a common complication of heart failure as discussed above. Resting pulmonary vascular resistance predicts exercise tolerance in heart

Table 43.4 Changes in Pulmonary Vascular Resistance to Various Maneuvers

<table>
<thead>
<tr>
<th>Condition</th>
<th>RAP (mmHg)</th>
<th>PCWP (mmHg)</th>
<th>PAP (mmHg)</th>
<th>TPG (mmHg)</th>
<th>CO (L/min)</th>
<th>PVR (dyne-sec-cm⁻¹)</th>
<th>SVR (dyne-sec-cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>10</td>
<td>15</td>
<td>60/24/35</td>
<td>20</td>
<td>3.6</td>
<td>400</td>
<td>1,666</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>5</td>
<td>20</td>
<td>40/24/30</td>
<td>10</td>
<td>4.5</td>
<td>178</td>
<td>1,067</td>
</tr>
<tr>
<td>Milrinone</td>
<td>9</td>
<td>15</td>
<td>55/22/32</td>
<td>17</td>
<td>5.3</td>
<td>257</td>
<td>830</td>
</tr>
</tbody>
</table>

CO, cardiac output; PA, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; RA, right atrial pressure; TPG, transpulmonary gradient.
failure and is inversely correlated with oxygen consumption in these patients. The right ventricular (RV) response to chronic afterload increase is even more important than the load itself. Indeed, exercise capacity is better predicted by RV ejection fraction than by the left ventricular ejection fraction or pulmonary vascular resistance, reflecting the importance of the interaction between the pulmonary vasculature and right heart in limiting exercise capacity in heart failure.

In heart failure, the elevated left ventricular end-diastolic pressure and thus elevated left atrial pressure result in a passive or reactive increase in the pulmonary venous pressure and a consequent increase in the upstream pulmonary arterial pressure. These passive changes may also be accompanied by an increase in the transpulmonary gradient (mean PA minus mean PCWP) reflected by increases in pulmonary vascular resistance (PVR) and right ventricular afterload. These changes in PVR in heart failure are mediated by alterations in pulmonary smooth muscle vascular tone as well as by structural changes in the pulmonary vessels. Changes in smooth muscle tone are generally reactive and reversible over the course of hours to days, whereas structural remodeling of the pulmonary vascular tree has less plasticity but may be reversible over the course of months to years, especially with chronic LV unloading as with ventricular assist devices (see below).

Pulmonary hypertension becomes a concern in the pretransplant setting when the pulmonary artery systolic pressure is >60 mmHg, the transpulmonary gradient is >15 mmHg, and/or the pulmonary vascular resistance is >4 Wood units (320 dynes-second-cm⁻²). Although in the Bethesda consensus conference on heart transplantation PVR of >6 to 8 Wood units was considered high-risk, most centers do not use a fixed cutoff value for an acceptable PVR. In fact, in some patients with severe pulmonary hypertension who have successfully undergone heart transplantation or long-term ventricular assist device support, pulmonary pressures have returned to normal. Therefore, it is essential to ensure that pretransplant elevations in PVR are reversible. If so, specific chronic interventions such as continuous inotropic support or a ventricular assist device (VAD) may be required to keep their PVR low while patients await transplantation. This reduces the risk of allograft right ventricular failure in the early transplant course.

Costard-Jacklé and Fowler at Stanford reported the predictive value of acute testing of pulmonary vasoreactivity with nitroprusside in 301 consecutive cardiac transplant candidates. The 3-month post-transplant mortality in this cohort was high in those candidates with a baseline PVR of >2.5 Wood units (or 200 dynes-second-cm⁻²; 17.9% versus 6.9% for PVR <2.5 Wood units). Using graded incremental doses of nitroprusside in patients with either a PVR of >2.5 Wood units or a PA systolic pressure of >40 mmHg, the hemodynamic response was predictive of outcome. If the PVR could be reduced to <2.5 Wood units without hypotension (>85 mmHg), the 3-month mortality was only 3.8%. In contrast, if the PVR could not be reduced to <2.5 Wood units or only at the expense of hypotension, the mortality was high (40.6% and 27.5%, respectively). In addition, in their series, all patients who died of right heart failure were from these latter two groups.

At the Mayo Clinic (Rochester, MN) and University Hospitals Case Medical Center (Cleveland, OH), nitroprusside is started at 0.5 to 1.0 µg/kg/minute and increased in 0.5 to 1.0 µg/kg increments every 3 minutes with reassessment of the pulmonary vascular resistance (PCWP, mean PA, and cardiac output) after each change in dose. Cardiac output is best assessed with thermodilution in this setting unless it is possible to directly measure oxygen consumption during each phase of infusion. Smaller increments or slower titration schemes should be considered when left ventricular filling pressures are low (<10 mmHg).

Various other agents have been used to assess the reversibility of pulmonary hypertension (Table 43.5), although the mechanism by which PVR falls differs between agents. High-flow oxygen should be considered first, especially if the baseline arterial saturation is <95%. Nitroprusside, an endothelium-independent nitric oxide donor, decreases PVR by both decreasing the transpulmonary gradient and increasing the cardiac output. Dobutamine and other inotropes increase pulmonary blood flow with subsequent recruitment of parallel vessels in the pulmonary circulation and produce flow-mediated vasodilation. Bolus milrinone is simple and attractive since it avoids the need for titration. Using 50 µg/kg over 1 minute via a systemic vein, the peak lowering of PVR occurs within 5 to 10 minutes and is typically not associated with changes in systemic blood pressure or heart rate. Milrinone lowers the PVR by approximately 30% with a concomitant significant increase in the cardiac output but with little change in the transpulmonary gradient.

Selective pulmonary vasodilators are also attractive alternatives since they lack the systemic hypotensive effects of traditional vasoactive agents. For example, inhaled nitric oxide lowers PVR by decreasing the transpulmonary gradient and increasing the left ventricular filling pressure without significant changes in cardiac output or mean PA pressure. Although not useful for chronic therapy owing to its short half-life and potential toxicity, nitric oxide has been used for assessing pulmonary vasoreactivity in cardiac transplant candidates, supporting high-risk surgical patients undergoing coronary bypass or valve replacement and treating right ventricular dysfunction after heart transplantation or implantation of a ventricular assist device. Phosphodiesterase inhibitors may also potentiate nitric oxide-dependent vasodilation by preventing the degradation of cGMP. Thus, in similar clinical contexts, the phosphodiesterase type 5 inhibitor sildenafil has been used successfully to decrease the PVR. When left ventricular function is normal, the increase in left ventricular filling from increased volumetric flow across the pulmonary circulation can be easily accommodated without significant symptomatic increases in the filling pressure. However, when left ventricular diastolic function is not normal and baseline
Table 43.5  Agents that can be Used to Assess Pulmonary Vasoreactivity

<table>
<thead>
<tr>
<th>Agent</th>
<th>PVR</th>
<th>PAP Mean</th>
<th>PCWP</th>
<th>CI</th>
<th>SVR</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitroprusside</td>
<td>▼36%</td>
<td>▼23%</td>
<td>▼27%</td>
<td>▲30%</td>
<td>▼31%</td>
<td>Start at 0.5–1.0 μg/kg/min and increase by 0.5–1.0 μg every 3 min until normalization in PCWP and PA or hypotension or intolerance. Most useful when PCWP is elevated (&gt;15 mmHg) and SBP is &gt;90 mmHg</td>
</tr>
<tr>
<td>Milrinone</td>
<td>▼31%</td>
<td>▼12%</td>
<td>▼16%</td>
<td>▲42%</td>
<td>▼30%</td>
<td>50 μg/kg intravenous bolus, no need for titration, more proarrhythmic than nitroprusside</td>
</tr>
<tr>
<td>Nitric oxide</td>
<td>▼47%</td>
<td>NC</td>
<td>▲24%</td>
<td>▼9%</td>
<td>NC</td>
<td>80 ppm over 5 min, useful when PCWP is normal or near normal (&lt;20–25 mmHg) but concern for pulmonary edema if PCWP is higher</td>
</tr>
<tr>
<td>Prostaglandin E1</td>
<td>▼47%</td>
<td>▼21%</td>
<td>▼13%</td>
<td>▲23%</td>
<td>▼31%</td>
<td>Titrated in incremental doses of 0.02, 0.05, 0.10, 0.20, 0.30 μg/kg per min; use when PCWP is normal as for nitric oxide</td>
</tr>
<tr>
<td>Adenosine</td>
<td>▼41%</td>
<td>NC</td>
<td>▲12%</td>
<td>▲9%</td>
<td>NC</td>
<td>100 μg/kg per min; use when PCWP is normal as for nitric oxide</td>
</tr>
</tbody>
</table>

Cl, cardiac index; NC, no change; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance.

filing pressures are elevated, the increase in pulmonary blood flow can result in further increases in left ventricular filling pressure in a noncompliant ventricle and may produce alveolar pulmonary edema.80 However, in some patients there may be acute elevation in PCWP that remains asymptomatic,44 Adenosine85 and prostaglandin E186 produce similar effects. For these reasons, we generally avoid pulmonary-specific vasodilators for acute vasoreactivity testing when the PCWP or LVEDP is >20 to 25 mmHg and instead use nitroprusside, nitroglycerin, or milrinone. Table 43.5 summarizes the use of various acute vasodilators to assess reversibility of pulmonary hypertension in the catheterization lab. Endothelin antagonists also selectively vasodilate the pulmonary circulation87 and have been used in primary forms of pulmonary hypertension when left ventricular function is normal.88 However, oral endothelin antagonists in heart failure do not appear to be beneficial in clinical trials, and these agents have not been used for acute testing of pulmonary vasoreactivity.

**CASE 43.3**  Tricuspid Regurgitation (TR) After Cardiac Transplantation. A 56-year-old man presented for routine surveillance endomyocardial biopsy 1 week following cardiac transplantation for an idiopathic dilated cardiomyopathy. He had been awaiting cardiac transplantation in the hospital on intravenous milrinone, which had reduced his pulmonary vascular resistance from 340 to 200 dynes-second-cm⁻². A bivacal anastomosis was used during transplantation with an ischemic time of 150 minutes. Postoperatively, he required atrial pacing for sinus node dysfunction and prolonged inotropic and pressor support. His weight was 5 kg more than his preoperative weight. Routine three-drug immunosuppression had been initiated without difficulty.

At right heart catheterization (Figure 43.9), his right atrial pressure waveform was ventricularized consistent with severe TR. The right ventricular waveform was also characterized by a steep rapid early filling wave and an elevated end-diastolic pressure. Left-side filling pressures were normal. The cardiac output was 4 L/minute, and the PVR was 180 dynes-second-cm⁻². Echocardiography confirmed normal left ventricular systolic function without mitral regurgitation and severe TR in the hypokinetic, dilated RV.

**Illustrative Points.** Within days of transplantation, hemodynamics demonstrate evidence of right ventricular (RV) systolic and diastolic dysfunction characterized by the presence...
Tricuspid regurgitation early after transplantation is common. Generally, it is a secondary phenomenon and a reflection of right ventricular dilation and dysfunction, which is universal after transplantation. In this setting, right ventricular dysfunction is a consequence of ischemic injury, increased pulmonary vascular resistance, and volume overload. Therapy for right ventricular failure should include prolonged intravenous inotropic support, aggressive volume control, and pulmonary vasodilators, such as nitric oxide and sildenafil. With appropriate treatment, even severe degrees of tricuspid regurgitation can be resolved. In rare instances, of a rapid y descent (larger in magnitude than the x descent), lack of an inspiratory decline in the right atrial pressure (the Kussmaul sign), and sometimes ventricularization of the atrial waveform suggestive of significant tricuspid regurgitation (Figure 43.10). The right ventricular tracing is marked by a steep rapid filling wave and elevation of end-diastolic pressure. The pulmonary capillary wedge pressure may demonstrate a prominent V wave (as much as twofold larger than the atrial wave) in the absence of significant mitral regurgitation and reflects a volume-overloaded state and a poorly compliant left atrium and ventricle. Volume loading or straight-leg raise may also bring out similar findings after transplantation if initial resting hemodynamics are normal, reflecting the often occult nature of this restrictive picture. This hemodynamic profile usually improves with time, although the pace of improvement is variable. Bhatia et al. reported that left and right filling pressures decline within weeks with concomitant decreases in PVR and TR despite persistent RV enlargement (Table 43.6). Evidence of elevated right ventricular end-diastolic pressures is unusual late after transplant in the absence of severe TR. If present, consideration should be given to constrictive pericarditis, albeit rare in the post-transplant setting.

Tricuspid regurgitation early after transplantation is common. Generally, it is a secondary phenomenon and a reflection of right ventricular dilation and dysfunction, which is universal after transplantation. In this setting, right ventricular dysfunction is a consequence of ischemic injury, increased pulmonary vascular resistance, and volume overload. Therapy for right ventricular failure should include prolonged intravenous inotropic support, aggressive volume control, and pulmonary vasodilators, such as nitric oxide and sildenafil. With appropriate treatment, even severe degrees of tricuspid regurgitation can be resolved. In rare instances,
tricuspid valve repair or replacement may be necessary. However, aggressive pharmacologic therapy and appropriate diuresis should be exhausted first, which may take days to weeks.

Tricuspid regurgitation late after transplantation is usually the consequence of biopptide injury to the tricuspid valve or allograft coronary artery disease. Some centers have been able to decrease the incidence of this problem by placing the biopsy sheath across the tricuspid valve to avoid inadvertent injury to the valve apparatus.93 Tricuspid regurgitation is also more frequent with the traditional biventricular anastomosis technique and less frequent with the more contemporary operation using bicaval anastomosis.93 Rejection also appears to be a risk factor for late TR.94 Indications for surgery are similar to those in the nontransplant state and should be entertained if there is significant decline in exercise capacity or if right heart failure becomes refractory to diuretics.95

Myocardial rejection is usually asymptomatic and is rarely predictable from hemodynamic abnormalities (Figure 43.11), even when rejection is severe.96 Because rejection is most common in the first year after transplantation, biopsies are frequent and are used to guide the titration of the immunosuppressive regimen (see Chapter 26). As time from transplant lengthens, rejection becomes less common and biopsy frequency declines. Some centers stop routine surveillance biopsies after the second year because rejection is uncommon.97,98

### Table 43.6: Hemodynamic Changes After Cardiac Transplantation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Preop</th>
<th>2 Weeks</th>
<th>3 Months</th>
<th>1 Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right atrial pressure (mmHg)</td>
<td>15 ± 5</td>
<td>9 ± 4</td>
<td>8 ± 4</td>
<td>7 ± 4</td>
</tr>
<tr>
<td>Mean pulmonary artery pressure (mmHg)</td>
<td>38 ± 9</td>
<td>22 ± 5</td>
<td>21 ± 7</td>
<td>19 ± 5</td>
</tr>
<tr>
<td>Pulmonary wedge pressure (mmHg)</td>
<td>30 ± 8</td>
<td>14 ± 5</td>
<td>13 ± 5</td>
<td>12 ± 4</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>3.5 ± 1.1</td>
<td>—</td>
<td>—</td>
<td>6.3 ± 1.5</td>
</tr>
<tr>
<td>PVR (dynes·sec·cm⁻⁵)</td>
<td>213 ± 113</td>
<td>—</td>
<td>—</td>
<td>99 ± 36</td>
</tr>
</tbody>
</table>

VENTRICAL ASSIST DEVICES

When advanced heart failure cannot be stabilized despite maximal medical therapy (typically involving inotropic and vasoactive agents and/or intra-aortic balloon counterpulsation), surgically implantable ventricular assist devices (VADs) can be used as bridges to cardiac transplantation or to myocardial recovery, or even as a permanent solution to end-stage heart disease (e.g., “destination therapy”). Implantable VADs have been in clinical use since 1986 and are now used in >25% of patients eventually undergoing transplantation because donor shortage has forced longer and longer waiting times to transplantation. Several devices are currently approved for bridge-to-transplant, but only the HeartMate XVE and HeartMate II LVADs (Thoratec Corporation, Pleasanton, CA; Figure 43.12) are currently approved for destination therapy. One total artificial heart (TAH) system (SynCardia Systems, Tucson, AZ) has been approved for biventricular support as a bridge to transplant and currently has an FDA Humanitarian Use Device (HUD) designation for destination therapy. There are no currently approved intracorporeal RVADs for sole RV support, and contemporary RVADs are extracorporeal short-term pulsatile pumps. Two percutaneous devices, the TandemHeart pVAD (CardiacAssist, Pittsburgh, PA) and the Impella Heart Pumps (Abiomed, Danvers, MA), are also in clinical use for short-term LV support (see Chapter 27). Currently approved long-term devices are predominantly continuous-flow pumps, in contrast to the first approved destination LVAD, the HeartMate XVE, which provides asynchronous pulsatile flow.

As bridges to transplant, surgically implantable VADs are very effective with two-thirds of patients making it to transplant with a post-transplant survival comparable to that of patients who have not required pretransplant VAD support. Complications of VADs include mechanical failure, infection, bleeding, thromboembolism (particularly stroke and pump thrombosis), aortic insufficiency, and immunosensitization of the pretransplant candidate.

Continuous-flow LVADs are now the preferred heart pumps for both short- and long-term circulatory support owing to their improved durability, smaller size, decreased energy requirements, and quieter function. In a head-to-head comparison of the continuous-flow LVAD, the HeartMate II, with the pulsatile device, the HeartMate XVE, for destination therapy, the HeartMate II was also associated with improved survival and fewer complications (although stroke rates did not differ, 0.1 events/patient-year).99 Importantly, device thrombosis is rare (<0.04 events/patient-year) with the HeartMate II despite the need for chronic anticoagulation, which is not required for the pulsatile-flow HeartMate XVE.100 End-organ function, including cognitive ability, does not appear
Figure 43.11 Hemodynamic profiles of the transplanted heart do not predict the presence, absence, or severity of rejection. MAP, mean arterial pressure; RA, right atrial; PAW, Pulmonary artery wedge pressure; CI, cardiac index. (Reproduced with permission from Uretsky, BF. Physiology of the transplanted heart. *Cardiovasc Clin* 1990;20(2):41.)

pulmonary capillary wedge pressure of >20 mmHg, and systolic blood pressure of <80 mmHg, despite inotropic/pressor agents and/or the need for intra-aortic balloon counterpulsation. In chronic heart failure, these hemodynamic criteria do not need to be met, but most patients will be inotrope dependent.106,107 In these patients, VAD support allows for nutritional and physical rehabilitation, fall in pulmonary vascular resistance, and discharge of patients home with long anticipated wait times to the transplantation procedure. Clinical considerations at the time of implantation include the proposed clinical endpoint (e.g., recovery, transplant, or destination), need for biventricular support, and predicted surgical mortality in the postsurgical period. Commonly, the proposed clinical endpoint may not be apparent and the implantation of an LVAD may be used as a “bridge to decision” where transplant, destination, or recovery may all be practical goals ultimately.

The assessment in the catheterization laboratory prior to LVAD implantation should include coronary angiography to assess right ventricular and septal blood supply (to ensure adequate right ventricular function when only LVAD is planned) and in particular, right ventricular hemodynamics (e.g., right atrial pressure [RA], pulmonary vascular resistance [PVR], and right ventricular stroke work index [RVSWI = (mean PA – CVP) × (CI/heart rate)]). A right atrial pressure of >15 mmHg, an RA/PCWP ratio of >0.6,108 and an RVSWI of <450 mL-mmHg per square meter109 predict right ventricular failure after LVAD placement and should trigger consideration of biventricular VAD support if not modifiable (Figure 43.13). However, in patients with significant pulmonary vascular resistance but with right atrial pressures of <15 mmHg, LVAD therapy alone or in combination with pulmonary vasodilators82 can suffice and may eventually lead to normalization of the pulmonary vascular resistance110,112 (see also subsequent discussion).

Appreciation of the VAD anatomy is also crucial before invasive hemodynamic assessment of the patient on VAD support. The inflow cannula is typically placed in the ventricular apex, but may instead be placed in the atria, especially if bridge to recovery is anticipated. The outflow graft is usually anastomosed to the anterior aspect of the great artery (aorta or pulmonary artery) several centimeters above the native outflow valve. Outflow graft kinking or obstruction can be a cause of increased LVAD afterload and can be assessed via a pullback along the graft and contrast CT angiography. Depending on the device and body size, the pump itself is placed within the abdomen, intrapericardially (e.g., HVAD [HeartWare, Framingham, MA]), or extracorporeally connected by percutaneous tubing.

Because of the rapid adoption of continuous-flow LVADs for long-term circulatory support, the assessment of VAD dysfunction has evolved dramatically from the pulsatile era.113 Postimplant VAD surveillance protocols vary widely between centers but generally include a clinical assessment, echocardiographic examination, and right heart catheterization.106 During such patient visits, vasodilators and diuretics as well
Figure 43.12 A fully implantable continuous flow left ventricular assist device (LVAD), the Thoratec HeartMate II (see text for discussion).

Figure 43.13 Univariate and multivariate risk factors for RV failure in the HeartMate II BTT population. (Reproduced with permission from: Kormos RL, et al. Right ventricular failure in patients with the HeartMate II continuous-flow left ventricular assist device: incidence, risk factors, and effect on outcomes. *J Thorac Cardiovasc Surg* 2010;139:1316–1324.)
as adjustment of pump parameters are used to optimize volume status, pulmonary hypertension, right ventricular function, LV decompression, and aortic valve opening.

**CASE 43.4 LVAD Dysfunction.** A 60-year-old man with a continuous-flow LVAD presented with progressive shortness of breath and lower extremity edema. A Thoratec HeartMate II had been placed 3 months ago as a bridge to transplant owing to advanced heart failure from an idiopathic cardiomyopathy complicated by severe pulmonary hypertension despite inotropic and vasodilator therapy. He had returned to part-time employment and was awaiting cardiac transplantation at home. Over the course of a few weeks, he had also noted progressive increase in his blood pressure and abdominal bloating. Interrogation of the LVAD settings demonstrated a pump speed of 9,600 rpm with a calculated pump flow of 4 to 5 L/minute, pulsatility index (PI) of 4 to 6, and power outputs of 5 to 7 watts without evidence for PI events or power surges. On exam, he appeared well without pallor. His blood pressure was 140/105 mmHg with an atrioventricular (AV) paced intrinsic heart rate of 80. His venous pressure was 18 cm of water and he was breathing comfortably at rest. His lungs were clear, but the precordial exam demonstrated an RV heave, a systolic murmur of tricuspid regurgitation, an RVSP of 65 mmHg, an enlarged left ventricle with a midline ventricular septum, moderately severe tricuspid regurgitation, an RVSP of 65 mmHg, an enlarged right ventricle with a midline ventricular septum, and intermittent opening of the aortic valve with mild aortic insufficiency.

Cardiac catheterization was performed to investigate the etiology of the recurrent heart failure despite the LVAD. The hemodynamics are shown in Table 43.7. The wedge and right atrial pressures were elevated (normally post-LVAD, the wedge pressure should be <15 mmHg), and pulmonary hypertension was confirmed. Calculated cardiac output was larger than the calculated pump flow displayed by the LVAD power base unit, reflecting the contribution of native LV stroke volume through intermittent opening of the aortic valve leading to forward flow both in series (LV then LVAD) and in parallel (LV and LVAD). The elevated mean arterial blood pressure was felt to have led to decreased flow from the continuous-flow LVAD resulting in back pressure into the LV and consequent increase in LVEDP, and increased LV ejection through the native aortic valve according to Starling’s law.

Nipride was given to lower the mean blood pressure to 80 mmHg. The displayed pump flow increased and approximated the measured cardiac output; the pulse pressure fell to 20 mmHg. The PVR remained elevated (albeit lower than baseline) although the mean PA pressure fell due to the fall in PCWP. Pump thrombosis was considered but was thought to be unlikely in the absence of power surges, decreased PIs, or hemolysis. The patient was aggressively treated for volume overload and hypertension and ultimately returned to a well-compensated state.

**Illustrative Points.** Continuous-flow LVADs, such as the HeartMate II, are valveless and follow the native LV pulse. In the case of the HeartMate II, a small impeller is rotated at 8,000 to 12,000 rpm in an electromagnetic field within the blood pool and held in place at its poles with ruby bearings in small ceramic cups. According to Archimedes’ principle, blood then moves from the low-pressure to the higher-pressure chamber. Flow across the pump is a reflection of pump speed and afterload (Figure 43.14). Pump power is determined by the pump speed selected and the afterload to be overcome. In contrast to pulsatile LVADs, which are preload sensitive and afterload insensitive, continuous-flow pumps are preload insensitive and afterload sensitive. Thus, the flow across the continuous flow pump will vary over the cardiac cycle as the difference (i.e., afterload) between the distal (i.e., aortal) and the proximal (i.e., LV) pressure varies with systole and diastole (Figure 43.15). When afterload is high, for example, during diastole when the difference between aortic pressure and LV pressure (LV diastolic pressure) is the highest, flow will decrease. When afterload is low, for

---

**Table 43.7**

<table>
<thead>
<tr>
<th>Condition</th>
<th>BP (mmHg)</th>
<th>CI (L/min/m²)</th>
<th>RAP (mmHg)</th>
<th>PCWP (mmHg)</th>
<th>PAP (mmHg)</th>
<th>PVR (dyne-sec/cm⁵)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>140/105 (115)</td>
<td>2.1</td>
<td>18</td>
<td>25</td>
<td>60/25 (40)</td>
<td>350</td>
</tr>
<tr>
<td>SNP</td>
<td>90/70 (75)</td>
<td>2.4</td>
<td>8</td>
<td>15</td>
<td>45/15 (30)</td>
<td>291</td>
</tr>
</tbody>
</table>

BP, blood pressure; CI, cardiac index; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure.
example, during systole when the difference between aortic pressure and LV pressure (LV systolic pressure) is the lowest, flow will increase. This "pulsatility" of flow across the pump is reflected in the PI, which is calculated as a dimensionless value of (maximum flow - minimum flow)/average flow. Clinically, this parameter can therefore be used to assess pump and hemodynamic status. For example, a low PI (e.g., <3) may reflect hypovolemia when LV systolic pressure approaches LVEDP or pump obstruction because the obstruction "prevents" oscillation of the difference between distal and proximal pressures. The pump speed is typically chosen with echocardiographic guidance to maximize LV decompression without excessive "suction," which may lead to RV dysfunction from leftward shift of the ventricular septum.
and ventricular arrhythmias from contact of the inflow conduit with the endocardium of the LV. The pump speed must also be balanced to provide enough LV preload to stimulate intermittent aortic valve opening. In general, some degree of intermittent aortic valve opening is desired to prevent aortic leaflet commissural fusion, aortic root blood stasis, and eventual aortic insufficiency. In a study of the continuous-flow LVAD Jarvik 2000 (Jarvik Heart Inc, New York, NY), a pulse pressure of >15 mmHg suggested native LV ejection through the aortic valve and could be used in the absence of echocardiography to guide speed selection to allow aortic valve opening114 (Figure 43.16).

Right ventricular failure (RVF) (e.g., need for postoperative RVAD or prolonged inotropic support) is a significant limitation of LVAD therapy, and RV function should be vigorously defined pre-implantation. Perioperative mortality rises dramatically after LVAD implantation if prolonged RV failure ensues. A number of preoperative variables (Table 43.8) and scoring systems108,115,117 have been used to predict RVF, although there is no consensus on (1) which variables are the most important, (2) when they should be collected, and (3) how changes in these variables affect outcomes. Echocardiographic assessment of tricuspid regurgitation, RV size, RVEF, and tricuspid annular plane systolic excursion (TAPSE) is predictive of postimplant RVF and should also be performed. At catheterization, an elevated RA pressure relative to the PCWP, low PA pressure, and a low RVSWI109 (Figure 43.17) are particularly worrisome. Following LVAD implant, careful adjustment of the pump speed to prevent

<table>
<thead>
<tr>
<th>Table 43.8</th>
<th>Selected Hemodynamic and Echocardiographic Variables Associated with Post-LVAD Right Heart Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hemodynamic</strong></td>
<td></td>
</tr>
<tr>
<td>– Right atrial pressure</td>
<td>&gt;15 mmHg</td>
</tr>
<tr>
<td>– Right atrial/pulmonary capillary wedge press.</td>
<td>&gt;0.6</td>
</tr>
<tr>
<td>– Right ventricular stroke work index</td>
<td>&lt;450 ml-mmHg/m²</td>
</tr>
<tr>
<td>– Mean pulmonary arterial pressure</td>
<td>&lt;35 mmHg</td>
</tr>
<tr>
<td>– Pulmonary vascular resistance</td>
<td>&gt;8 WU</td>
</tr>
<tr>
<td>– Transpulmonary gradient</td>
<td>&gt;20 mmHg</td>
</tr>
<tr>
<td><strong>Echocardiography</strong></td>
<td></td>
</tr>
<tr>
<td>– Tricuspid regurgitation</td>
<td>&gt;3+</td>
</tr>
<tr>
<td>– Right ventricular ejection fraction</td>
<td>&lt;30%</td>
</tr>
<tr>
<td>– RV/LV dimension</td>
<td>&gt;0.7</td>
</tr>
<tr>
<td>– Tricuspid annular plane systolic excursion</td>
<td>&lt;1.0 cm/s</td>
</tr>
</tbody>
</table>

Figure 43.16 The percentage opening of the aortic valve correlates with the magnitude of the pulse pressure during support with a continuous-flow LVAD. (Reproduced with permission from: Myers TJ, et al. Assessment of arterial blood pressure during support with an axial flow left ventricular assist device. J Heart Lung Transplant: Off Publ Int Soc Heart Transplant 2009;28:423–427.)

Figure 43.17 The right ventricular stroke work index prior to LVAD implant is predictive of the need for prolonged inotropic support. For example, 40% of those with an RVSWI of <600 mL-mmHg/m², in contrast to <5% of those with an RVSWI of >900 mL-mmHg/m², remained on inotropic support 14 days after implant.
suction events and leftward displacement of the ventricular septum is mandatory. Postoperatively, inotropic support, nitric oxide, and keeping the RA pressures at \(<15\) mmHg are generally needed to prevent frank RV failure.

Pump thrombosis is a rare but catastrophic complication of continuous-flow pumps and should be considered in the setting of biventricular heart failure following continuous-flow LVAD implantation. If thrombosis is sudden and extensive, acute pulmonary edema and hypotension can occur and often in conjunction with laboratory evidence of hemolysis. In this setting, there may be surges in pump power as the thrombus transits through the device increasing the drag on the bearings or rotor with a concomitant decrease in PI. In the subacute or chronic setting, power may decrease if the thrombus obstructs the inflow; the PI may or may not be diminished. Right heart catheterization and echocardiography should be performed if pump thrombosis is suspected in the differential diagnosis, since changes in pump parameters may or may not be present. Hemodynamics will generally demonstrate hypotension, a low measured systemic cardiac output, and increased RA and PCW pressures; by echocardiography, the LV will be distended, accompanied by low flows into the apical conduit with a lack of aortic valve opening. Severe aortic insufficiency should also be considered since the hemodynamic and echocardiographic profiles may be similar in both cases. Therapy for pump thrombosis will usually require a device exchange, although case reports have documented successful treatment with thrombolytic therapy.

## Giant Cell Myocarditis

Unexplained heart failure from systolic dysfunction is a common clinical problem in the catheterization laboratory, and the decision to proceed to endomyocardial biopsy is often debatable. (In Chapter 26, the role of endomyocardial biopsy is discussed in greater detail.) Currently, cardiac MRI is commonly employed before endomyocardial biopsy when a diagnosis of myocarditis is considered since specific patterns for gadolinium hyperenhancement are characteristic of myocarditis.\textsuperscript{117} However, diagnostic yield improves when both modalities are used.\textsuperscript{118} Although many potential diagnoses can be made by endomyocardial biopsy, myocarditis is probably the most common distinct histopathologic diagnosis. The positive predictive value of the endomyocardial biopsy for myocarditis is high, but the negative predictive value is low,\textsuperscript{119,120} which has tempered the enthusiasm for the procedure in many catheterization laboratories. Furthermore, conventional immunosuppressive therapies appear ineffective,\textsuperscript{121} sustaining the argument that therapy is unlikely to change on the basis of biopsy findings. Yet, the diagnosis of myocarditis in certain situations is important, especially when specific types of myocarditis can be identified.

### CASE 43.5 Giant Cell Myocarditis

A 39-year-old woman without significant prior medical history presented with 1 month of cough, dyspnea, weakness, and nausea. She denied fever, sick contacts, or chest pain. In the emergency room, she was pale, cool, and confused. Her blood pressure was 75/60; her heart rate was 140 and irregular; and she was tachypneic. The chest radiograph demonstrated pulmonary edema without cardiomegaly, and the electrocardiogram was notable for low volts and rapid atrial fibrillation. Urgent echocardiography demonstrated a nondilated left ventricle but a dilated right ventricle, severe biventricular dysfunction, and moderate mitral and tricuspid regurgitation. She was brought urgently to the cath lab where an intra-aortic balloon was inserted, and angiography demonstrated normal coronary arteries. Hemodynamics were notable for a right atrial pressure of 22 mmHg, pulmonary capillary wedge pressure of 26 mmHg with V waves to 40 mmHg, and a cardiac index of 1.3 L/minute/m\(^2\). An endomyocardial biopsy was obtained. The following day, biventricular assist devices were placed owing to persistent shock despite maximal inotropic/vasopressor support, mechanical ventilation, and an intra-aortic balloon pump. The endomyocardial biopsy revealed diffuse giant cell myocarditis with multifocal areas of healing injury. Over the course of 2 weeks, she was treated with immunosuppressive agents with significant improvement in her ventricular function. Following a successful VAD weaning trial, the ventricular assist devices were successfully explanted and she was eventually discharged to rehabilitation with normal ventricular systolic function.

**Illustrative Points.** The presence of cardiogenic shock in the absence of myocardial infarction or extensive coronary artery disease should elicit a consideration of fulminant myocarditis (see later discussion) and obtaining an endomyocardial biopsy. In fact, viral myocarditis may mimic acute myocardial infarction.\textsuperscript{122} The initial size and geometry of the dysfunctional ventricle may also be clues to the chronicity of the myocardial inflammation since lack of dilation and sphe-ricity implies an acute-onset cardiomyopathy. The rapidly progressive nature of heart failure culminating in shock is characteristic of giant cell myocarditis although other forms of myocarditis, including lymphocytic, may also present in this manner.\textsuperscript{123} Giant cell myocarditis, in particular, is important to identify because of its natural history and implications for therapy.\textsuperscript{121} It can be diagnosed only histologically since it may clinically mimic other types of myocarditis and may even be confused histologically with cardiac sarcoidosis. In a multicenter registry of 63 patients with this disorder, the rate of death or cardiac transplantation was 89% with a median survival of only 5.5 months from the onset of symptoms. As compared with lymphocytic myocarditis, giant cell myocarditis is more likely to be associated with ventricular tachycardia, heart block, more severe depression in ventricular function, and a worse prognosis.\textsuperscript{124,125} Afflicted patients tend to be relatively young (mean age 44 in registry), Caucasian (88% in registry), and previously healthy. There is an
interesting association with autoimmune disorders, especially Crohn’s disease and ulcerative colitis, implying a unifying autoimmune pathogenesis. The pathophysiology appears to be dependent on CD-4 positive T lymphocytes, and an experimental Lewis rat model has been created using autoimmunization against myosin. Treatment with immunosuppression by either azathioprine or cyclosporine may extend survival to as long as a year although corticosteroids alone do not appear to have any impact. The treatment of choice is cardiac transplantation, but a high early postoperative mortality that approaches 15% should be anticipated. Even more disheartening is that the disease may recur in the transplanted heart. In the multicenter registry, 9 out of 35 patients who underwent transplantation developed biopsy evidence of recurrence on an average of 3 years after transplantation, but most did not develop recurrent heart failure.

Lymphocytic myocarditis is a more common form of myocarditis and quite lethal with a 1-year mortality of 15% to 20%. It is presumed to be viral in etiology, although this hypothesis has been difficult to prove. The utility of searching for this entity in new-onset dilated cardiomyopathy remains unclear, especially since the yield for a pathologic diagnosis is highly variable (ranging from 0% to 63% in 30 studies) and specific therapy remains undefined. In the Myocarditis Treatment Trial, using a consensus panel of experienced cardiac pathologists, only 214 of 2,233 patients with unexplained heart failure had histopathologic evidence of myocarditis. The yield may increase if biopsies are limited to those individuals with symptoms of 6 months or less.

Despite these limitations, histologic evidence of myocarditis can prove useful, especially for predicting prognosis. A clinicopathologic classification was developed at the Johns Hopkins Hospital, Baltimore, MD, that combines histologic evidence of myocarditis with specific features of the clinical course (see Chapter 26 for a more extensive discussion). In this classification system, fulminating myocarditis is defined by severe hemodynamic compromise requiring vasopressors (>5 μg/kg per minute of dopamine or dobutamine) or a left ventricular assist device. In addition, at least two of three clinical criteria are required to be met: fever, a viral prodrome of less than 2 weeks before hospitalization, and the distinct onset of heart failure symptoms (fatigue, dyspnea, or new-onset edema). Fulminant myocarditis is also characterized by a higher degree of right heart failure and a lower systemic vascular resistance when compared with acute myocarditis despite similar pulmonary capillary wedge pressures and cardiac output. The presence of significant pulmonary hypertension appears to be especially lethal in myocarditis, with an almost twofold increase in mortality (RR 1.83, CI: 1.50 to 2.29) for every 5 mmHg increase in mean pulmonary artery pressure. Fortunately, a fulminating course is a relatively uncommon clinical manifestation of myocarditis (15 of 147 myocarditis patients in the Hopkins series). Fulminant myocarditis should be contrasted with the more common form of myocarditis (the so-called acute myocarditis), which is characterized by a less distinct onset, a more indolent course, and lack of spontaneous recovery.

Ironically, a distinct clinical course consistent with fulminant myocarditis predicted a good prognosis with a transplant-free survival of 93% after 11 years. Concomitant with clinical recovery and improvement in left ventricular function is long-term survival if the patient can be successfully supported with either mechanical or pharmacologic means during cardiovascular collapse. Interestingly, immunosuppression does not appear to improve survival in this situation.

### HEART FAILURE WITH PRESERVED EJECTION FRACTION AND THE RESTRICTIVE CARDIomyopathies

Half of the patients with HF have preserved left ventricular EF (HFrEF), and with the changing age demographics in the United States, the prevalence of HFrEF relative to HFrEF is increasing by 1% per year. Despite the presence of a normal LVEF, morbidity and mortality in HFrEF are essentially indistinguishable from those in HFrEF. HFrEF was formerly referred to as “diastolic heart failure,” but recent studies have identified multiple nondiastolic abnormalities in systolic, chronotrophic, endothelial, and vascular reserve capacity that play important roles in the pathophysiology. It is important to remember that diastolic dysfunction is not tantamount to HFrEF, as many patients display diastolic dysfunction in the absence of clinical heart failure. Signs (edema, jugular distention, rales) and symptoms (dyspnea, fatigue) at presentation are indistinguishable between HFrEF and HFrEF yet diagnosis of HFrEF is frequently challenging. For example, when a patient presents with dyspnea and is found on echocardiography to display depressed LVEF, the diagnosis of HFrEF is confidently rendered. However, in the dyspneic patient with normal EF, the differential diagnosis includes a large number of cardiac and noncardiovascular conditions (Table 43.9). Positive diagnosis of HFrEF relies upon objective evidence of the hemodynamic derangements in HF, specifically inadequate cardiac output or, more commonly, elevation in cardiac filling pressures. Because assessment of volume status is often challenging from physical exam and echocardiogram alone, and because many patients may have dyspnea or fatigue of noncardiovascular etiologies, hemodynamic catheterization is increasingly being utilized to diagnose (or exclude) HFrEF. Moreover, because filling pressures and cardiac output are frequently normal at rest in patients with early-stage HFrEF, some laboratories now utilize provocative maneuvers such as exercise or saline loading to identify HFrEF based upon invasive hemodynamic responses and distinguish it from noncardiac dyspnea.

HFrEF can be defined as clinical signs and symptoms of heart failure with normal LV chamber size, preserved EF (≥50%), and objective evidence of cardiac dysfunction. The latter is most commonly assessed in the cath lab by an increase in LV filling pressures. In HFrEF, this is generally related to a combination of prolonged LV early diastolic relaxation.
and increases in passive chamber stiffness.\textsuperscript{137,138} LV diastolic stiffening is reflected in the pressure–volume dimension as a leftward and upward shift in the diastolic pressure–volume relationship (DPVR, Figure 43.18), so that filling pressure is higher for any given increment in LV diastolic volume.\textsuperscript{139} LV relaxation is assessed in the cath lab by quantifying the rate of LV pressure decay during isovolumic relaxation, which is prolonged in HFpEF (Figure 43.18). Neither of these gold standard parameters is typically assessed in clinical practice, as the diagnosis of HFpEF is usually made when observing high LV filling pressures in a normal sized LV (e.g., by echocardiography or ventriculography) in the absence of other causes. It is important to remember that LV end-diastolic pressures can be elevated because of nondiastolic factors such as enhanced external cardiac restraint (as in constrictive pericarditis, upward-shifted DPVR) or LV “overfilling” (e.g., as in high-output heart failure; Figure 43.18).\textsuperscript{139}

HFpEF typically is seen in older aged (mean 74 years) patients, in women more than in men (2:1), and usually with a history of systemic arterial hypertension (~75%), obesity, and diabetes mellitus.\textsuperscript{135} When elevation in cardiac filling pressures coexist with normal LVEF in patients without any of these risk factors, pericardial constrictions, restrictive cardiomyopathy, and ischemia should be strongly considered.

When restrictive cardiac physiology is documented by hemodynamics, an endomyocardial biopsy should be performed to assess its etiology (see also Chapter 26).\textsuperscript{140} Primary restrictive cardiomyopathies (RCM) are characterized physiologically by marked diastolic dysfunction and structurally by ventricular hypertrophy or fibrosis that occurs in the absence of chronic load alteration known to cause concentric remodeling (e.g., hypertension or aortic stenosis). Hemodynamically, there is impaired relaxation, normal or small LV end-diastolic volume, high LV filling pressures, and biventricular enlargement. Examples of RCM include infiltrative conditions, such as amyloidosis, hemochromatosis, and sarcoidosis, as well as rarer conditions, such as idiopathic restrictive cardiomyopathy, endomyocardial fibrosis, and Fabry disease.\textsuperscript{140} In addition to RCM, there are a number of other specific cardiac diseases that cause the clinical syndrome of HF in the setting of normal EF; which must be distinguished from “garden variety” HFpEF (Table 43.9) because they each have their own specific treatment. Most of these entities can be readily distinguished from HFpEF by physical examination, echocardiography, coronary angiography, simultaneous right and left heart catheterization, and occasionally endomyocardial biopsy.

### Table 43.9 Diseases Commonly Confused with HFpEF

<table>
<thead>
<tr>
<th>Cardiovascular</th>
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<tbody>
<tr>
<td>Hypertrophic cardiomyopathy</td>
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<tr>
<td>Infiltrative or restrictive cardiomyopathy</td>
</tr>
<tr>
<td>Pulmonary arterial hypertension</td>
</tr>
<tr>
<td>Constrictive pericarditis</td>
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<tr>
<td>High-output heart failure</td>
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<tr>
<td>Valvular heart disease</td>
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<tr>
<td>Coronary artery disease</td>
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<tr>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Right ventricular myopathies</td>
</tr>
<tr>
<td>Noncardiovascular</td>
</tr>
<tr>
<td>Pulmonary disease</td>
</tr>
<tr>
<td>Anemia</td>
</tr>
<tr>
<td>Obesity</td>
</tr>
<tr>
<td>Deconditioning</td>
</tr>
<tr>
<td>Renal artery stenosis</td>
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<tr>
<td>Thyroid disease</td>
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<tr>
<td>Neuromuscular disease</td>
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**Case 43.6 Progressive Exertional Dyspnea.**

A 70-year-old woman presented with 1-year history of progressive exertional dyspnea of unclear etiology with intermittent exertional chest tightness. She had chronic systemic arterial hypertension, treated obstructive sleep apnea, obesity, and mild chronic kidney disease. Physical examination revealed no jugular distention or gallops and only trace peripheral edema. Chest radiography, pulmonary function tests, electrocardiogram, and plasma B-type natriuretic peptide (BNP) levels were normal. Transthoracic echocardiography showed normal LV size, EF 69%, mild left atrial enlargement, mild diastolic dysfunction, and an estimated PA systolic pressure of 36 mmHg. An adenosine perfusion scan was normal. Cardiopulmonary exercise testing revealed reduced peak oxygen consumption (13.9 mL/kg per minute, 70% predicted), though this was interpreted as being due to obesity and deconditioning rather than cardiac limitation.

Cardiac catheterization at rest revealed an RA pressure of 7 mmHg, a mean PA pressure of 24 mmHg, a PCWP of 12 mmHg, and a cardiac output of 5.7 L/minute (Figure 43.19A). Given that the patient’s symptoms were noted during physical activity and not at rest, invasive exercise testing was performed. With passive leg elevation prior to exercise (engaging feet in the ergometer pedals), PCWP increased to 18 mmHg. At 20 Watts of cycling, the patient developed 9/10 dyspnea, while RAP increased to 21 mmHg, PCWP to 37 mmHg (V wave 55 mmHg), and mean PA pressure to 52 mmHg (Figure 43.19B). Simultaneous echocardiography showed only trace mitral regurgitation. Cardiac output increased to 7.8 L/minute, while oxygen consumption increased from 216 to 743 mL/minute. Coronary angiography showed mild nonobstructive disease. Chlorthalidone and
Invasive characterization of diastolic function. A. The kinetics of diastolic relaxation are quantified by the monoexponential time constant of pressure decay during isovolumic relaxation (τ, τ). With diastolic dysfunction, pressure relaxation is prolonged (red curve), resulting in an increase in τ. B. Left ventricular diastolic stiffness is depicted by the curvilinear diastolic pressure–volume relationship (DPVR). Normally the LV fills with a large volume of blood with minimal increase in pressure (black line). In patients with diastolic dysfunction, the DPVR is shifted up and to the left (red), resulting in higher LVEDP. LV filling pressures may also increase in the absence of LV stiffening if there is a parallel shift upward in the DPVR (green). This may be seen in pericardial constriction, where the myocardium is normal but constrained by extrinsic forces. Finally, LVEDP may be elevated even in a normal heart if the LV is “overfilled” to the steep portion of its DPVR (dotted black line). (Reproduced with permission from Borlaug and Kass. Invasive hemodynamic assessment in heart failure. Cardiol Clin 2011;29:269–280.)

Right and left heart filling pressures at rest (A) and during exercise (B). At rest, PCW (black) and RA pressures (red) were normal. With low-level exercise, there is dramatic elevation in both PCWP and RA pressure indicative of heart failure. The PCWP “V” wave increased dramatically during exercise, though simultaneous echocardiography showed only trivial mitral regurgitation.
Illustrative Points. This case demonstrates the key role of catheterization lab in the diagnostic evaluation of exertional dyspnea of uncertain etiology. The patient had significant symptoms but no clear-cut volume overload by physical examination, radiography, or BNP levels, and there was no adequate evidence to positively make the diagnosis of heart failure. It is well known that BNP levels are lower on average in HFpEF as compared to HFrEF\(^ {34,141}\). This is not surprising considering that the stimulus for BNP release is LV end-diastolic pressure, which is markedly different in the two forms of HF. Laplace’s law describes how wall stress (\(\sigma\)) varies directly with LV pressure (\(P\)) and chamber radius (\(r\)), and inversely with wall thickness (\(h\)). In both HFpEF and HFrEF, LV end-diastolic pressure is similarly elevated, but in contrast to HFrEF, HFpEF is characterized by normal or small cavity size and increased wall thickness (Figure 43.20).\(^ {34,135}\) In addition, BNP levels are known to be lower in obese patients as compared to nonobese,\(^ {143}\) and obesity is common in HFpEF; it was present in the case above. Finally, many patients with early stage HFpEF display intermittent elevation in filling pressures, as during physical exercise.\(^ {47}\) Is it also not uncommon for patients with HFpEF to complain of exertional angina in the absence of epicardial coronary disease, as in the present case. This is probably related to demand ischemia from microvascular dysfunction or vascular rarefaction in the setting of acute elevation in wall stress during exercise. Elevation in echocardiographic estimates of PA pressure in older patients with normal EF should always raise the possibility of HFpEF,\(^ {144}\) since the PH in these patients is ultimately an expression of the elevation in PCWP downstream.\(^ {47}\) Exercise capacity and peak oxygen consumption are equally impaired in HFpEF and HFrEF.\(^ {145}\) In the present case, cardiopulmonary exercise testing revealed low peak oxygen consumption, though it was not deemed to be related to cardiac limitation because a typical “plateau” pattern was not observed. One shortcoming of noninvasive cardiopulmonary testing is that cardiac output is not directly measured but inferred from the oxygen consumption pattern.\(^ {40,146}\)

Most laboratories are not equipped to perform upright exercise protocols, so supine exercise strategies are often used. At the Mayo Clinic (Rochester, MN) and University Hospitals Case Medical Center (Cleveland, OH), we favor supine cycling to maximal volitional fatigue and/or severe breathlessness.\(^ {47,136}\) Dramatic elevations in the PCWP pressure and PA pressure with exercise despite “normal” or compensated hemodynamics at rest will confirm heart failure as the cause of exercise intolerance. We have noted that over half of the patients with normal examination, radiography, and BNP levels (as the case above) will display this pattern during exercise.\(^ {47}\) Characteristically, a prominent V wave will also be present as the left atrium is filling to the steep, noncompliant portion of its pressure–volume relationship (Figure 43.19). This large V wave is usually not attributable to dynamic mitral regurgitation in patients with HFpEF, in contrast to HFrEF, where exercise-induced (or exacerbated) mitral regurgitation is an important contributor to cardiac output limitation and secondary pulmonary hypertension.\(^ {47}\)

During exercise, there are often dramatic fluctuations in cardiac and PA pressures owing to the wide swings in intrathoracic pressure during forceful tachypnea. Ideally, PCWP should be measured at mid–A wave during end expiration, though it is also worthwhile to report the mean PCWP from the entire respiratory cycle, particularly in patients with wide pressure swings. Normative data regarding exercise PCW, RA, and PA pressures are unfortunately lacking. The World Health Organization had previously defined pulmonary hypertension by a resting mean PA of \(\geq 25\) mmHg or an exercise mean PA of \(\geq 30\) mmHg. However, recent meta-analyses from Kovacs and colleagues have shown that above the age of 50 years, elevation in PA pressure to this extent may be seen in nearly half of apparently healthy controls (Table 43.10).\(^ {148,149}\) Even though the data from Kovacs et al. are a welcome addition to the literature and serve as a general guide to the interpretation of exercise hemodynamics, several caveats apply: (1) there was little standardization regarding where manometers were zeroed and where in the respiratory cycle pressures were assessed, (2) sample sizes (particularly for older

![Figure 43.20](image-url)

Wall stress in HFpEF and HFrEF. Laplace’s law states that wall stress varies directly with intracavitary pressure (\(P\)) and radius (\(r\)), and inversely with wall thickness (\(h\)). In HFrEF (top), \(P\) and \(r\) are elevated while \(h\) is normal or low. In contrast, HFpEF (bottom) is typically characterized by high \(P\) but much lower \(r\) and increased \(h\), leading to reduction in systolic and diastolic wall stress.
patients) were fairly small, (3) many of the normal controls were trained athletes, who may display marked elevation in PA and PCW pressures during exercise that are not observed in healthy sedentary controls, (4) the resting cardiac index in the Kovacs series (4.2 L/minute/m²) falls in the range of “elevated” cardiac index in most laboratories, and (5) the oxygen consumption data (and thus exercise workload) reported during “light” exercise (1.021 ± 233 mU/minute) defined by Kovacs et al. is significantly higher than what we observe during the range of exercise workload (20 Watts) that is typically tolerated by elderly patients with dyspnea referred to the Mayo laboratory (601 ± 146 mU/minute).

The rapidity with which PCWP increases during exercise may also be important. We have reported that >80% of the total increase in PCWP during supine exercise occurs at low level, while Maeder et al. found that the slope of the increase in PCWP to work performed best distinguished HFrEF from controls, rather than the absolute PCWP value at maximal exercise. What exactly constitutes a “normal” PCWP response to exercise remains unclear. Some investigators have advocated values as low as 15 to 18 mmHg to indicate HF, but in our experience, this is not uncommon in normal individuals. We utilize a more conservative partition value to define abnormal, with an end-expiratory PCWP of ≥25 mmHg or a mean respiratory PCWP of ≥20 mmHg representing sufficient evidence of HF. Even though not as physiologically relevant as exercise, volume loading has also been used to “unmask” diastolic dysfunction in the catheterization lab by showing an abnormal increase in PCWP. In the case above, an increase in PCWP to 18 mmHg was noted simply with straight leg raise (which increases venous return from the lower extremities), providing an important clue to the diagnosis of HFrEF. Bolus saline infusion may also be performed diagnostically, though the degree of PCWP that defines HFrEF with sufficient specificity is not currently known.

The other key hemodynamic finding in HF is inability to enhance cardiac output with stress. At low levels of exertion, increases in left ventricular end-diastolic volume and LVEF are the primary determinants of enhanced stroke volume through the Starling mechanism, though in the supine position, there is less increase in end-diastolic volume as compared with upright exercise. At high levels of exertion, tachycardia is accompanied by a stable or slightly decreased end-diastolic volume, often despite a progressive increase in filling pressure, so that stroke volume must be maintained by a further decrease in end-systolic volume. Beyond this point, increases in cardiac output are entirely owing to increases in heart rate because the stroke volume is fixed. Multiple prior studies have shown that cardiac output should increase by ~6 mL/minute for each 1 mL/minute increase in oxygen consumption. To make these measurements, the laboratory must have the capacity to directly measure oxygen consumption simultaneously with exercise. In the case above, oxygen consumption increased by 527 mL/minute, so the normal increase in cardiac output (i.e., the appropriate increase relative to metabolic needs) should have been +3.2 L/minute. The observed increase (+2.1 L/minute) was substantially lower than this value (66%), indicative of cardiac output limitation in addition to the elevation in filling pressures and secondary pulmonary hypertension observed. This provides further evidence for cardiac etiology of the patient’s symptoms.

### Table 43.10 Normal Resting and Exercise Hemodynamics

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>mPAP (mmHg)</th>
<th>PCWP (mmHg)</th>
<th>TPG (mmHg)</th>
<th>PVR (WU)</th>
<th>VO₂ (mL/min)</th>
<th>CO (L/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest (n = 882)</td>
<td>14.0 ± 3.3</td>
<td>8.0 ± 2.9</td>
<td>6 ± 2</td>
<td>0.9 ± 0.4</td>
<td>296 ± 89</td>
<td>7.3 ± 2.3</td>
</tr>
<tr>
<td>Exercise &lt;50 y</td>
<td>19.6 ± 5.0 (n = 522)</td>
<td>10.9 ± 3.9 (n = 236)</td>
<td>9 ± 3 (n = 51)</td>
<td>0.7 ± 0.3 (n = 51)</td>
<td>1,027 ± 237 (n = 444)</td>
<td>12.7 ± 2.8 (n = 311)</td>
</tr>
<tr>
<td>Exercise ≥50 y</td>
<td>29.4 ± 8.4 (n = 114)</td>
<td>16.8 ± 6.5 (n = 65)</td>
<td>10 ± 3 (n = 16)</td>
<td>0.9 ± 0.3 (n = 16)</td>
<td>1,003 ± 224 (n = 77)</td>
<td>11.2 ± 2.0 (n = 36)</td>
</tr>
</tbody>
</table>

CO, cardiac output; mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; TPG, transpulmonary gradient; VO₂, oxygen consumption.


### CASE 43.7 Recurrent Pulmonary Edema

An 81-year-old woman with prior Bjork-Shiley aortic valve replacement 25 years ago presented with recurrent episodes of acute breathlessness and orthopnea. Past history was remarkable for systolic arterial hypertension, which was difficult to control because of intermittent lightheadedness and orthostasis. Prior to this visit, she had presented to the emergency room twice in the past 6 months, with separate episodes of pulmonary edema in the setting of severe hypertension. Each time, she responded rapidly to low-dose nitroglycerin and mild diuresis (1 to 2 L negative). Duplex ultrasound was performed, which showed no evidence of renal artery stenosis. A third episode of acute dyspnea prompted hospital admission...
and cardiac catheterization. Echocardiography showed normal LV size and function with left atrial enlargement, normal prosthetic valve function, LV diastolic dysfunction, and an estimated PA systolic pressure of 60 mmHg. Coronary angiography was performed and revealed no significant stenosis. Hemodynamic assessment revealed aortic pressure of 192/80 mmHg, elevated PCWP of 34 mmHg, severe pulmonary hypertension with PA pressure of 72/35/50 mmHg, and normal cardiac output (Figure 43.21). Low-dose nitroprusside (1 μg/kg/minute) was administered, resulting in aortic pressure dropping to 98/40 mmHg, with lowering of PCW and PA pressure to normal values (12 and 30/14/20 mmHg, respectively) coupled with slight drop in stroke volume and cardiac output. Five minutes after discontinuing nitroprusside, systemic arterial pressure and PCWP had returned to baseline values. Amlodipine was added to her medical regimen and she was discharged from the hospital, though she continued to experience intermittent breathlessness, pulmonary edema, and lightheadedness.

Illustrative Points. In contrast to Case 43.6, there is no diagnostic uncertainty regarding HFpEF, as the patient presented with multiple episodes of pulmonary congestion associated with uncontrolled hypertension. Investigators from Wake Forest showed in an elegant echocardiographic study that this phenomenon is not owing to transient systolic dysfunction or mitral insufficiency, identifying the key role for diastolic dysfunction.156 In such patients, acute management is straightforward, as most patients respond to mild diuresis and reduction in afterload and preload with better blood pressure control and venodilation. In contrast to HFrEF, where patients with decompensation frequently have many liters of excess extravascular and intravascular fluid, HFpEF patients with hypertensive pulmonary edema tend to be only a few liters up from baseline weight. In these patients, mild perturbations in filling pressures and cardiac afterload lead to dramatic fluctuations in blood pressure and cardiac output.157 This is related to the ventricular-vascular stiffening, in particular to the steep ESPVR, characteristic of HFpEF. Acute afterload increase, as with handgrip exercise, promotes dramatic elevation in LV systolic pressure (Figure 43.22). This acute afterload increase may in turn prolong LV early diastolic relaxation, leading to an acute increase in the time constant of isovolumic relaxation (τ, τ) contributing to a marked elevation in LVEDP. As was seen in this case, the converse occurs with afterload reduction. In striking contrast to the patient with HFrEF who may tolerate Herculean doses of vasodilators, patients with HFpEF develop much larger hypotensive effect with relatively little enhancement in stroke volume (Figure 43.23).34 A series from the Mayo Clinic found that despite elevated LV filling pressures (mean PCWP 20 to 25 mmHg), 35% of HFpEF patients experienced a reduction in stroke volume with acute administration of nitroprusside (Figure 43.23).34 This suggests increased reliance on higher filling pressure in this group to achieve an adequate LV end-diastolic volume (the true “preload” of the ventricle). This is also in stark contrast to the behavior of HFrEF patients, who frequently tolerate normal PCWP with no drop in ejection performance.28

**Figure 43.21** Baseline and nitroprusside (SNP) hemodynamics. At rest, there is marked systemic aortic hypertension with wide pulse pressure (red), consistent with central vascular stiffening, with elevated PCWP (black). With low dose SNP, there is dramatic (~100 mmHg) drop in blood pressure associated with normalization in PCWP (right panel). Cardiac output and stroke volume dropped slightly with SNP, suggesting reduction in preload from excessive venodilation.
**Figure 43.22** Hypertensive response to exercise in HfPfEF. Resting pressure–volume loops show mild systemic hypertension with normal LVEDP. With transient isometric handgrip (red), there is dramatic elevation in end-systolic LV pressure, coupled with acutely prolonged relaxation (increase in $\tau$) and increase in LVEDP. (Reproduced with permission from Kawaguchi et al. Combined ventricular systolic and arterial stiffening in patients with heart failure and preserved ejection fraction: Implications for systolic and diastolic reserve limitations. Circulation 2003;107:714–720.)

**Figure 43.23** Pressure–flow responses with nitroprusside (SNP) in HfPfEF and HfReF. **A**, cumulative distribution plot shows that over one-third of HfPfEF patients may experience reduction in stroke volume (despite mean PCWP of $>20$ mmHg) with SNP, suggesting higher vulnerability to preload reduction. **B**, Increased ventricular–arterial stiffening in HfPfEF leads to exaggerated drop in BP for any reduction in arterial elastance. **C**, SNP reduces PCWP similarly in HfPfEF and HfReF; yet the improvement in stroke volume is marginal in HfPfEF. **D**, Similar to the effect of systemic vascular resistance reduction, patients with HfPfEF have larger reduction in pulmonary artery systolic pressure (PASP) for any degree of reduction in pulmonary vascular resistance (PVR). (Reproduced with permission from Schwartenberg, et al. Effects of vasodilation in heart failure with preserved or reduced ejection fraction: Implications of distinct pathophysiologies on response to therapy. J Am Coll Cardiol 2012;59:442–451.)
A 60-year-old man presented with persistent heart failure and weight loss. He had suffered an inferior myocardial infarction and had undergone right coronary stenting 5 years previously. He began to experience dyspnea and recurrent angina 6 months ago and had undergone repeat cardiac catheterization at that time. Coronary angiography demonstrated a new high-grade ulcerated plaque in the proximal circumflex and a widely patent previously stented right coronary artery. Ventriculography demonstrated an ejection fraction of 40% with no mitral regurgitation or wall motion abnormalities. Hemodynamics were remarkable for decompensated heart failure: RA 12/12/10 mmHg, RV 55/11 mmHg, PA 55/27/36 mmHg, PCWP 30 mmHg, CI 1.4 L/minute/m² (Figure 43.24). He underwent circumflex stenting and was admitted for heart failure management. He returned 24 hours later with stent thrombosis, which was successfully treated with repeat angioplasty.

He continued to have severe fatigue, weight loss, and exertional angina. He was intolerant of angiotensin-converting enzyme inhibitors (ACEI) owing to hypotension and excessive azo temia. He had recently developed atrial fibrillation and had undergone a left popliteal arterial thrombectomy for an acutely painful cold left foot. There had been no history of hypertension or diabetes, but he had only recently stopped smoking and drinking alcohol.

On exam, he was chronically ill with a blood pressure (BP) of 85/70, had a heart rate of 95 and irregular, and was breathing comfortably. Multiple ecchymoses were noted. His venous pressures were elevated at 12 cm of water with weak carotid upstrokes. His lungs were dull at the base. His cardiac exam revealed distant heart sounds without gallop or murmur. His liver was enlarged and pulsatile, but the abdomen was without frank ascites. The extremities were tepid to touch and without significant edema.

Electrocardiography demonstrated atrial fibrillation, low limb voltage, a rightward axis, and prior inferior myocardial infarction (IMI; Figure 43.25). Echocardiography was notable for severe concentric hypertrophy, myocardial speckling, a mild decrease in left ventricular function, and biatrial enlargement (Figure 43.26). Fat pad aspirate and duodenal biopsy were negative for amyloid, but a serum protein electrophoresis demonstrated a monoclonal spike consistent with multiple myeloma. Endomyocardial biopsy demonstrated myocyte hypertrophy, separation of myofibrils by infiltrating amyloid protein, and green birefringence with Congo red, consistent with amyloid (Figure 43.27). Bone marrow confirmed multiple myeloma. Melphalan and prednisone were initiated, which transiently improved his symptoms, but he died 3 months later. At autopsy, classic “wax drippings” lined the left atrium, confirming endocardial deposition of amyloid protein (Figure 43.27).

**Illustrative Points.** In patients with heart failure and preserved systolic function, simultaneous right and left heart hemodynamics should be measured to distinguish restrictive heart disease from pericardial constriction. If restrictive physiology is noted in the absence of extrinsic causes (such as chronic systemic hypertension, diabetes, obesity, etc.), an endomyocardial biopsy should be performed, especially if the hemodynamics are not diagnostic of constriction. In clinical practice, restrictive physiology is most likely encountered in the context of previous mediastinal radiation, diabetes, “burned out” hypertrophic cardiomyopathy, anthracyclines, and amyloidosis. In general, true restrictive cardiomyopathies such as idiopathic restrictive cardiomyopathy, storage diseases (e.g., hemochromatosis and Fabry disease), and endomyocardial fibrosis are quite rare, and are described further in Chapter 26.

The hemodynamics of restrictive heart disease (Figure 43.24) classically demonstrate advanced right heart failure and poor left atrial compliance (large V waves). A rapid early filling wave in the ventricular diastolic pressure tracing (square root sign), dramatic x and y descents in the atria (M or W sign), and the Kussmaul sign may also be present. Traditionally, restrictive processes affect the left ventricle to a larger extent than to which they affect the right ventricle and the LVEDP will be higher than the RVEDP, though occasionally the converse will be seen with extensive right ventricular involvement. Severe pulmonary hypertension may be present, in contrast to constrictive pericarditis, which typically produces only modest pulmonary hypertension (e.g., <50 mmHg). Unfortunately, most of these hemodynamic characteristics are not specific enough to distinguish the restrictive profile from constrictive pericarditis. Hurrell et al. found that enhanced ventricular interdependence during deep respiration is more reliable in separating cases of constriction from those of restriction. In constriction, in the first beat where the preceding diastolic filling period has been affected by negative infrathoracic pressure during inspiration, there should be an increase in RV systolic pressure coupled with a decrease in LV systolic pressure. In restriction, both RV and LV are in phase, with both pressures dropping during inspiration and increasing during expiration.

**Amyloidosis.** Amyloidosis is caused by the fibrillar deposition of insoluble amyloid (meaning starch or cellulose) proteins into various organs, causing dysfunction and ultimately death. There are three forms of amyloidosis defined by the type of amyloid protein deposited. In primary amyloidosis (AL)—the most common form—monochlonal light-chain immunoglobulins (Bence Jones proteins) are generated by plasma cells, which get deposited in the heart and kidney resulting in heart failure and nephrotic syndrome. In secondary or reactive amyloidosis (SAA), the amyloid protein is serum amyloid A, an acute phase reactant, which is produced in response to untreated chronic inflammatory illnesses such as tuberculosis and rheumatoid arthritis. Although renal insufficiency and hepatosplenomegaly are common, heart failure is very rare. Familial amyloidosis (ATTR) is caused by transthyretin, a thyroxine transport protein capable of forming beta-pleated fibrillar sheets. Depending on the type of transthyretin, the clinical syndrome may be...
Hemodynamics of amyloidosis, a restrictive cardiomyopathy. The elevated right atrial pressure, Kussmaul sign, and prominent y descents (A) as well as the dip and plateau in the right ventricular tracing (B) are indicative of severe right ventricular dysfunction and not constriction. Prominent V waves (C) are present in the wedge tracing despite the lack of mitral regurgitation and reflect the volume overload in the stiff atrium, characteristic of amyloid. Classically, the involvement of the left ventricle is more than that of the right, and simultaneous assessment of right and left ventricular end-diastolic pressures show that LVEDP - RVEDP > 5 mmHg. Severe pulmonary hypertension is also consistent with restrictive heart disease (D). Also note a prominent A wave in left ventricular end-diastolic pressure (E). Respiratory ventricular systolic concordance (F) is more consistent with restrictive heart disease, even though other hemodynamic findings are suggestive of constrictive pericarditis. Both the ventricular systolic pressures fall with inspiration (black arrows) and peak with expiration (cross-hatched arrows).
familial or associated with aging. Heart failure tends to be less severe with both peripheral and autonomic neuropathies dominating the picture, though some familial types may be rapidly progressive, causing death from electromechanical dissociation or intractable pump dysfunction. In clinical practice, only AL and ATTR are of concern since SAA is rare in the absence of some untreated chronic infectious or inflammatory disease.

Amyloid heart disease is a common cause of true restrictive cardiomyopathy and should be considered in any patient with none of the typical risk factors for HFrEF (older age, hypertension, diabetes, obesity). Angina may be present, even in the absence of obstructive epicardial coronary disease, and post mortem evaluation may reveal amyloid infiltration in the vasa vasorum around small intramyocardial arterioles. Noninvasive clinical clues include echocardiographic evidence of biventricular enlargement, pseudohypertrophy, speckling of the myocardium, small ventricular cavities, and restrictive mitral inflow profiles (see echo images; Figure 43.26). Electrocardiography may demonstrate low limb lead voltage, Q waves/pseudo-infarct pattern, and various levels of AV block (Figure 43.25). Atrial fibrillation is common as well and reflects the consequences of both chronically elevated atrial pressures and atrial infiltration by amyloid. The cardiovascular exam is dominated by signs of right heart failure with elevation in venous pressures, rapid y descents, an inspiratory increase in venous distension (the Kussmaul sign), and hepatomegaly. The amplitude of the A wave may be diminished from loss of atrial contractile function. The diagnostic evaluation begins with high clinical suspicion and a tissue diagnosis of an affected organ system. The heart should be biopsied if heart failure is present. A bone marrow biopsy to assess plasma cell abundance, and serum and urine immunofixation electrophoresis should also be performed, especially if the biopsy confirms the presence of amyloid. Primary amyloidosis is almost uniformly fatal with a mean survival of <6 months if heart failure is present unless treatments to arrest protein deposition can be promptly administered.

Therapy is generally limited owing to the physiology of restrictive heart disease. Cardiac output is essentially heart rate–dependent since stroke volumes are small and fixed and cannot be increased with vasodilator therapy. For
this reason, angiotensin antagonists, beta-blockers, and calcium channel blocking agents are extremely poorly tolerated and not recommended. Amyloid, in particular, appears to get worse with calcium channel blockers, which are often initiated for treatment of diastolic dysfunction. In amyloidosis, orthostatic hypotension is also common and limits tolerability of vasodilators, which further complicates hemodynamic therapy. Digoxin is contraindicated because of an idiopathic sensitivity to toxicity. Finally, thromboembolic complications are common and are attributable to the thrombogenicity of amyloid protein on the endocardial atrial surfaces (seen at pathology testing as waxlike drippings). Most patients should be anticoagulated if contraindications do not exist. In primary amyloidosis, therapy is directed at the malignant plasma clones. Chemotherapy with melphalan and prednisone is palliative; heart, liver, and bone marrow transplantation have been successfully performed when heart failure is present and there is no extensive multiorgan involvement.

REFERENCES


mechanism of decrease in dynamic mitral regurgitation during
survivors of cardiac transplantation or sustained medical therapy
for stable heart failure.


115. Matthews JC, Koelling TM, Pagani FD, Aaronson KD. The right ventricular failure risk score: a pre-operative tool for assessing the risk of right ventricular failure in left ventricular assist device candidates. J Am Coll Cardiol 2008;51:2163–2172.


Pericardial disease can manifest as fluid accumulation owing to injury or inflammation (pericardial effusion, possibly leading to pericardial tamponade) or as progressive thickening of the parietal and/or visceral pericardium (possibly leading to pericardial constriction). Both tamponade and constriction impede diastolic filling, elevate right and left heart diastolic pressures, and reduce cardiac output, but these two processes differ significantly in the pattern of diastolic filling impairment during each cardiac cycle and in the hemodynamic response to respiration. There are thus distinctive echocardiographic and hemodynamic profiles for tamponade versus constriction, and for constriction as opposed to restrictive cardiomyopathy, in which impaired left ventricular diastolic filling is owing to reduced myocardial compliance without pericardial involvement. For a detailed description of the hemodynamic characteristics of tamponade, and constrictive and restrictive physiology, the reader is referred to Chapter 23. In this chapter, we review profiles associated with pericarditis, pericardial tamponade, pericardial constriction, and restrictive cardiomyopathy.

**PERICARDITIS, PERICARDIAL EFFUSION, AND TAMPONADE**

Discussion of the myriad causes of pericarditis and pericardial effusion is beyond the scope of this chapter, but suffice it to say that virtually any pathologic process can affect the pericardium and cause a detectable pericardial effusion whenever the rate of accumulation of pericardial contents (transudate, exudate, pus, blood, or gas) exceeds the reabsorption ability of the pericardium. The most common causes of pericardial effusion include idiopathic pericarditis (presumably viral), trauma (including iatrogenic catheter injury to the cardiac chambers or vessels), malignancy, postmyocardial infarction, uremia, connective tissue disease, autoimmune disorders, myxedema, and radiation. Infectious or purulent pericarditis is caused most commonly by *Staphylococcus aureus*, followed by other Gram-positive organisms, fungi or mycobacteria. Myocarditis and pericarditis frequently coexist, and elevations of cardiac troponin levels can be seen in both. Acute pericardial injury of any type can also trigger an autoimmune process that can lead to continued or recurrent effusion.

Patients with acute pericarditis often experience sharp, aching, or pressurelike precordial pain that is worsened by cough, inspiration, and recumbency. Pain may radiate to the shoulders and may be confused with angina or acute myocardial infarction, particularly since the ECG may show diffuse concave ST-segment elevation. One distinguishing feature, however, is the concomitant depression of the PR segment and the absence of reciprocal ST depression. A pericardial friction rub and fever may be present, but rigors or spiking fevers should raise the concern of purulent pericarditis. The mainstay of diagnosis is echocardiography, which clearly shows an effusion. Fluid first accumulates posteriorly and then extends anteriorly. Small effusions have <10-mm clear space between the heart and parietal pericardium, moderate effusions have a 10- to 20-mm gap, and large effusions have a >20-mm gap. The size of the effusion correlates roughly with prognosis. Effusions may be loculated (partitioned) by non-uniform fibrous adhesions that form between the parietal and visceral pericardium, a pattern typically observed after cardiac surgery. Echocardiography also reveals the extent to which the pericardial pressure is compromising cardiac function, showing early diastolic collapse of the right ventricle as pericardial pressure transiently exceeds intracavitary pressure. In idiopathic pericarditis, the effusion usually resolves spontaneously or after symptomatic treatment with nonsteroidal anti-inflammatory agents and sometimes with colchicine or corticosteroids.

Drs. Beverly Lorrell and William Grossman contributed material for this chapter in previous editions.
Chronic idiopathic effusions may also persist without symptoms or signs of tamponade despite effusion, and volumes >500 mL may be followed conservatively with serial echocardiograms if asymptomatic. On the other hand, significant pericardial effusion with even early signs of hemodynamic compromise is usually an indication for prompt drainage (pericardiocentesis, or surgical subxiphoid window placement). The pericardial pressure is normally subatmospheric (−5 to +5 mmHg) and it tracks the intrathoracic pressure during the inspiratory/expiratory cycle. As discussed in details in Chapter 23, during inspiration the pericardial pressure falls more than the systemic venous pressure. The net result is an increase in right atrial filling gradient leading to augmentation of atrial filling and right ventricular stroke volume. If an excess of pericardial fluid accumulates in the pericardial space beyond its limited capacity to stretch, the pericardial pressure rises and begins to progressively compress the underlying cardiac chambers. The diastolic y descent becomes absent, owing to impairment of rapid atrial emptying secondary to compression by the pericardial effusion. By the time the classic bedside findings of jugular venous distension and pulsus paradoxus (fall in systolic arterial pressure on normal inspiration) develop, only a small further accumulation of fluid separates the patient from frank hemodynamic collapse. As shown in Figure 44.1, the abnormal physiology of cardiac tamponade is relieved when (a) the pericardial pressure falls to a level ≤0 mmHg and separates from the right atrial pressure and (b) the right atrial pressure falls to the normal range and exhibits return of a normal diastolic y descent, indicating restoration of normal rapid atrial emptying and early ventricular diastolic filling.

**DIAGNOSTIC AND THERAPEUTIC PERICARDIOCENTESIS**

The main pericardial procedure performed in the catheterization laboratory is needle puncture and catheter drainage of pericardial fluid—pericardiocentesis (Chapter 38). Diagnostic pericardiocentesis may be performed to evaluate the etiology of pericarditis, particularly for suspected purulent or tuberculous pericarditis, persistence or recurrence of a large effusion, or a high suspicion of malignant effusion without a tissue diagnosis from the primary site. The diagnostic yield for pericardial fluid analysis is quite low, with as few as 6% of diagnostic procedures and 29% of therapeutic procedures yielding useful information. Diagnostic yield tends to be higher in large pericardial effusions.

Pericardial fluid always should be sent for cell count; Gram, acid-fast bacteria (AFB), and special stains; cultures (aerobic, anaerobic, AFB, fungal); and cytology. Although differentiation between an exudate and a transudate can be accomplished with determination of fluid protein and LDH levels, such differentiation is of dubious value because the timing of sampling and effects of treatment may alter values and because sensitivity and specificity are poor with significant overlap between the exudative and transudative groups. Since most effusions are serosanguineous or hemorrhagic, fluid appearance is not useful in differentiating various etiologic groups with the exception of purulent fluid, which is specific but not sensitive for infection. As long as adequate samples are obtained, fluid cytology has 92% to 95% sensitivity and 100% specificity for malignant pericardial effusion, although nonmalignant effusions are also common in patients with underlying malignancy. There are no specific pericardial fluid findings for postpericardiomyotomy syndrome, radiation or uremic pericarditis, hypothyroidism, or trauma. Special circumstances may require additional analysis for the following: viral cultures for viral infection; fluid cholesterol level in myxedema; fat studies for chylopericardium; latex fixation for rheumatoid antigen; gamma globulin complexes and fluid complement levels for rheumatoid arthritis; fluid antinuclear antibody levels for systemic lupus erythematosus; and tuberculosis stains and/or cultures, fluid adenosine deaminase determination, or polymerase chain reaction for tuberculosis (see also Chapter 38). Purulent pericarditis may be associated with low pH, high protein levels, glucose levels <35 mg/dL, and elevated leukocyte counts in the range of 6,000 to 240,000/mm³.

**PERICARDIAL BIOPSY**

The diagnostic yield of pericardiocentesis may be increased by retrieval of pericardial tissue by a surgical pericardial biopsy performed via thoracotomy, subxiphoid incision, or thoracoscopy. Percutaneous pericardial biopsy (assisted by pericardioscopy) has led to a specific diagnosis in 49% to 53% of patients in several limited series. The pericardioscopy technique is not widely available and requires surgical or 16F percutaneous pericardial access. In hemorrhagic effusion, obtaining adequate parietal pericardial visualization may require 2 to 3 days of active drainage,replace pericardial effusion with saline, and instillation of 100 to 300 mL of air. Several small uncontrolled series suggest that this approach may increase the likelihood of obtaining a definitive diagnosis in patients with large recurrent pericardial effusions and in patients in whom there is a strong clinical suspicion of malignant pericarditis or tuberculous pericarditis. In a prospective series of 141 patients with unexplained pericardial effusions who underwent 142 surgical pericardioscopy including cytological fluid analysis, visualization of the pericardium, and guided biopsy, a specific etiologic cause (neoplastic, infected purulent, or sterile radiation-induced effusion) was identified in 49%, whereas 51% were considered idiopathic. Of note, an unrecognized cause not detected by pericardioscopy–biopsy was subsequently discovered in 4%. No deaths were attributable to pericardioscopy but in-hospital mortality was 5.6% related to underlying disease.
Simultaneous right atrial (RA) and intrapericardial pressure (scale 0 to 40 mmHg) and femoral artery (FA) pressure (scale 0 to 100 mmHg) recorded in a patient with cardiac tamponade. A. Recordings before pericardiocentesis show the presence of systemic hypotension and the elevation and equalization of the RA and intrapericardial pressures. Note that a systolic x descent is present, but the diastolic y descent is absent, suggesting that RA emptying in early diastole is impeded because of cardiac compression by the pericardial effusion. B. After aspiration of 100 mL of pericardial fluid, RA and intrapericardial pressures have fallen and are beginning to separate, and systolic arterial hypertension has improved as compared with baseline. C. After aspiration of a total of about 300 mL of pericardial fluid, tamponade physiology is relieved, as evidenced by (a) restoration of intrapericardial pressure to zero, (b) restoration of RA pressure to a normal level, and (c) reappearance of the diastolic y descent in the RA waveform, indicative of the relief of cardiac compression in early diastole. Note the negative fluctuation in intrapericardial pressure during inspiration, accompanied by an increased steepness in the fall of RA pressure during the x and y descents. Although this degree of fluid aspiration completely relieved tamponade physiology, an additional 1,500 mL of fluid was removed from the pericardial space.

In another series, 35 patients with pericardial effusion owing to inflammatory disease underwent pericardioscopy, and pericardial biopsies were performed. Diagnoses of viral pericarditis, lymphocytic perimyocarditis, bacterial pericarditis, and antibody-mediated autoreactive pericarditis were obtained; however, it was unclear if this resulted in a change of management strategy. The same authors reported a series of 14 patients with idiopathic pericarditis
and 15 patients with malignant pericarditis who underwent percutaneous pericardioscopy with both pericardial and epicardial biopsy from a registry of 136 patients undergoing pericardiocentesis. In this study, subxiphoid pericardiocente-
sis and sampling of fluid for cytology, immunologic studies, and culture were performed first, followed by evacuation of pericardial fluid, placement of warmed clear sterile saline in the pericardial sac, and introduction of both rigid and flexi-
ble pericardioscopes. Both epicardial biopsies and pericardial biopsies were obtained with a resterilizable bioptron, after site selection by both pericardioscopy and biplane fluoroscopy, before the saline was evacuated. In this series of patients with proven malignant pericarditis, fluid cytology was diag-
nostic in 71% and epicardial biopsy in 80%.\(^{21}\)

In a more recent study by Seferovic, 49 patients with a large pericardial effusion underwent parietal pericar-
dial biopsy using fluoroscopy or pericardioscopy guidance (for more extensive sampling). Diagnostic efficiency was improved by extensive sampling (4–20 biopsies) as com-
pared with a single biopsy\(^{19}\) (40% versus 8.3%, \(P < 0.05\)). In our experience and in several series of pericardiocentesis in patients with malignant effusion, cytologic examination is positive in about 80% to 85% of cases and false-negative cytologic analysis is rare in carcinomatous pericarditis (as opposed to malignant involve ment by lymphoma or mesothelioma). In the era of molecular diagnostic tools, a clear role for diagnostic pericardioscopy and directed pericardial and/ or epicardial biopsy is not yet defined relative to cytologic examination of recovered fluid.

Therapeutic pericardiocentesis is indicated for any sign or symptom of tamponade, limiting dyspnea,\(^{14}\) symptoms of compression of surrounding structures such as lung or esophagus, and acute hemopericardium with circulatory compromise following a catheter-based or surgical intervention. The diagnosis of early tamponade is usually made echocardiographically. Hemodynamically, the diagnosis of tamponade is made if there is identical elevation of left- and right-side diastolic pressures with loss of the y descent in a patient with pericardial effusion. However, it may be noted

that pericardiocentesis is contraindicated for hemopericar-
dium or tamponade in the presence of a diagnosed ascending aortic dissection, as it can accelerate bleeding and shock,\(^{22}\) making immediate surgery preferable in such situations. Another particular example in which emergency pericardiocentesis is required is when catheter injury to a cardiac chamber or vessel produces acute hemopericardium. This may happen as the result of temporary pacemaker placement in the right ventricle, passage of a stiff right heart catheter, endomyocardial biopsy, trans-septal puncture, retrograde crossing of a stenotic aortic valve with a straight guidewire, coronary atherectomy or high-pressure stent dilation, or passage of a stiff hydrophilic guidewire into a small coronary branch in a patient receiving a glycoprotein Ilb/Ilia platelet antagonist.

The patient may complain of chest pain, followed by progressive hypotension and tachycardia. Bradycardia may also appear owing to stimulation of the vagal nerve by blood in the pericardium, but the hypotension persists even after the bradycardia is resolved by atropine administration. Careful fluoroscopy of the right and left heart borders may show that the normal pulsations of the heart have been replaced by an immobile tense pericardial shadow, and right heart catheterization may show the classic hemodynamic findings described below as well as inability to advance the right heart catheter fully to the right atrial border. Urgent pericardiocen-
tesis may be lifesaving in this situation. When the cause of bleeding into the pericardium is injury to a coronary artery, either placement of a fabric-covered stent or coil embolization of a small bleeding distal branch may be required. Ongoing bleeding after initial drainage and reversal of anticoagulation, however, usually warrants emergency surgery.

While percutaneous pericardiocentesis is the procedure commonly used for acute pericardial tamponade, surgical or balloon pericardiotomy is performed for recurrent effusions. The techniques of pericardiocentesis, balloon pericardiotomy, and the pericardial approach to epicardial ablation for ven-
tricular arrhythmias and for left atrial appendage exclusion are described in Chapter 38.

**CASE 44.1 Pericardial Tamponade.** A 55-year-
old man presented with unstable angina. Severe stenoses in the proximal and mid LAD were stented, but a shelllike step-
up was seen within the stented segment. That area was postdi-
lated at 16 atm, with vessel perforation noted immediately on deflation (Figure 44.2). Hypotension ensued, and the 3.0-mm balloon was reinflated to block the vessel as emergency sub-
xiphoid pericardiocentesis was performed. The contralateral femoral artery was punctured to allow introduction of an 8F XB3.5 guiding catheter, through which a second BMW wire was advanced to the distal vessel. The 3.0-mm balloon was
deflated and removed through the initial 6F guiding catheter as a 3.0 × 16 mm jomed covered stent was advanced to span the area of perforation. Delivery of the stent and postdilation at 18 atm sealed the perforation. Cardiac surgeons were pre-
ent in the catheterization laboratory, who agreed with contin-
ued nonoperative management, given that bleeding had been stopped and the vessel was patent. No further pericardial prob-
lems were noted, and the drain came out the next day. The patient did have moderate myocardial infarction (MI) owing to occlusion of diagonals, but the stent remained open at restudy on day 3, and the patient went home on day 4.
reaccumulation of pericardial effusion and signs of tamponade. Right heart catheterization showed a mean right atrial pressure of 16 mmHg, mean PCW pressure of 22 mmHg, and mean pericardial pressure of 15 mmHg with some separation of pericardial and right atrial pressures. Cardiac index was mildly depressed at 2.4 L/minute/m², with a 15 mmHg paradox.

After needle pericardiocentesis and removal of 100 mL of bloody fluid, the pericardial pressure decreased to 0 mmHg with little change in the right atrial (RA) pressure. Balloon pericardiectomy (Figure 44.3) was performed by advancing a guidewire through the drainage catheter, predilating with a 4.0 × 40 mm balloon, and final dilation with inflation of a 15 × 40 mm balloon straddling the pericardial edge. The pericardial waist resolved fully, and the balloon was exchanged for a drainage catheter, which was left in place overnight. The cardiac index improved to 3.4 L/minute/m², and repeat echocardiography at 1 month showed no reaccumulation of pericardial fluid.

**CASE 44.3** Pericardial Effusion in a Patient with Systemic Sclerosis. A 38-year-old woman was admitted to the hospital with progressive dyspnea. Her past medical history was significant for systemic sclerosis and pulmonary hypertension. Initial echocardiographic evaluation revealed a large pericardial effusion. There were no echocardiographic indications of cardiac tamponade. The left ventricle was hyperdynamic, the right ventricle was moderately dilated, and the right ventricular systolic performance was severely reduced. The right ventricular systolic pressure was estimated at 60 mmHg. Owing to the presentation with progressive dyspnea and concerns that the large pericardial effusion was contributing to the patient’s symptoms, she was referred for right heart catheterization and possible pericardiocentesis. The mean right atrial pressure was 11 mmHg, the right ventricular pressure was 80/15 mmHg, the pulmonary artery pressure was 78/35 mmHg with a mean of 45 mmHg, and the mean pulmonary capillary wedge pressure was 30 mmHg. Pericardial pressure was 10 mmHg. Cardiac output was 4.14 L/minute and the cardiac index was 2.55 L/minute/m². A total of 50 cc of pericardial fluid was removed, and the patient was transferred to the CCU with a pericardial drain in place. Over the next 2 days, a total of 600 cc was slowly drained at a rate of 100 cc every 8 hours.

Repeat hemodynamic measurements in the CCU revealed a decrease of the pulmonary capillary wedge pressure to 8 mmHg, while the pulmonary artery systolic pressure was 70 mmHg. Her dyspnea was resolved. A pericardial rub developed on the day of discharge. The patient was discharged from the hospital with prednisone as well as on sildenafil. She continued to improve, and on the day of discharge she was able to tolerate a 6 minute walk test without development of dyspnea or oxygen desaturation.

Clinical Considerations. Pericardial effusion is a relatively common finding in late stages of pulmonary hypertension. The typical findings of pericardial tamponade including right atrial diastolic collapse, right ventricular diastolic collapse, and changes in Doppler transmitral flow velocity tend to be absent in this setting. Importantly, poor outcomes including
a high mortality rate have been observed in patients with pulmonary hypertension or systemic sclerosis undergoing drainage of large pericardial effusions.\textsuperscript{23,24} It should be noted that acute left and right ventricular failure are known complications of pericardiocentesis. The pathophysiology of acute left and right ventricular failure is unclear (see Chapter 38 for a detailed description of available hypotheses), although there exists a general agreement that rapid drainage of large amounts of fluid can contribute to its development. Whether the high mortality rate observed after drainage of pericardial effusions in patients with pulmonary hypertension is secondary to acute left and right ventricle dysfunction remains to be determined, although it is a plausible hypothesis. Therefore, in this case meticulous attention was paid to avoid drainage of a large amount of fluid in a short period of time.

**CONSTRUCTIVE PERICARDITIS**

Constrictive pericarditis is a symmetrical process in which scarring of both the parietal and visceral pericardial layers constrains all cardiac chambers. Localized constriction may rarely produce external compression and stenosis of the mitral and tricuspid valves.\textsuperscript{25} In the chronic stage of constriction, pericardial calcification may develop, but calcification may be absent in more recent constriction despite severe hemodynamic compromise. Although tuberculosis was once the most important cause of constrictive pericarditis, the most common causes today are recurrent idiopathic or viral pericarditis, delayed constriction after mediastinal radiation therapy (sometimes years later), and pericarditis after open heart surgery.\textsuperscript{26-28} Less common causes include any cause of acute pericarditis including neoplasm, septic pericarditis including opportunistic AIDS-related infections, chronic renal failure, post-myocardial infarction syndrome (Dressler), drugs, and connective tissue/autoimmune disorders. Some patients with acute pericarditis may develop transient mild pericardial constriction that resolves spontaneously within a few months of the initial illness.\textsuperscript{29} Constrictive pericarditis should be considered in any patient with unexplained jugular venous distension, systemic edema, hepatic congestion, and dyspnea. It should also be considered in the postoperative heart surgery patient who has unexplained tachycardia, low cardiac output, and venous congestion in the first months after surgery.
The clinical features of constrictive pericarditis reflect the physiologic effects produced as the constricting pericardium restricts cardiac filling and causes the gradual development of systemic venous and pulmonary venous hypertension followed by reduction of cardiac output. In patients in whom right and left atrial pressures are elevated to the range of 10 to 18 mmHg, symptoms and signs of systemic venous congestion predominate. These include leg edema, postprandial discomfort, hepatic congestion, and ascites. As right and left heart filling pressures become elevated to a level of 18 to 30 mmHg, exertional dyspnea and orthopnea appear, and pleural effusions may develop. As stroke volume falls, compensatory increases in systemic resistance and sinus tachycardia develop, which initially help maintain cardiac output and systemic blood pressure at rest, although the inability to augment cardiac output during exercise causes exertional fatigue and dyspnea. As resting cardiac output then begins to fall, severe lethargy and cardiac cachexia may occur.

The electrocardiogram usually shows reduced voltage and diffuse ST–T wave abnormalities that may be mistaken for ischemic coronary artery disease. Atrial fibrillation is present in about 10% of patients. The chest roentgenogram may show a small, normal, or modestly enlarged cardiac silhouette with redistribution of pulmonary flow or pleural effusions. The finding of pericardial calcification on the lateral projection may be present in about 50% of cases. Pericardial thickening, when present, is best demonstrated by cine and gated magnetic resonance imaging (MRI) and computed tomography (CT) with and without contrast enhancement. The mean normal pericardial thickness in adults is 1.2 ± 0.8 mm (two standard deviations (SD)—a pericardial thickness of >3.5 mm indicates pathologic thickening, whereas any thickness >6 mm is specific for pericardial constriction. The finding of a pathologic increase in pericardial thickening supports the diagnosis, but does not confirm that constrictive physiology is present; conversely, hemodynamically significant constriction can be present with a tough but minimally thickened pericardium. CT or MR may also demonstrate small deformed ventricles, dilated left atrium, and dilated venae cavae. Measurement of pericardial thickness can also be achieved by transesophageal echocardiography, which may show pericardial thickening, dilatation of the superior and inferior vena cavae, diastolic flattening of the posterior ventricular wall, and abrupt cessation of ventricular dimension change in early diastole.

Right and left heart catheterization and angiography should be performed in every patient with suspected constrictive pericarditis (a) to confirm the presence of constrictive physiology (Chapter 23) and assess its severity before considering pericardectomy; (b) to assist in differentiating pericardial disease from restrictive cardiomyopathy (Chapter 23); (c) to exclude major coexisting causes of right atrial hypertension, such as severe pulmonary hypertension; and (d) to exclude rare instances of localized constriction causing external valvular constriction or pinching of the epicardial coronary arteries. Endomyocardial biopsy (see below and also Chapter 26) is sometimes useful in excluding a restrictive cardiomyopathy before surgical exploration for pericardial stripping is contemplated.

Both pericardial constriction and cardiac tamponade increase ventricular interdependence (see above), in which filling of one ventricle limits simultaneous filling of the other ventricle, owing to the shared mechanical constraint of the pericardium and the interventricular septum. The pericardial constraint on the left and right ventricles are coupled in cardiac tamponade by uniform liquid pressure on the heart, whereas they are uncoupled in constriction given regional differences in surface pressure. Coupled constraint (tamponade) produces greater ventricular interdependence, so that increased inspiratory filling of the right ventricle results in highly coupled reduction in filling of the left ventricle (hence the occurrence of pulsus paradoxus), whereas uncoupled constraint (constriction) has a more modest effect on ventricular interdependence but more prominently reduces the effective elastance of the thin-walled right ventricle (hence the Kussmaul sign, an increase in right atrial pressure during inspiration). This provides a framework for understanding the steady state and respiratory-related events that are detected by complementary echo-Doppler and hemodynamic evaluations in constrictive pericarditis and cardiac tamponade (see Chapter 23).

The right and left ventricular pressures should be measured simultaneously at equisensitive gains, with meticulous attention to zeroing, calibration, and elimination of waveform damping. In constrictive pericarditis with elevated atrial pressures, early diastolic filling of the ventricles is unimpeded and abnormally rapid, but late diastolic filling is abbreviated and halts abruptly when total cardiac volume expands to the volume limit set by the stiff pericardium. This is reflected in the diastolic dip-and-plateau pattern in the right and left ventricular waveforms. Right and left ventricular diastolic pressures are typically equalized or nearly so. In the right atrial waveform, a prominent and rapid diastolic y descent is followed by a steep A wave and a blunted systolic x descent because the atrium is attempting to eject blood into a right ventricle that is already filled to capacity. In the right or left atrial waveform, the x and steep y descents impart the characteristic M or W appearance (Figure 44.4). Right and left atrial pressures may differ if coexisting mitral or tricuspid regurgitation is present associated with a large V wave in either atrium. In a patient with constriction and superimposed hypovolemia, a rapid volume challenge of 1,000 mL normal saline solution may be useful to unmask the hemodynamics of constrictive pericarditis. Tachycardia, inadequate transducer zeroing, and transducer underdamping may obscure the evaluation of diastolic waveforms (Figure 44.5).

Examination of respiratory fluctuations in hemodynamics is an important component of the cardiac catheterization for constriction. In severe pericardial constriction, negative intrathoracic pressure during inspiration is not communicated to the intrapericardial space and the right heart. There is typically little respiratory variation in right atrial pressure.
Figure 44.4 Right atrial (RA) pressure recording from a patient with constrictive pericarditis. Note the prominent y descent in the right atrial waveform, which indicates that the RA emptying is rapid and unimpeded in early diastole. The nadir of the y descent corresponds with the abrupt cessation of early diastolic ventricular filling. The prominent x and y descents give the RA waveform its characteristic M- or W-shaped appearance in constrictive pericarditis. The mean value of the RA pressure is more than twice normal, at 18 to 20 mmHg.

This contrasts with both normal subjects and patients with cardiac tamponade who demonstrate a fall in systemic venous and right atrial pressures during inspiration. In extreme cases, systemic venous pressure increases during inspiration (the Kussmaul sign), as illustrated in Figure 44.6.\textsuperscript{32} Using micro-manometer pressure measurements, Hurrell et al.\textsuperscript{33} reported that discordance of right and left ventricular systolic pressures during respiration is an indicator of increased ventricular interdependence in constrictive pericarditis. As illustrated in Figure 44.7, the inspiratory augmentation of right heart filling, stroke output, and right ventricular systolic pressure occurs simultaneously with a fall in left ventricular systolic pressure, which results from an inspiratory fall in intrathoracic and pulmonary venous pressures and a reduction of left heart filling and stroke volume. This finding helps distinguish patients with surgically proven constrictive pericarditis from patients with other causes of heart failure. Stroke volume is almost always reduced in patients with constrictive pericarditis, but resting cardiac output may be preserved owing to tachycardia. Studies of atrial pacing in patients with constrictive pericarditis showed that increases in heart rate up to about 140 beats per minute increased cardiac output in the presence of unchanged stroke volume and ventricular filling pressure.\textsuperscript{34} After pericardectomy, when ventricular filling was no longer impeded and confined to early diastole, atrial pacing caused a normal pattern of improvement in cardiac output at higher heart rates. In advanced constrictive pericarditis, resting cardiac index is depressed in association with systemic arterial vasoconstriction and arterial hypotension. In the absence of extensive coexisting myocardial fibrosis, left ventricular ejection fraction is usually normal or increased, and both isovolumetric and ejection phase indices of contractile function (e.g., peak $\frac{dP}{dt}$) are preserved.\textsuperscript{33,35} Important exceptions to this are those patients with extensive coexisting myocardial fibrosis, which is a complication of radiation-induced pericardial constriction, and conditions in which...
velocity studies in constrictive pericarditis typically show an exaggerated inspiratory increase in tricuspid flow velocity and a reduction in mitral flow velocity (>25% inspiratory reduction in mitral flow velocity), which may also be seen in tamponade, but is usually absent in restrictive cardiomyopathy. Tissue Doppler, which measures displacement and velocities of left ventricular motion, usually shows high or normal early-diastolic velocity in patients with constrictive pericarditis, whereas this is usually reduced in restrictive cardiomyopathy. In addition, pulmonary venous flow by transesophageal echocardiography shows higher pulmonary venous peak systolic flow velocity in constrictive pericarditis as compared with restrictive cardiomyopathy. Because none of these echo measurements has perfect discriminatory ability, they need to be considered in the context of the clinical presentation and hemodynamic findings (see below).

Coronary angiography should be performed as part of the cardiac catheterization evaluation of constrictive pericarditis. In addition to defining significant occult atherosclerotic coronary artery disease, the angiogram can detect the rare problem of external pinching or compression of the coronary arteries by the constricting pericardium prior to pericardectomy. Studies indicate that pericardial constriction limits coronary flow reserve measured by adenosine-induced hyperemia and causes abrupt cessation and rapid deceleration of the normal pattern of early-diastolic flow velocity. Left ventriculography may not be required during cardiac catheterization if a current high-quality imaging study (echocardiography, gated CT, or MRI) has defined global and regional

Figure 44.6 Right atrial (mean, RA) and pulmonary capillary wedge (phasic, PCW) pressure tracings from a patient with constrictive pericarditis. An arrow marks the beginning of the inspiratory phase of each respiratory cycle. Note that the mean right atrial pressure increases during inspiration (the Kussmaul sign). The PCW pressure is out of phase with RA pressure and begins to fall during inspiration as RA pressure is rising.

infiltrative processes such as amyloid may involve both pericardium and myocardium.

When pericardial thickening is not evident, it is important to distinguish constrictive pericarditis from restrictive cardiomyopathy, which may produce similar clinical, hemodynamic, and echocardiographic findings. Doppler flow

Figure 44.7 Respiratory (insp and exp) changes in left ventricular (LV) and right ventricular (RV) pressures measured with micromanometer catheters in a patient with constrictive pericarditis (left) and in a patient with restrictive cardiomyopathy (right). Peak inspiration is indicated in beat 2 in each cardiac cycle. In the patient with constrictive pericarditis (left), there is a discordant change in LV and RV systolic pressures during respiration: LV systolic pressure falls to its minimum value during peak inspiration simultaneously with an increase in RV systolic pressure to its highest value in the cardiac cycle. These findings indicate the presence of ventricular interdependence owing to the constricting pericardium and suggest that as LV filling and stroke volume decreases, there is a corresponding increase in RV filling and stroke volume. In contrast, in the patient with cardiomyopathy (right), there are concordant changes in LV and RV pressures during respiration. (Adapted from Hurrell DG, Nishimura RA, Higano ST, et al. Value of dynamic respiratory changes in left and right ventricular pressures for the diagnosis of constrictive pericarditis. Circulation 1996;93:2007.)
left ventricular ejection fractions and volumes, and excluded significant coexisting valvular heart disease.

Treatment

Medical management is purely palliative with control of edema and arrhythmias. The definitive treatment of constrictive pericarditis is surgical pericardiectomy, which should be reserved for symptomatic patients, in whom there are typical noninvasive imaging and hemodynamic findings. An experienced cardiovascular surgical team should perform a complete visceral and parietal pericardiectomy, facilitated by the ability to mobilize the heart on cardiopulmonary bypass. Outcome is excellent in patients in whom the operation is performed early in the disease before development of dense epicardial fibrosis that is less amenable to resection, end-stage depression of rest cardiac output, and poor organ perfusion. For example, a recent surgical series of 21 patients from a major tertiary center reported no perioperative mortality, mean postoperative hospital stay of 7 days, and return to functional NYHA Class I status in all patients. Mayo Clinic studies of 58 patients showed that abnormalities of diastolic filling detected by Doppler mitral flow velocity signals were present in about 40% of patients 3 months after pericardiectomy, with approximately 34% showing abnormalities at 21 months postoperation. Most patients improve quickly postoperatively with diuresis and resolution of edema and hepatic congestion. Others recover more slowly over months, but atrial arrhythmias may persist. Poorer surgical outcome is predicted by inadequate pericardial resection, inability to relieve epicardial constriction with scoring or meshing of the epicardium, uncorrected coronary disease, older age, post radiation pericarditis, and pericarditis accompanied by peripheral organ failure.

CASE 44.4 Constrictive Pericarditis. A 59-year-old man was admitted for cardiology evaluation after 4 years of progressive peripheral edema, which had recently become resistant to increasing doses of oral diuretics. For the 2 weeks prior to hospital admission, he had noted increasing fatigue and dyspnea on exertion and orthopnea, increasing abdominal girth, increasing leg and scrotal edema, and a rapid weight gain of at least 15 pounds. Physical examination showed a chronically ill appearing white male with dyspnea at rest. Blood pressure (BP) was 140/95; the heart rate was irregular and 150 beats per minute. The chest x-ray showed dullness at both bases, and heart sounds were distant. The cardiac exam showed an irregular tachycardia with distant heart sounds, and no rubs, gallops, or murmurs were appreciated. His abdomen was distended with ascites and showed an enlarged liver and mild right upper quadrant tenderness. There was marked scrotal edema. Extremities showed significant pitting edema to the level of the groin with chronic venous stasis changes of the skin of his legs bilaterally. Laboratory examination was normal (including thyroid function) except for mild elevation of total bilirubin and liver transaminases.

Echocardiography showed biatrial dilation, moderate hypokinesis of the ventricles with a left ventricular ejection fraction of 35%, and no regional wall motion abnormalities. There was +1 mitral regurgitation and +1 tricuspid regurgitation with an estimated right ventricular systolic pressure of 29 mmHg by Doppler. There was a thickened pericardium with “railroad tracking” around the left ventricular apex and right ventricular free wall.

Cardiac catheterization revealed equalization of diastolic pressures with a left ventricular end-diastolic pressure (LVEDP) of 22 mmHg, a mean pulmonary capillary wedge pressure of 22 mmHg, a pulmonary artery pressure of 29/22 mmHg, and a right atrial pressure of 21 mmHg. The mean right atrial pressure increased with inspiration (the Kussmaul sign), and the right and left ventricular diastolic pressures were equal. The resting tachycardia and atrial fibrillation obscured the evaluation of the x and y descents in the right atrial pressure tracing. (See Figures 44.5 through 44.7.) Cardiac output and index measured by thermodilution were reduced at 3.7 L/minute and 1.7 L/minute/m², respectively. Coronary angiography showed normal right dominant coronary arteries. Left ventriculography showed a normalized left ventricle with a calculated ejection fraction of 42% and calcification of the anterolateral, apical, and inferior pericardium (Figure 44.8).

The patient underwent pericardial stripping, during which the pericardium was described as thickened, heavily calcified, and having the consistency of bone. The parietal pericardium was densely adherent to the epicardium. The calcified anterior pericardium was removed piecemeal after identifying and preserving the phrenic nerves. The right atrium was entered inadvertently, requiring the institution of cardiopulmonary bypass and repair. Histology showed focal calcification.

Figure 44.8 Left ventriculography. Note pericardial calcification.
fibrosis, calcification, and chronic inflammation with aggregates of lymphocytes and mesothelial cells. Routine stains and cultures were negative, as was cytology.

Postoperatively, the patient maintained sinus rhythm, but required pharmacologic inotropic and pressure support for several days. He required intravenous diuretics and thoracentesis, but eventually diuresed 15 kg over the next week, and his peripheral edema largely resolved. By 3 months after surgery, he resumed normal activities and within another 3 months was able to walk several miles a day without symptoms. He remained free of edema on reduced doses of once-daily furosemide and free of atrial fibrillation on Quinaglute and digoxin.

**EFFUSIVE–CONSTRICTIVE PERICARDITIS**

Failure of right atrial pressure to fall to normal levels following pericardiocentesis for tamponade suggests a coexisting cause of right atrial hypertension. Persistent elevation of right atrial pressure with appearance of a prominent y descent and a dip-and-plateau pattern in the right ventricular waveform suggests the presence of effusive–constrictive pericarditis. In this condition, relief of cardiac tamponade unmasks significant residual visceral pericardial constriction.\(^{44,45}\) The jugular venous pulse may resemble that of constriction, with prominent x and y descents, rather than blunting of the y descent that typically occurs in tamponade.\(^{46}\) Diastolic pressures remain equalized between the right and left heart after pericardiocentesis. Effusive–constrictive pericarditis is important to recognize and diagnose, since definitive treatment requires extensive visceral and parietal pericardiectomy.\(^ {47}\) The most common causes are idiopathic or related to malignancy, radiation, rheumatoid arthritis, and tuberculosis.

**CASE 44.5  Effusive–Constrictive Pericarditis.**

A 29-year-old female was admitted to the hospital complaining of positional chest pain, progressive dyspnea on exertion, and orthopnea. She complained of orthostatic dizziness and had a resting tachycardia of 120 beats per minute. Two years earlier she had been diagnosed with stage IV nodular sclerosing Hodgkin’s disease with a large mediastinal mass. Chemotherapy resulted in diminution of the mediastinal mass, but new disease activity developed in several bony locations, which was treated by high-dose chemotherapy and an autologous peripheral stem cell rescue. A CT of the chest 3 months prior to admission had revealed a partial response, with reduction in the size of the mediastinal mass and a normal pericardium, with no pericardial effusion (Figure 44.9A).

Physical exam revealed her BP to be 90/60, with a pulsus paradoxus of 18 mmHg and elevated jugular venous pressure of 18 cm water without an apparent Kussmaul sign. There was +1 edema of the lower extremities bilaterally. An echocardiogram revealed normal chamber dimensions with normal global and segmental ventricular function. A moderate anterior and posterior pericardial effusion with minimal inferior and apical effusion and right ventricular and right atrial diastolic collapse was noted. There was >50% variation in tricuspid valve inflow velocities and >30% variation in mitral valve inflow velocities by Doppler, consistent with the tamponade physiology. There was a homogeneous echogenic mass, >12 mm in thickness, seen encasing the heart in multiple views. Bedside, right atrial pressure measure via a central line showed a mean of 25 mmHg with a prominent y descent, and an inspiratory increase in mean pressure. Chest CT revealed a large mediastinal mass encasing the heart and a moderate pericardial effusion (Figure 44.9B), with a clear decrease in pericardial volume as compared with the previous CT 4 months earlier.

**Figure 44.9**

A. Computed tomography (CT) of the chest 3 months prior to admission. Note the normal pericardial thickness and lack of effusion. B. CT of the chest on admission. Note the mass in the right hemithorax, scattered masses throughout the lung fields, thickened and encased pericardium, decreased pericardial cross-sectional area, and small pericardial effusion.
Subxiphoid pericardiotomy was performed surgically; 200 mL of serous fluid was returned and a pericardial drain placed. Pericardial biopsy revealed histiocytoid cells and mixed inflammatory infiltrate consistent with nodular-sclerosing Hodgkin lymphoma. Her right atrial pressure dropped from 23 to 18 mmHg with removal of the pericardial fluid, but she remained hypotensive and dyspneic, despite adequate filling pressures. After discussions with the patient, family, and oncologists, a decision was made to forgo more aggressive therapy, and comfort measures were initiated. The patient expired 1 week later.

### RESTRICTIVE CARDIOMYOPATHY

The differentiation between constrictive pericarditis and restrictive cardiomyopathy is often difficult but important, because only the former can be effectively treated with pericardectomy. In restrictive cardiomyopathy, there is an abnormality of diastolic function, and the ventricular walls are noncompliant and resist filling. Systolic function is usually preserved. The most common etiologies of restrictive cardiomyopathy include idiopathic, amyloidosis, sarcoidosis, endomyocardial fibrosis, radiation, and anthracycline toxicity (see Chapter 26). Less common causes include familial; scleroderma; pseudoxanthoma elasticum; diabetes; storage diseases such as Gaucher, Hurler, Fabry, and glycogen storage disease; hemochromatosis, carcinoid, hypereosinophilia, metastatic cancers, and drugs. The clinical features of restrictive cardiomyopathy are often similar to those of constrictive pericarditis—both disorders manifest impaired ventricular diastolic filling and elevated diastolic pressures with symptoms of congestive heart failure such as exercise intolerance, weakness, and fatigue. Central venous pressure is elevated with peripheral edema, liver enlargement, ascites, and anasarca in advanced cases. Stroke volume is fixed or reduced in both, although systolic contractile function may be essentially normal. In both disorders, patients may complain of chest and neck discomfort during exertion that may be related to impaired coronary reserve and/or neck vein distension. In both disorders, the electrocardiogram commonly shows abnormal voltage and ST–T wave abnormalities, and atrial fibrillation may occur.

Echocardiography may show thickening of the left ventricular wall and an increase in ventricular mass. Patients with restrictive cardiomyopathy have an increased early left ventricular filling velocity (E), a decreased atrial filling velocity (A), with E/A ratios of ≥2, and a decreased isovolumic relaxation time. Tissue Doppler, which measures displacement and velocities of left ventricular motion, usually shows normal early-diastolic velocity in patients with constrictive pericarditis versus reduced velocities in restrictive cardiomyopathy. Color M-mode Doppler spatial velocity distribution using the slope of the first aliasing contour shows a slower slope in constrictive pericarditis than in restrictive cardiomyopathy. In addition, pulmonary venous flow by transesophageal echocardiography shows that peak systolic pulmonary venous flow velocity is less than diastolic flow velocity in restrictive cardiomyopathy and that there is reversal of diastolic flow after atrial contraction with inspiration in the hepatic and pulmonary veins. Measurement of pericardial thickening may be accomplished by transesophageal echocardiography, CT, or MRI, and if present, favors constrictive pericarditis. None of these echo measurements has perfect discriminatory ability; all need to be considered in the context of the clinical presentation and hemodynamic findings. On the other hand, echocardiographic findings of thickened cardiac valves, a granular sparkling appearance of the myocardium, and the presence of thickened ventricular walls with reduced electrocardiographic R-wave voltage suggest the presence of an infiltrative process such as amyloid, but their absence does not exclude the presence of restrictive cardiomyopathy.

In most cases, careful attention to hemodynamics at cardiac catheterization can permit identification of the patient whose symptoms of congestive failure are owing to restrictive cardiomyopathy. Right and left ventricular diastolic pressures should be recorded simultaneously at equisensitive gains. Right atrial pressure is usually elevated and has a prominent y descent followed by a rapid rise with an M- or W-shaped waveform as in constrictive pericarditis. The respiratory variation in right atrial pressure may be lacking, and the y descent may become steeper with inspiration. Diastolic pressures in both ventricles may be elevated, with a dip-and-plateau configuration, but left ventricular diastolic pressure is usually higher than right ventricular diastolic pressure. There is usually concordance in the fall of right and left ventricular systolic pressures with inspiration. Supine exercise usually causes higher elevation of left ventricular diastolic pressure than of right ventricular diastolic pressure. Pulmonary hypertension is usually more common and more severe in restrictive cardiomyopathy than in constrictive pericarditis, and pulmonary systolic pressures of >45 to 50 mmHg are common. However, in cohorts of patients with constrictive pericarditis versus restrictive cardiomyopathy, there is frequently an overlap in these measurements between individuals in each group.

Thus, the diagnosis of restrictive cardiomyopathy requires careful clinical judgment and integration of both noninvasive imaging data and hemodynamic analyses. A clinical history suggestive of pericarditis makes a diagnosis of constrictive pericarditis more likely, as does a history of tuberculosis, trauma, or cardiac surgical procedures. No diagnostic technique is totally reliable in differentiating these two entities, and in some patients the only reliable way to make the diagnosis is to perform pericardectomy.
with dilated cardiomyopathy—a specific etiologic diagnosis is obtained in <10% of patients, and a treatable process is found in about 2%—biopsy does play an important role in the evaluation of the symptomatic patient with potential constriction versus restrictive cardiomyopathy. Myocardial biopsy is valuable in making a definitive diagnosis in patients with restrictive cardiomyopathy owing to amyloid as well as other specific causes such as myocarditis, metabolic storage disease, and hemochromatosis. In patients with cardiac irradiation injury in which both pericardium and myocardium may be involved, the documentation of extensive myocardial fibrosis and myocyte dropout should temper the decision to proceed to surgical pericardectomy (see also Chapter 26).

**OTHER CONDITIONS ASSOCIATED WITH CONSTRUCTIVE PHYSIOLOGY**

The normal pericardium functions to restrain and to couple the function of both ventricles in conditions in which the pericardium has not expanded to accommodate an increase in cardiac or effusion volume. In the presence of normal cardiac volumes and low filling pressures, cardiac volumes dynamically fluctuate during respiration and with changes in posture within the loose, lubricated pericardial sac with minimal pericardial constraint and minimal ventricular interaction. However, as right ventricular volume increases to a level associated with a diastolic pressure of about 10 to 12 mmHg, pericardial constraint appears and ventricular interdependence increases. Ventricular interdependence can be recognized when increments in diastolic pressure in one ventricle cause a similar gain in diastolic pressure of the opposite ventricle, and when respiratory filling of one ventricle causes marked reduction of filling of the opposite chamber. This phenomenon has been shown to be important in dilated cardiomyopathy, in which reductions in elevated right heart filling result in the augmentation of left ventricular filling via ventricular interaction.

Acute right ventricular infarction in humans and experimental animal models may cause constrictive physiology with right ventricular dilation, elevation and equilibration of right and left ventricular pressures, a dip-and-plateau ventricular waveform, and reduced right ventricular pulse pressure. Right ventricular volume overload owing to subacute tricuspid regurgitation with an intact pericardium can also cause increased pericardial constraint and ventricular interdependence, as illustrated in Figure 44.10. In a classic paper, Bartle and Hermann reported that acute and subacute mitral regurgitation can cause a striking hemodynamic pattern suggestive of pericardial constriction. Acute pulmonary embolism with secondary right ventricular dilatation and moderate pulmonary hypertension in the setting of a nonhypertrophied right ventricle can also result in constrictive physiology owing to pericardial constraint.

**ANOMALIES OF THE PERICARDIUM**

Congenital anomalies of the pericardium may cause confusion during cardiac catheterization and angiography unless their characteristic features are recognized. Pericardial cysts, which are filled with clear fluid, are usually located at the right costophrenic angle and come to attention as unexplained protrusion of the right heart border on the chest roentgenogram or during fluoroscopy at cardiac catheterization. Rarely, cysts may cause chest pain or right ventricular outflow obstruction. Although most cysts can be managed conservatively, large pericardial cysts located at the costophrenic angle can be decompressed by percutaneous aspiration under fluoroscopic guidance.

Congenital pericardial defects are rare and mostly occur in males, with associated congenital abnormalities of the heart and lungs in up to 30% of patients. Isolated congenital absence of the pericardium encompasses a range from a small foramen to complete absence. Total absence of the pericardium is extremely rare and usually not associated with symptoms. Complete absence of the left side of the pericardium is more common, and patients may be referred for cardiac catheterization because of stabbing sharp chest pain that is occasionally
positional, palpitations, or dyspnea. These patients have prominent apical impulses that displace with body position, electrocardiographic findings of right axis deviation and clockwise displacement of the precordial transition zone, chest roentgenogram findings of a leftward displacement of the heart with loss of right heart border, and a “tongue” of lung interposed between the main pulmonary artery and aortic knob. Echocardiographic findings mimic right ventricular volume overload with enlarged right ventricle and abnormal septal motion, and the left atrial appendage is laterally displaced. This anomaly can be accurately diagnosed with cardiac MRI. Smaller left-side atrial pericardial defects are uncommon; however, cardiac catheterization and angiography can be helpful in their detection and diagnosis. These patients frequently complain of chest pain and are at risk for sudden death owing to herniation and strangulation of the heart or left atrial appendage through the defect. Echocardiographic findings are similar to those for the other congenital defects mentioned above, and the left atrial appendage is laterally displaced. A definitive diagnosis can be made by CT or MRI, with a myocardial crease caused by the edge of the pericardium considered a high-risk feature. Partial right-sided pericardial defects can also be accompanied by severe chest pain related to inspiratory herniation of the right atrium.

REFERENCES

Profiles in Congenital Heart Disease

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Congenital heart disease has become more common not only in the pediatric but also in the adult catheterization laboratory, owing to increasing survival of patients with lesions surgically corrected in childhood and to the increasing availability of catheter-based treatments for lesions that do not present until adulthood. Some basic issues regarding catheterization in such patients have been reviewed in Chapter 9, and some of the interventional techniques have been reviewed in Chapter 35. This chapter presents a series of real-world profiles illustrating some of these basic principles.

CASE 45.1

A 72-year-old woman presented with a loud murmur since birth and several years of progressive shortness of breath. Pulse oximetry showed an arterial oxygen saturation of 90% to 91% at baseline, falling to mid-80s during a stress test. Transthoracic echo demonstrated valvar pulmonary stenosis with a peak instantaneous gradient of approximately 115 mmHg. A bubble contrast injection was positive for a right-to-left shunt at the atrial level, consistent with a diagnosis of patent foramen ovale (PFO).

In the cath lab under intravenous sedation, an 8F sheath was placed in the femoral vein and a 5F sheath was placed in the femoral artery. A multipurpose catheter was advanced from the femoral vein to obtain right-side pressures and saturations and to cross the PFO to obtain left-side data. Oxygen saturation in the pulmonary veins was 96% (room air) with a simultaneous aortic saturation of 89%, defining a right-to-left shunt. Right atrial (RA) and left atrial (LA) filling pressures were elevated (RA mean, 15 mmHg; LA mean, 12 mmHg) with the mean RA pressure being 2 to 3 mmHg higher than the mean LA pressure. There was severe right ventricular (RV) hypertension, consistent with the echocardiographic gradient (RV pressure, 130/15), with mildly elevated pulmonary artery (PA) pressure (Figure 45.1). There were no additional obstructions at the branch PAs. There was no mitral stenosis, obstruction of the left ventricular outflow, or aortic arch. Coronary angiography showed no obstructive disease.

A Berman catheter was placed in the right ventricle and a right ventricular angiogram was obtained. The ventricle was severely hypertrophied with preserved systolic function. The pulmonary valve was thin and doming, with a jet of contrast seen through the small orifice of the doming valve (Figure 45.2). There was post-stenotic dilatation of the main pulmonary artery (MPA) and the left pulmonary
Figure 45.1 Pullback across the stenotic pulmonary valve. Systolic pressure increases simultaneously with change in diastolic pressure tracing, indicating a gradient at the valve. The peak-to-peak gradient was >100 mmHg. MPA, main pulmonary artery; RV, right ventricle.

Figure 45.2 Domeing pulmonary valve leaflets in early systole and the jet of contrast emerging into the MPA from the stenotic valve orifice (arrows). MPA, main pulmonary artery; RV, right ventricle.

Figure 45.3 Right ventricular angiogram demonstrating the dilated PA branches and the subvalvar narrowing of the outflow tract. White arrows indicate the level of the valve annulus. RPA, right pulmonary artery; LPA, left pulmonary artery; RV, right ventricle.

was dynamic subvalvar muscular (infundibular) narrowing of the outflow tract.

The pulmonary valve was dilated with the Inoue balloon technique—techniques of balloon valvular dilation vary, with some operators preferring the relative ease and simplicity of the Inoue balloon methodology, while others prefer a greater sense of waist and compliance assessment that can be afforded by standard single- and double-balloon dilation (see Chapters 33 and 40). An Inoue balloon was selected with a maximum inflation diameter a few millimeters larger than the measured diameter of the valve annulus, but was prepared with only enough volume to expand to the size of the annulus. A stiff exchange-length 0.032-inch guidewire was advanced through a multipurpose catheter into the distal LPA. The Inoue balloon was straightened and introduced through a 14F sheath at the femoral vein. The balloon was advanced over the wire to the RA, where the straightening rod was removed to ease passage through the two valves. (In some cases, manipulation through the tricuspid valve and the RV outflow tract can be facilitated by partial inflation of the balloon.) Once in the MPA, the distal portion of the balloon was inflated and pulled back against the valve tissue. Then the proximal portion and middle waist were inflated. There was a pop as the indentation of the valve on the balloon was eliminated. The stiff guide wire provided...
with the Inoue was advanced through the balloon to the LPA. A side-arm valve was added to the back of the catheter, and a pressure transducer was attached to the side port of the valve. The balloon was then withdrawn, over the wire, back into the RV to assess the residual gradient.

On pullback, an increase in the gradient across the RV outflow tract was noted. However, closer inspection of the pullback tracing revealed that the gradient had shifted from the level of the valve to the subvalvar (infundibular) area (Figure 45.4). On pullback 1, from the MPA into the RV, the diastolic tracing confirmed that the catheter was in a ventricular chamber, with virtually no systolic gradient across the valve. Pullback 2, identified that the systolic gradient was located within the ventricular chamber, at the subvalvar level. Arterial saturations fell acutely into the mid-80s following valvuloplasty. A repeat angiogram revealed markedly improved mobility of the valve leaflets with a larger valve orifice (Figure 45.5). However, there was profound dynamic obstruction at the level of the valve (Figure 45.6). The patient was hydrated intravenously and started on an intravenous beta-blocker infusion. Over 10 to 15 minutes, systemic arterial oxygen saturations rose to the mid-90s (%), as the gradient fell; over the subsequent 6 weeks, the peak instantaneous gradient by Doppler decreased even further, systemic arterial saturations normalized, and oral beta-blocker therapy was discontinued.

**Discussion**

Valvar pulmonary stenosis (PS) is far less common in the adult population than in children and young adults, but when left untreated into adulthood, it can cause significant symptoms. Unlike the aortic valve, the pulmonary valve does not

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**Figure 45.4** Following dilation of the valve, pullbacks from the main pulmonary artery (MPA) to right ventricular (RV) outflow tract show little residual systolic gradient and a large degree of intraventricular obstruction.

**Figure 45.5** Marked improvement in valvar excursion after balloon dilation (compare with Figure 45.2). White arrows denote tips of valve leaflets. MPA, main pulmonary artery; RV, right ventricle.

**Figure 45.6** Following dilation of the valve, there is severe subvalvar dynamic outflow obstruction (thick arrows). The thin arrows denote the level of the valve leaflets. MPA, main pulmonary artery; RV, right ventricle.
generally calcify and is thus typically amenable to balloon dilatation. The long-term follow-up of repaired valvar PS, by surgical or balloon valvuloplasty, demonstrates that in most cases it is a highly successful, if not curative, procedure. Late valvar insufficiency may also cause symptoms of shortness of breath, or fatigue, on exertion, but is more frequently a product of surgical intervention.

Severe infundibular stenosis after valvuloplasty, which has been termed the "suicide" right ventricle in surgical series, is physiologically identical to left ventricular outflow tract obstruction in hypertrophic cardiomyopathy; hypovolemia and increased inotropic states augment the degree of obstruction, which is typically a product of long-standing PS with RV hypertrophy. The cyanosis in this patient was driven by long-standing RV hypertrophy and reduced RV diastolic compliance sufficient to elevate RA pressures and resistance to filling, contributing to preferential right-to-left shunt across the patent foramen ovale.

In children, in whom most PS repairs are performed, standard valvuloplasty balloons are very effective, and also inexpensive. In adults and in teenagers, the size of the valve annulus is such that a double-balloon technique is often required to obtain enough dilating force and diameter. The Inoue balloon (see earlier discussion) can be selected to suit larger diameters and is variable in its inflation size, so that a larger inflation size can be used without needing to change the catheter.

Balloon valvuloplasty is a highly effective and extremely safe catheter intervention. It should be considered the procedure of choice for valvar PS.

### COARCTATION OF THE AORTA

**CASE 45.2** A 32-year-old man presented with poorly controlled hypertension and bilateral lower extremity claudication. He had been prescribed, and was compliant with, beta-blocker and ACE inhibition therapy, with continued poor blood pressure control and slightly impaired renal function. Blood pressure in the right arm was 165/90, with no palpable femoral pulses and a blood pressure of 75/40 in the lower extremities. There was an apical click, a soft systolic murmur, and a diastolic decrescendo murmur. Cardiac magnetic resonance (CMR) revealed a discrete coarctation of the aorta approximately 2 cm distal to the left subclavian artery.

Under intravenous propofol sedation, sheaths were placed in the femoral artery and vein. Right-side hemodynamics were obtained. A pigtail catheter advanced from the femoral artery would not pass around the aortic arch. A floppy-tipped wire was then manipulated through a multipurpose catheter around the aortic arch, after which the pigtail catheter was re-advanced over the wire and an ascending angiogram was obtained (Figure 45.7). With a proximal aortic isthmus diameter of 18 mm and a distal descending aortic measurement of approximately 21 mm, the minimum dimension at the coarctation site was approximately 2.5 mm. The angiogram demonstrated filling of the descending aorta from intercostal and internal mammary collaterals.

A stiff wire with a hand-formed loop was advanced through the pigtail catheter around the arch to the ascending aorta, and the pigtail catheter was removed. A 10F Mullins sheath (through which the pigtail catheter was replaced to the ascending aorta) was advanced over the wire to the descending aorta (Figure 45.8). The pigtail catheter was removed, and the long sheath was advanced through the coarctation to the ascending aorta. At the treating center, predilatation of the coarctation site, to allow assessment of aortic compliance, was not performed. A balloon-dilatable Palmaz iliac stent (Johnson & Johnson) was mounted on a 10-mm balloon catheter and advanced through the sheath to the level of the coarctation site. The sheath was withdrawn into the descending aorta, and an angiographic injection was performed through the side port of the Mullins sheath to help position the stent. The balloon was inflated rapidly, expanding the stent to 10 mm (Figures 45.9 and 45.10).

The pigtail catheter was reinserted, and repeat measurement of simultaneous pressures was carried out (Figure 45.11). There was a small residual gradient across the stent, but the ascending aortic pressure was markedly reduced, and the descending aortic pressure increased to the normal range. Because of the small initial diameter of the coaractation segment, we elected to do full dilation in two stages. The sheaths were removed, and hemostasis was obtained. Six months later, the patient returned with a small
persistent gradient, though with improved blood pressure (BP) control and elimination of the symptoms in his lower extremities. From a femoral access, a 15-mm and then an 18-mm balloon (Figures 45.12 and 45.13) were used sequentially to redilate the stent to equal the size of the proximal aorta, thus eliminating the residual pressure gradient.

**Discussion**

De novo diagnosis of coarctation in the adult population is uncommon, but patients who have had previous aortic coarctation surgery may have residual obstruction at surgical sites. Any patient with systemic arterial hypertension should have examination of the lower extremity pulses, and the four extremity pressures should be checked at least once during their lifetime to rule out this disease. In children who have not reached full adult size, surgery was historically the preferred therapy for native coarctation, although increasingly, centers with appropriate expertise offer primary balloon angioplasty when it is both anatomically and physiologically suitable. For recurrent coarctation after surgical repair in children, however, balloon angioplasty is accepted as the procedure of choice, when feasible. Stenting is generally not used in younger children given their growth potential, but has become widely accepted in older children, as well as in adults with coarctation.\(^5\)\(^6\) Stenting appears to provide more control in dilating the coarcted segment and eliminates the need for oversizing of the balloon with attendant risks of aortic rupture, tear, or dissection.

Many centers are increasingly performing “predilation” (balloon expansion at the site intended to ultimately receive a stent) in a staged fashion and with limitations in permitted waist–balloon diameter ratio, so as to assess compliance of the aortic wall and to presumably decrease...
the risk of both underdilation and vessel rupture. In this patient’s case, predilation was not chosen by the intervention center—though dilation was performed in a staged approach—owing to the small size of the native vessel. The initial stent size was limited to 4 to 5 times the initial diameter of the coarctation lesion; the patient returned after 6 months (with presumptive healing of the stent site) for fuller stent expansion.

Stent placement is also possible in more proximal lesions, such as coarctation that involves the transverse arch and isthmus, and may impinge on the left subclavian or even the carotid vessels. Lesions in each of these locations have been successfully treated with stent angioplasty without adverse neurologic events or arm ischemia. Some congenital interventional cardiologists have endorsed the use of covered stents to reduce the risk of acute aortic injury. These stents have been utilized as “rescue” treatment in patients with periprocedural dissection, rupture, or aneurysm formation, and have been suggested for use (a) for postprocedural (surgery or percutaneous) aneurysms located at or near the coarctation site, (b) in patients in need of repair with native or repaired coarctation, who have particular risk of procedural complication (e.g., anatomy with atretic/near atretic coarctation, tortuosity, and long segmental involvement), and (c) for stent failure (stent fracture or in-stent restenosis). Anecdotal data support use of covered stents under specific local and FDA protocol for periprocedural dissection or rupture. For any other indication, it should be noted that covered stents do not have FDA approval for treatment of aortic coarctation in the United States. They have been utilized as implantation therapy mainly in Europe, but very scarce data are available on the longer-term follow-up in patients who have undergone
this treatment. The ongoing Coarctation of the Aorta Stent Trial (COAST) is a nonrandomized, multicenter, open-label study addressing the safety and efficacy profile of covered Cheatham Platinum stent use in children, adolescents, and adults with coarctation of the aorta and estimated or measured transcoarctation pressure gradient of at least 20 mmHg. This study will be useful to better define the clinical indications and efficacy of this type of stent in percutaneous treatment of coarctation of the aorta.

**ATRIAL SEPTAL DEFECT**

**CASE 45.3** A 43-year-old woman with no past medical history presented with increasing shortness of breath on exertion. Oxygen saturation was normal by pulse oximetry. An echocardiogram revealed a dilated right atrium and right ventricle with a tricuspid regurgitation velocity of approximately 3.8 cm/second; transesophageal echo revealed a 1.7-cm atrial septal defect with predominantly left-to-right shunting (Figure 45.14).

The patient was taken to the cardiac catheterization lab, and two sheaths were placed in the right femoral vein under local anesthesia and conscious sedation. Through the first, an intracardiac echo (ICE) catheter (Acuson, Siemens) was passed to the right atrium for imaging the septum. Through the second sheath, a multipurpose catheter was inserted to perform hemodynamic measurements. There was only moderate pulmonary hypertension (PA pressure of 68/14 mmHg with simultaneous aortic pressure of 140/78 mmHg). The calculated Qp/Qs ratio was 2.3:1 with an indexed pulmonary vascular resistance of 3.2 Units (see Chapter 12).

The multipurpose catheter was then used to cross the atrial septal defect and was manipulated to the left upper pulmonary vein. A stiff guidewire was passed into the pulmonary vein. A balloon-sizing catheter was advanced over the wire to straddle the defect and was inflated until flow stopped by ICE (Figure 45.15). At that point, the diameter of the waist on the balloon catheter was 19 mm. Circumferential septal rims were adequate (as assessed by echo), and a 20-mm Amplatz Septal Occluder (AGA Medical, Minneapolis, MN) was selected (Figure 45.16). The balloon catheter was removed, and a 9F Mullins sheath was advanced over the wire and into the left atrium. The Amplatz device was collapsed and advanced through the delivery sheath until the left atrial side of the occluder opened in the left atrium and was pulled back toward the septum (Figure 45.17). When the left atrial disc of the occluder was adjacent to the septum, the middle waist and right atrial side were opened, and the device was allowed to return to its native shape. In this case, because of the relatively deficient retroaortic rim (current FDA regulations recommend avoidance of device implantation in such circumstances), the device appears splayed out somewhat over the aortic root (Figure 45.18), but is in position with no residual shunt. The device was released without difficulty, sheaths were removed, and the patient was discharged 4 hours later.
Discussion

Transcatheter closure of atrial septal defects (ASDs) has become well accepted, with reasonable demonstrated safety and efficacy. A low potential for thrombus formation, device-induced erosion of the atrial wall, and occurrence of symptomatic atrial arrhythmia exists and requires continued study.8·9 Particular anatomic variants of ASD remain unsuitable for the currently available devices.

Most natural history studies of atrial septal defects preceded the modern echo era and generally included patients who were symptomatic and had larger defects. With the routine use of transesophageal echo, smaller defects are more likely to be identified in asymptomatic patients, and it is not known whether the presence of such smaller ASDs is associated with any additional morbidity.

Standard of care supports closure of an ASD in patients of any age with dilated right-side cardiac chambers and a significant left-to-right shunt. Particular expertise in assessing hemodynamics with and without temporary defect closure may be important in patients with associated pulmonary hypertension10; when pulmonary vascular resistance is particularly elevated, the sustenance of an atrial level shunt may actually improve survival, analogous to patients with idiopathic pulmonary arterial hypertension who have either native atrial defects or catheter-created defects.11 Many such patients with higher pulmonary vascular resistance have some degree of right-to-left shunting at the atrial level with associated cyanosis, owing to RV dysfunction; closing the atrial septal defect eliminates the “pop-off” route for unloading the right heart. By forcing all systemic venous return through the RV and into the high-resistance pulmonary arteriolar bed, the RV may fail more rapidly than if the ASD had been left alone. In the patient discussed above, RV systolic pressures were less than one-half of systemic levels in the setting of a large left-to-right shunt, making the patient suitable for closure despite elevation of PA pressure.

On occasion, an ASD with left-to-right shunting will be newly discovered in a patient with left ventricular (LV) myocardial dysfunction presenting with progressive systolic or diastolic congestive heart failure. It may be difficult to
determine, noninvasively, whether the LV myocardial disease or the left-to-right shunt is primarily responsible for the patient's symptoms. As in the case of the patient with pulmonary hypertension, the ASD in these circumstances may allow a "pop-off," decompressing the left atrium and permitting sharing of diastolic properties between the right and left cardiac chambers. In such a patient, the interventionalist may perform a test occlusion of the ASD with a balloon-sizing catheter (with a second catheter through the defect into the LA). If the LA pressure remains within a relatively normal physiologic range (mean <20 to 25 mmHg), and if there are no symptoms of pulmonary edema, some interventionalists may choose to close such defects. Typically such patients appear to return to baseline LA pressures within a few days after closure. If mean LA pressure rises acutely with balloon occlusion to >25 to 35 mmHg, pulmonary venous congestion, acute pulmonary edema, and systemic desaturation may occur, indicating that the LV may be too compromised in its current state to allow ASD closure (Figure 45.19); most congenital cardiologists will further optimize loading conditions outside of the catheterization laboratory, and consider bringing the patient back at a future time for repeat hemodynamic assessment.

After transcatheter ASD closure, all previously symptomatic patients tend to notice improvement in exercise tolerance. Objective measures of exercise capacity have corroborated these clinical observations, though in uncontrolled trials. Transcatheter closure of atrial septal defects is now an established therapy within the mainstream of interventional cardiology for congenital heart disease and is an excellent alternative to open heart surgery in most of the affected persons.

**POST-MYOCARDIAL INFARCTION VENTRICULAR SEPTAL RUPTURE SHUNT REDUCTION**

**CASE 45.4** A 72-year-old man, s/p prior CABG, with diabetes, a single kidney with renal failure, hypertension, and hypercholesterolemia, presented 72 hours after first onset of chest pain, with pulmonary edema and cardiogenic shock, requiring mechanical ventilation and circulatory support. A harsh systolic murmur prompted echocardiography, which demonstrated mildly reduced global LV systolic function, with a posteroinferior ventricular septal rupture.

Cardiac catheterization was performed, and an intra-aortic balloon pump was inserted. Oximetric measurement revealed a superior vena cava (SVC) saturation of 57%, PA saturation of 88%, aortic saturation of 98%, and Qp/Qs >3, with a systemic cardiac index of 1.5 L/minute/m². Coronary angiography and assessment of coronary grafts revealed only a mid-obtuse marginal-branch subtotal occlusion, which, after joint discussion between the medical and surgical teams, was revascularized with stent implantation. Given his medical comorbidities, the decision was made to pursue a percutaneous approach to ventricular septal rupture closure.

After trans-septal puncture from a right femoral venous approach, a balloon end-hole catheter was passed from LA to LV and guided through the ventricular septal rupture to the RV and PA, where a 280-cm guidewire was inserted to maintain this position. The guidewire was snared via a catheter placed from the ipsilateral femoral vein and retrieved out through the second sheath, to create an "arteriovenous" guidewire loop through the ruptured septum (Figure 45.20).

Localized angiography within the ruptured segment was performed using a side-hole angiographic catheter advanced over the guidewire (Figure 45.21). The ruptured segment was estimated to have a minimal diameter of 25 mm, and a 38-mm CardioSEAL occlusion device (NMT Medical, Boston, MA) was chosen for implantation via a 12F delivery system. A long sheath was placed from a venous approach, in this case using the trans-septal access from RA to LA to LV to RV, to allow passage of the device-delivery system to the sheath tip and subsequent complete expansion of the distal device arms within the RV. With traction on the expanded RV occluder, the device conformed to the septal and apical surfaces within the RV (Figure 45.22). (Another approach that has been used in posterior-inferior ventricular septal defect (VSD) closure is retrograde placement of a balloon flotation...
catheter in the LV, passage across the VSD, with snaring of the guidewire from an internal jugular puncture.) The device was centered within the ruptured segment, and proximal arms were allowed to expand on the LV side of the rupture (Figure 45.23). Appropriate positioning was confirmed via fluoroscopy; the device was released and demonstrated stable positioning, with reduction of shunt flow (Figure 45.24).

Oximetry performed immediately postimplantation revealed SVC saturation of 68%, PA saturation of 78%, and aortic saturation of 98%; Qp/Qs was 1.5, with improved systemic cardiac index. Intra-aortic balloon counterpulsation was continued for 36 hours and subsequently discontinued, as was mechanical ventilation. The patient returned home on day 7 posthospitalization and remained with functional class II symptoms 1 year after presentation. Minimal shunting is still visualized by echocardiography, with mildly reduced global LV systolic function.
Deployment of CardioSEAL proximal device arms, fully expanded and conforming with septal and apical right ventricular surfaces, within the ruptured segment.

Discussion

Despite advances in the management of acute coronary syndromes, rupture of the interventricular septum remains one of the most threatening mechanical complications of myocardial infarction. Surgical strategies emphasizing total exclusion of infarcted regions of the ventricular septum and closure of the defect carry very high risk. Based on the experience with percutaneous closure of congenital VSDs in the late 1980s and early 1990s, the following steps for successful VSD closure have been suggested: (1) use of left ventricular approach to intubate the defect (to ensure positioning through the widest aspect of the passage); (2) use of the trans-septal approach to the left ventricle to decrease intraprocedural, catheter-induced, aortic regurgitation, and allowing for either transvenous or transarterial device delivery, as appropriate by defect location; (3) use of local contrast injection angiography within the defect; (4) ensuring maintenance of position with secure extra-long stiff wires to best enable delivery system and device passage to, and within, the defect. Double-umbrella devices appear adequate for the closure of muscular VSDs given their ability to (1) have differing conformations (flattening against the interventricular septum or remaining partially expanded, to provide for best defect occlusion), (2) be applied from either an RV or an LV approach, to allow for safest and most secure device deployment, and (3) be retrieved or repositioned with relative ease and safety.

Closure of post-myocardial infarction ventricular septal ruptures throws up more challenges in addition to those seen with congenital muscular VSD closure. The defects are typically complex tears through the necrotic septum, with poorly aligned entry and exit sites on LV and RV surfaces. Continuing necrosis and scar retraction lead to defect expansion over the first days or weeks. Our experience with transcatheter ventricular septal rupture closure with double-umbrella devices highlights technical feasibility in nearly all patients. However, device evolution, to allow larger device sizes and the ability to auto-adjust to defect expansion over the first few weeks after implantation, is necessary to bestow the potential for longer-term success in acutely ruptured segments. Increasing experience with this technique is expected to extend its application from a presently limited number of centers and to allow more rigorous comparison of its safety and efficacy to that of currently practiced surgical therapies.

PATENT DUCTUS ARTERIOSUS

A 3-year-old asymptomatic child presented with a soft continuous murmur that was not previously appreciated. Transthoracic echo imaging with Doppler color flow mapping demonstrated a patent ductus arteriosus (PDA), with a continuous high-velocity flow jet entering the MPA adjacent to the bifurcation of the branch PAs (Figure 45.25).

The patient was taken to the cardiac catheterization laboratory, where femoral arterial and femoral venous sheaths were placed under intravenous sedation. The patient had normal right-side pressures. There was a slight widening in the aortic pulse pressure (aorta, 90/45), consistent with the diastolic runoff of the flow from the aorta into the pulmonary artery (with
physiology similar to that seen in patients with aortic regurgitation). The calculated Qp/Qs ratio was erroneously estimated as 2.1, recognizing that with the current standards of practice in the catheterization laboratory, it is impossible to accurately measure pulmonary blood flow in the presence of a PDA (as there is no location distal enough from the shunt source to obtain a truly representative sample). An aortic angiogram was obtained in anteroposterior (AP) and lateral projections (Figure 45.26), revealing a PDA with a wide aortic ampulla and a funnel shape with a 3-mm minimum dimension at its MPA end. Based on these images, an Amplatzer Duct Occluder (AGA Medical, Minneapolis, MN; Figure 45.27), with PA end of the device exceeding the MPA dimension of the PDA by 2 to 3 mm, was chosen for implantation.

A multipurpose catheter was manipulated to the MPA from the femoral vein, and a floppy-tipped torque wire (0.035-inch) was advanced through the PDA into the descending aorta. A delivery sheath was advanced from the femoral vein over the wire into the descending aorta. The device was loaded into the sheath and was advanced out through the end of the sheath, opening only the retention disk in the aorta. The sheath was then withdrawn until the disk lodged firmly against the aortic ampulla of the PDA (Figure 45.28). As traction was maintained against the aortic ampulla, the delivery sheath was slowly withdrawn, which allowed the body of the device to open within the funnel of the PDA (Figure 45.29). As it is quite common in patients with larger PDAs, there was a small residual shunt, through the mesh of the device, immediately after implantation. Within 10 to 15 minutes, all flow had stopped, confirming complete PDA closure (Figure 45.30). The patient was discharged home 5 hours later.
Discussion

Patent ductus arteriosus can be discovered at any age, and may present with significant congestive heart failure in infants (especially premature infants), in whom surgical intervention may be generally preferable. In older children with small ductus (<2 mm in diameter), coil embolization remains the preferable closure method. For PDAs of >2.0 mm, the Amplatzer Duct Occluder is being used with increasing frequency.

Adults with previously undiagnosed PDA may manifest increasing symptoms as they age, as diastolic runoff into the pulmonary artery reduces aortic diastolic pressure and coronary perfusion. Therefore, similar to patients with severe aortic regurgitation, patients with moderate or larger PDA may present with angina even in the setting of nonobstructive coronary artery disease. Alternatively, patients who have had small shunts for many decades may become symptomatic as aortic impedance increases and left ventricular compliance decreases as part of the normal aging process, worsening the shunt and elevating LA pressure. Risk of infective endocarditis is the principal touted reason for closing a PDA in children; it remains unclear if such risk is substantive, or lessened by PDA closure, in adults. Current adult care guidelines, therefore, do not support closure of small PDA in the asymptomatic adult.

CORONARY ARTERIOVENOUS FISTULA

CASE 45.6 A 47-year-old premenopausal woman without atherosclerotic risk factors presented with episodic mid-chest pain, atypical for angina. Since childhood, symptoms had occurred in a non-uniform fashion both at rest and with
extreme exertion. A continuous murmur along the right sternal border had been noted since birth, but the patient had been active in high school and collegiate sports and had carried two uncomplicated pregnancies to term. A recent change in primary care provider had led to an evaluation with cardiac echo, which found increased right- and left-side chamber dimensions, as well as an abnormal velocity jet in the right atrium, near the ostium of the coronary sinus, and an excluded septal defect and patent ductus arteriosus. Nuclear exercise scintigraphy was remarkable for resting hypoperfusion in the anteroapical and inferior distributions of the left ventricle, without redistribution at rest.

Left and right heart catheterization was performed. Intracardiac and arterial pressures were normal, but oximetry showed an SVC saturation of 75%, with a step-up to 85% in the RA, RV, and both PAs. The calculated Qp/Qs was 1.7. Selective left coronary angiography demonstrated a normal left coronary artery without obstruction. However, it was difficult to fully opacify the dominant right coronary system. Nonselective ascending aortography showed a markedly dilated right coronary artery, with the presence of an arteriovenous fistula originating in the distal coronary and emptying into the coronary sinus (Figure 45.31). The distal RCA vasculature was again not well seen. The right coronary artery was engaged with a guiding catheter, through which a 5-F thin-walled steerable catheter was advanced into the distal vessel over a soft-tipped steerable guidewire. Angiography of the distal coronary artery showed a region of relative stenosis of the fistula near the ostium of the coronary sinus (Figure 45.32), with evidence of membranous obstruction at that site.

Nonselective aortography, demonstrating right coronary artery arteriovenous fistula, emptying into the coronary sinus (arrow).

Angiography within the dilated right coronary arteriovenous fistula, showing a region of non-opacification near the ostium of the coronary sinus (arrow), suggesting a membranous obstruction.

A steel vascular occlusion coil, chosen to be 1 mm larger than the size of the dilated arteriovenous fistula at the site of the presumed membranous obstruction, was extruded through the catheter positioned at the site, and angiography confirmed its stable position (Figure 45.33). Subsequent coronary angiography distally revealed closure of the defect, and visualization of the small RCA vessels was possible for the first time during the procedure (Figure 45.34). Proximal right
Opacification of the distal right coronary arterial branches is noted immediately on occlusion of the arteriovenous fistula.

Coronary arterial injection confirmed occlusion of the arteriovenous fistula, with normal filling of the distal right coronary arterial branches (Figure 45.35). No residual oximetric shunt was detectable. Postprocedure nuclear scintigraphy revealed normal rest and exercise perfusion, though occasional atypical chest pain continued to occur.

Discussion

Coronary arteriovenous fistulae may occur from either congenital or acquired causes, with passage of blood from the coronary arterial tree to any cardiac chamber, pulmonary artery, or systemic or pulmonary vein, competing with perfusion of the distal myocardial capillary tree (see Chapters 15 and 16).

Though highly variable in structure, fistulae are typically thin-walled, dilated, and follow a serpiginous course. Most have a single drainage site in the right heart, though multiple exit sites are also seen. Left-to-right shunting occurs from the aortic level to the right heart, resulting in biventricular volume loading, although most smaller fistulae do not produce measurable shunts (a fistula flow of 100 to 200 mL/minute is large as compared with coronary flow to the myocardium, but small as compared with the cardiac output of 4 to 5 L).

Symptomatic patients typically complain of dyspnea and less often of myocardial ischemia, though the presence and nature of symptoms have not been correlated with size of the shunt or fistula, or the drainage site. Symptoms of left atrial hypertension (dyspnea, development of atrial fibrillation) owing to high-volume shunting have been reported. Less symptomatic patients have long-term survival similar to unaffected individuals. Fistula repair may be indicated in the setting of documented ischemic or shunt-related symptoms, but surgical repair may be difficult owing to the typically distal and serpiginous nature of such fistulae (making exit sites difficult to identify and reach) in affected older patients. Transcatheter approach to coronary arteriovenous fistula closure allows accurate definition of fistula origin, potential for temporary fistula occlusion (with a balloon end-hole catheter) to allow angiography of distal vasculature, and closure of the fistula via an endovascular approach with a variety of occlusion devices.20 Although technically feasible, transcatheter closure of coronary artery fistulae is associated with long-term cardiac complications, including myocardial infarction, coronary thrombosis, and cardiomyopathy.21 Such complications seem to be more common for fistulae draining into coronary sinus, and in these cases, strategies including long-term anticoagulation should be considered.

Failing Right Ventricular Outflow Tract in Complex Congenital Heart Disease

CASE 45.7 A 38-year-old woman presented with increasing shortness of breath on exertion and brief episodes of palpitations. She had history of double-outlet right ventricle with ventricular septal defect, transposed great arteries, and pulmonary stenosis. She initially underwent creation of a Waterston shunt (a direct communication between the ascending aorta and the RPA) to improve pulmonary blood flow and promote systemic oxygen delivery, at a few months of age. Complete repair was performed at 9 years of age. This procedure included creation of a baffle between the left ventricle and the aorta via the ventricular septal defect (which was closed allowing the left ventricle to be in continuity with the transposed aorta), ligation of the native PA, and placement of a 20-mm Hancock valved conduit between the RV and the MPA.
At the time of the previous clinical evaluation a right ventricular heave was noted. A loud systolic murmur was best appreciated at the left upper sternal border, with posterior radiation; a harsh holodiastolic murmur was also present at the same location. Echocardiogram was performed, yielding only limited information owing to poor acoustic windows. The left ventricular size and function were normal. There was a dilated ascending aorta. The right ventricle, right ventricular outflow tract, Hancock valved conduit, and branch pulmonary arteries were not seen.

CMR was performed. There was a diffusely small (1.4 × 2.0 cm) conduit from the right ventricle to the pulmonary artery with flow acceleration in the proximal conduit. The conduit was located directly posterior to the sternum and close to the anterior chest wall. Right and left PAs appeared unobstructed and had balanced pulmonary blood flow. Moderate conduit regurgitation was present with a regurgitant fraction of 30%. The right ventricle was of normal size (indexed end-diastolic volume of 93 mL/m², Z = 1.3) and function (ejection fraction 60%). The ventricular septal configuration was consistent with a right ventricular systolic pressure at least half of the left ventricular pressure. The left ventricle was normal in size, with borderline depressed systolic function (ejection fraction 50%). The left ventricle-to-aortic valve pathway was unobstructed.

Nonsustained ventricular tachycardia was detected in two separate Holter monitor examinations.

 Catheterization was performed under general anesthesia. A 6F short sheath was placed in the right femoral artery; in consideration of documented bilateral femoral venous occlusions, ultrasound-guided access to right internal jugular vein (7F) was established.

An end-hole, balloon-tipped catheter was advanced through the right internal jugular vein. Intracardiac manipulation was improved by using a 0.035-inch torque wire. Simultaneously, a pigtail catheter was placed in the ascending aorta. Baseline hemodynamic assessment noted elevated right-side filling pressure with a mean RA pressure of 14 mmHg; the RV systolic pressure was 75 mmHg, with an elevated end-diastolic pressure of 14 mmHg. Simultaneous aortic pressure was 90/60 (70) mmHg. MPA pressure was 30/10 (13) mmHg. Pullback from the MPA revealed multiple levels of obstruction with a 20-mmHg peak pressure gradient at the level of the distal conduit, 10 mmHg in the middle segment of the conduit (at the level of the prosthetic valve), and 15 mmHg at the level of the anastomosis between the right ventricle and the conduit itself. The pulmonary capillary wedge pressure was 10 mmHg. Using Fick-based estimation of flow, systemic cardiac index was calculated as 2.4 L/minute/m²; calculated Qp/Qs was 1.

Localized angiography in the right ventricular outflow tract was performed through a large 12F guide sheath, confirming obstruction of the surgically implanted Hancock conduit. Minimal diameter of the conduit (lateral projection) was 14 mm, with posterior evidence of a remnant of a main pulmonary artery segment; several sites of additional obstruction were noted along the entire outflow tract. Simultaneous aortic root and conduit angiograms were performed demonstrating a close, but noncontiguous, relationship between the left main coronary artery and the conduit.

A stiffer exchange-length wire was advanced to the RPA through the end-hole catheter. An 18 mm × 4 cm ATLAS balloon was advanced over this wire to the level of the proximal conduit, and selective left main coronary artery angiography was performed during balloon inflation within the Hancock valved conduit; no coronary compression was detected. A waist was observed in the dilation balloon both distal and proximal to the primary site of narrowing. Multiple balloon dilations (using a 20 mm × 4 cm ATLAS balloon) were able to relieve the residual balloon waists at the additional sites of obstruction.

A Palmaz 40 XL stent was mounted over a 20-mm Cordis balloon. Both (stent and balloon) were advanced over the wire through the 12F sheath, and the stent was implanted in the distal conduit. A second Palmaz 40 XL stent was then implanted partially overlapping the first, at a more proximal location, removing all obstruction within the conduit; on repeat assessments there was no evidence of coronary artery compression by the conduit or stents.

Decision was made to complete transcatheter valve implantation in the dysfunctional conduit using the two Palmaz stents as a “landing zone.” A Melody valve (Medtronic Inc., MN, USA) was crimped over a deflated transcatheter delivery system, which consisted of a balloon-in-balloon catheter housed in a polytetrafluoroethylene sheath coverage to protect the valve during deployment. After the retrieval of the 12F venous sheath over the extra-stiff wire, the delivery system was inserted free of guiding sheath in the right internal jugular vein and advanced to the level of the Hancock valved conduit. Multiple angiographic views, including posterior-anterior projection with cranial angulation and lateral projection aiming at long-axis view of the right ventricular outflow tract, were used to confirm proper placement of the valve within the conduit. Valve deployment was completed with inflating the balloon-in-balloon deployment catheter to the nominal diameter of 22 mm. Pulmonary angiography performed after valve deployment confirmed proper valve function with optimal stent apposition, without paravalvular or valvar regurgitation. Hemodynamic evaluation at the end of the procedure demonstrated normal right-side filling pressure (mean right atrial pressure of 8 mmHg) and a right ventricular systolic pressure of 40 mmHg (simultaneous aortic pressure was 100/70 (85) mmHg) with a right ventricular end-diastolic pressure of 8 mmHg.

Discussion

Right ventricular outflow reconstruction is increasingly being performed in patients with complex congenital heart diseases, including conotruncal malformation (such as tetralogy of Fallot, transposition of the great arteries with pulmonary stenosis,
or double outlet right ventricle), congenital left ventricular outflow tract obstruction, and pulmonary atresia with intact ventricular septum. Progressive dysfunction of the surgically reconstructed right ventricular outflow tract, with either regurgitation or obstruction, almost invariably develops over time. In patients who have undergone right ventricle to pulmonary artery conduit implantation to reconstruct the right ventricular outflow tract, transcatheter replacement of pulmonary valve has emerged as a potential alternative in order to prolong conduit survival and postpone reoperation. Initially, Bonhoeffer and colleagues reported in 2000 that percutaneous implantation of a bovine jugular venous valve, mounted on a vascular platinum stent implanted in an RV-to-PA conduit, was feasible and effective in restoring conduit function, eliminating pulmonary regurgitation and reducing stenosis. This technique has been subsequently modified, and the successor of that valve, the Melody transcatheter pulmonary valve (Medtronic Inc., MN, USA) mounted on a balloon-in-balloon implantation system, has been available in Europe and in Canada for several years and has been recently approved for compassionate use by the FDA in the United States (see Chapter 35). A regulatory US clinical trial showed that this procedure can be performed safely by experienced operators at multiple centers with encouraging acute and short-term outcomes, utilizing predefined entry criteria and standardized implantation and follow-up protocols. In the presence of dysfunctional right ventricle to pulmonary artery conduits, additional criteria for Melody valve implantation include original conduit diameter of at least 16 mm (maximum available diameter for Melody valve is 22 mm) as well as presence, during catheterization, of a waist on the dilatation balloon, between 14 and 20 mm, during low-pressure dilation. Patients were excluded from participation in the presence of active endocarditis, major progressive noncardiac disease, or vascular access obstruction/occlusion, or if felt to be at increased risk for active intravenous drug abuse.

Melody valve implantation is typically performed under general anesthesia using right femoral venous access (though internal jugular and subclavian vein access sites have been utilized on occasion). Patients with demonstrated coronary compression during conduit dilation are routinely excluded from implantation. Predilation of the conduit is generally performed to better assess conduit compliance, as well as location and nature of additional sites of obstruction if any. Low-pressure conduit dilation (<8 atm) is generally performed with an angioplasty balloon with a diameter >2 mm larger than the narrowest diameter of the conduit, up to approximately 110% the original conduit diameter. Prestenting of the conduit with a bare metal stent, prior to Melody valve implantation, potentially allows for a more defined “landing zone,” and may relieve some of the stress and strain of conduit recoil from the Melody stent frame. Transcatheter implantation of a Melody valve for RV-to-PA conduit failure has been reported to be effective in eliminating pulmonary regurgitation and significantly reducing conduit stenosis in the great majority of treated patients. High success rates have been reported (85% to 98%). After Melody valve implantation, progressive reduction in right ventricular size and improvement in right ventricular function and stroke volume have been reported.

Complications of Melody valve implantation include conduit dissection or rupture, as well as residual stenosis owing either to lack of conduit compliance or to external compression. Stent fracture has been reported in 16% to 28% of patients, using varied deployment strategies; prestoning of the Melody valve “landing zone,” as described in the present case, may reduce the incidence of such occurrences. In some patients, residual obstruction has been treated either by surgical approach or via stenting of the previously implanted Melody valve with implantation of a second Melody valve. Overall, early (procedure-related) complication has been reported in 5% to 9% of procedures, with no reported deaths associated with Melody valve implantation.

REFERENCES


Early reperfusion therapy for acute stroke, similar to that for acute myocardial infarction, offers the best opportunity to reduce the significant morbidity and mortality. Treatment options include intravenous (IV) thrombolysis therapy and/or catheter-based therapy (CBT). Catheter-based therapies include local, intra-arterial administration of thrombolytic agents, mechanical thrombectomy, and percutaneous transluminal angioplasty (PTA) and stent techniques.

Fewer than 2% of acute stroke patients receive any form of reperfusion therapy, and sadly, little is being done to remedy this problem.1 Acute ischemic stroke is a leading cause of death and disability that will affect three-quarters of a million Americans this year.2,3 The therapeutic goal of acute stroke therapy, as with acute myocardial infarction (AMI) therapy, is early reperfusion to minimize end-organ damage. Frustratingly, even among the select centers participating in the Get With The Guidelines-Stroke (GWTG-Stroke) registry, fewer than one-third meet the goal of “door to needle time” of 60 minutes.4

While the national quality mandate for a 90 minute door-to-balloon time (D2B) has revolutionized AMI care,5 there are few hospitals offering “on-demand” catheter-based stroke therapy. Despite the fact that many acute stroke patients present too late (>3 to 4.5 hours) or are poor candidates for IV thrombolysis, many remain eligible for catheter-based reperfusion therapy.6,8

The nationwide shortage of interventional neuroradiologists is a significant barrier to providing on-demand stroke reperfusion treatment.9 One solution would be to expand the pool of stroke interventionalists by recruiting carotid artery stent (CAS)-capable physicians, that is, cardiologists, radiologists, vascular surgeons, and neurosurgeons, to join stroke teams.6,8,10,11 CAS-capable interventionalists, neurointerventionalists, and neurologists should be working together to build stroke teams.7,8,10,12

Ten years ago, the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Study Group’s randomized trial compared intravenous thrombolysis to placebo therapy in patients presenting within 3 hours of stroke onset and demonstrated a statistically significant but clinically modest benefit for this relatively small subset of acute stroke patients.13 The NINDS trial found no difference between the two groups’ neurological outcomes at 24 hours, but there was a tenfold higher (6.4% rt-PA versus 0.6% placebo, P < 0.001) risk of intracranial bleeding with lysis in the rt-PA group. At the 3-month follow-up, a higher percentage of lytic patients (34% lytic versus 21% placebo, P < 0.05) had achieved full recovery. Unfortunately, there was no difference in mortality between the groups. Ten years after the pivotal trial and despite the fact that IV thrombolysis is the only approved therapy for acute ischemic stroke, no more than 2% of ischemic stroke patients actually receive this treatment.1,14

Catheter-based therapy for stroke, like intravenous thrombolysis, is not without risks. Intracranial hemorrhage (symptomatic and asymptomatic) rates of 10% to 35% have been reported.15-17 Unfortunately, most clinical trials enroll relatively small numbers of patients, providing a small data set upon which to base clinical decision-making. The lack of large clinical trials of acute ischemic stroke treated with CBT makes it difficult to establish guidelines for the “optimal” therapy for stroke.
A 79-year-old male was electively admitted with recurrent ventricular tachycardia for an electrophysiologically guided ablation procedure. He had past medical history of nonischemic cardiomyopathy with ejection fraction of 40%, chronic atrial fibrillation, and hypertension. His medications included amiodarone, lisinopril, metoprolol, and warfarin; warfarin had been discontinued 4 days prior to admission.

The day following his ablation procedure, he developed sudden onset of a left middle cerebral artery (MCA) stroke, manifested by right-sided weakness and aphasia. An emergency computerized tomographic (CT) scan of the brain was negative for hemorrhage. His physical examination revealed dense right hemiplegia and expressive aphasia with a score of 14 on the National Institutes of Health Stroke Scale (NIHSS; severe impairment).

Within 40 minutes of symptom onset, he was brought to the catheterization laboratory where selective cervical-cerebral angiography was performed from a femoral artery access site. Cerebral angiography demonstrated a large filling defect, consistent with an embolus, in the M2 segment of the left MCA with diminished distal flow (Figure 46.1). The Merci® Retrieval System (Concentric Medical, Mountain View, CA) shown in Figure 46.2 was advanced to engage the embolus (Figure 46.3). The embolus was successfully retrieved, and final angiography revealed a widely patent vessel (Figure 46.4).

The patient immediately began to recover movement of his right arm and leg while on the catheterization table. By the following morning, his speech had normalized. At the time of discharge, 3 days later, his NIHSS score was 3 (minor impairment) with mild weakness of the right arm and leg.

**CASE 46.2** A 56-year-old woman presented to an outside hospital’s emergency department 1 hour following sudden onset of right-sided weakness and inability to speak. Six months earlier she had undergone successful mechanical mitral valve replacement. Her chronic anticoagulation with warfarin had been discontinued 5 days prior to presentation owing to uterine bleeding.

Her examination was consistent with an acute left MCA stroke. An emergency CT scan showed no intracerebral hemorrhage, and intravenous thrombolysis with 75 mg of tissue plasminogen activator (Alteplase, Genentech, South San Francisco, CA) was initiated. One hour after receiving intravenous thrombolysis she had failed to improve. She was transferred to Ochsner 220 minutes after symptom onset and 150 minutes after receiving full-dose intravenous thrombolysis. She had persistent right hemiplegia, expressive aphasia, and an NIHSS score of 17 (severe impairment).

Emergency cervical-cerebral angiography from the right femoral artery access site revealed occlusion of the superior branch of the MCA at the M1 bifurcation and a subtotal occlusion of the inferior branch (Figure 46.5). A 6F coronary JR-4 guiding catheter (Cordis, Miami Lakes, FL) was placed in the internal carotid artery, and a 0.014 inch coronary angioplasty guidewire (Choice PT, Boston Scientific Corp, Waterville, MA) was advanced across the occluded superior branch of M1. Next, a Merci® delivery microcatheter was advanced distal to the occlusion, and a contrast injection confirmed that the microcatheter was in the vascular lumen (Figure 46.6). Contrast injections through the proximal guiding catheter confirmed that the microcatheter and guidewire passage had disrupted the thrombus and restored antegrade flow in this branch of the MCA. Next, the 0.014 inch guidewire was placed into the inferior limb of M1, and (similar to the superior limb) mechanical disruption of the clot successfully recanalized the vessel obviating the need for mechanical thrombectomy. Final angiography confirmed the patency of both the superior and the inferior limbs of M1 (Figure 46.7).

By the following morning, the patient had significant improvement in her right-side extremity strength, with both upper and lower limbs demonstrating 4/5 strength. She had mild dysarthria but was able to speak. Her NIHSS score had improved to 8 (moderate impairment). Following a course of inpatient rehabilitation she was discharged, and she returned to independent living.

**Illustrative Points**

Both patients presented with profound neurologic deficits likely to result in severe disability, and both were dramatically improved after CBT reperfusion therapy. Common features associated with stroke lesions include a large clot burden,
organized thrombus, or embolization of atherothrombotic material that may render these intracerebral occlusions less responsive to thrombolysis than acute thrombi associated with myocardial infarction.

It is important to recognize the similarities and understand the fundamental differences between ischemic stroke and heart attack. Both represent ischemic events, but heart attack is usually the result of plaque rupture and in-situ thrombosis, whereas ischemic strokes more often result from atherothrombotic embolism.¹⁹ The treatment goal for both is safe and rapid reperfusion in order to restore blood flow to the ischemic tissue.

Our second case involved CBT as “rescue” therapy after failure to respond to intravenous thrombolytic therapy. Despite her early presentation, lytic therapy was not successful. Data from NINDS suggest that thrombolytic failure is not infrequent²⁰ and that large vessel occlusions are less likely to recanalize with lytic therapy alone.²¹,²² Catheter-based therapy with adjunctive mechanical thrombectomy or mechanical clot disruption with angioplasty techniques offers the potential for successfully opening occlusions resistant to thrombolysis.

CBT has become the treatment of choice for large disabling strokes within 6 hours of onset, in patients who are not candidates for IV thrombolytic therapy. With proper patient selection and technique, the outcome of CBT patients who are not candidates for lysis can be as good as that of patients who receive lysis. Recent data has suggested that CBT for large-vessel strokes can be performed by experienced cardiologists working with neurologists and/or neuroradiologists. It is important to remember that the anatomy, pathology, and treatment of acute stroke are different from those of AMI. Intracranial hemorrhage, the most common serious complication of stroke intervention, is usually fatal if it occurs in this setting.
A filling defect is seen at the first MCA bifurcation with occlusion of superior branch and decreased flow in the inferior branch of the bifurcation (arrow).

Microcatheter placed distal to superior MCA bifurcation obstruction confirming the intraluminal position of the catheter and distal patency of the artery (arrow).

Final angiogram after mechanical disruption of the embolus with restoration of normal flow in both superior and inferior branches of the MCA (arrows).

Both cases highlight the magnitude of benefit that can result from CBT in patients with disabling stroke. With the support of a multidisciplinary and cooperative stroke team, qualified physicians can effectively supplement the severe work force shortage of neurointerventionalists.

ELECTIVE INTRACRANIAL ANGIOPLASTY

Approximately 1 in 10 strokes is owing to intracranial atherosclerotic disease, with a higher incidence of the latter seen in Asians and African Americans. The initial treatment for patients with symptomatic >50% intracranial artery stenoses (IAS) is antithrombotic therapy.

The Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial demonstrated that aspirin was the preferred initial therapy over warfarin owing to an increase in adverse events with warfarin. In the WASID trial, 18% of patients had a recurrent stroke within 18 months despite “best” medical therapy, and of these strokes the majority (73%) occurred in the same territory as that of the previous stroke and almost half were disabling. In the Groupe d’Etude des Stenoses Intracranienes Atheromateuses symptomatiques (GESICA) study, symptomatic patients had a 38% risk of a transient ischemic attack (TIA) or stroke at 2 years of follow-up. Surgical extracranial-to-intracranial (EC-IC) bypass failed to reduce the rates of recurrent stroke, and this approach has been abandoned.
Patients with symptomatic IAS on anti-thrombotic therapy have a 2-year risk that ranges from 1:5 to 1:2 for recurrent stroke.26,29,30 Because of these very high recurrent stroke rates despite “best” medical therapy and the failure of surgical options, the use of catheter-based therapies has been explored.21 Early case reports and single-center series have suggested the safety and efficacy of intracranial angioplasty with or without stent placement.12,13,23

The continuous development of smaller, more flexible, and more deliverable interventional equipment has improved our access to intracranial lesions and lessened the technical challenges associated with intracranial CBT. Three stent systems are currently FDA approved for intracranial use: (i) Neuroform (Boston Scientific, Natick, MA), (ii) Wingspan (Boston Scientific, Natick, MA), and (iii) Enterprise (Cordis) Neurovascular/Cordis, Raynham, MA). The periprocedural risks of stroke or death with intracranial CBT have averaged about 10% (116/1,138) across multiple series34-42 with a median of 7.7% reported in a systematic review of 1,177 published procedures.43 A drawback of current stent devices used for IAS is the reported in-stent restenosis (ISR) incidence of 25% to 35%.44

Our experience at the Ochsner Clinic Foundation with CBT in 89 symptomatic patients with 99 (≥70% diameter) IAS treated by interventional cardiologists in cooperation with their neurology and neuroradiology colleagues has demonstrated a procedure success rate of 96/99 (97%) of the lesions and a rate of in-hospital periprocedural stroke and/or death of 3%. Our 1-year (5.7%) and 2-year (13.5%) risk of stroke or vascular death compares very favorably with the results of “best” medical therapy reported in the WASID trial of 15% at 1 year and 20% at 2 years.26

A recent setback for CBT in symptomatic IAS patients was the publication of the Stenting and Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis (SAMMPRIS) clinical trial (gov number NCT00576693). This trial compared intracranial primary stenting performed by neuroradiologists to medical therapy, and was stopped early for safety reasons. After 451 patients underwent randomization, the 30-day rate of stroke or death was 14.7% in the CBT group and 5.8% in the medical-management group45 (P = 0.002). Several significant concerns have been raised about the quality of data in this trial, and perhaps some methodological shortcomings that led to such very high periprocedural complication rates include (i) the choice of self-expanding stents (Wingspan, Boston Scientific, Watertown, MA), (ii) prohibition of poststent dilation, and (iii) a concern over the clinical skills of the operators.46

The natural history of patients with severe symptomatic IAS who have failed antithrombotic therapy is not very encouraging, and the relatively low complication rate for CBT in experienced hands makes it a reasonable alternative. However, the recent publication of the large, randomized SAMMPRIS trial should give us reason to redefine our patient selection criteria, rethink stent placement, reevaluate who performs the procedure and include high-volume coronary interventionalists, and refine the procedural techniques to minimize periprocedural complications.

Ultimately, the decision to proceed with CBT for symptomatic IAS patients requires balancing the procedure risks with the natural history of the disease on a case-by-case basis. Patients at the highest risk for recurrent stroke should be selected by lesion severity, lesion location, and documented failure of antithrombotic therapy. The natural history of such patients suggests that the recurrent stroke rates are high (20 to 55%), especially for restenoses49 (>70%). There is a need for newer, more flexible, self-expanding stents with better coverage and radial force and perhaps a role for drug-coated coronary balloons to improve the outcome of angioplasty in the intracranial circulation.

**CASE 46.3** This 35-year-old woman presented with a 2-month history of left hemispheric stroke manifested by aphasia and right-side weakness. After her stroke, she sustained three more transient episodes of right-side weakness and aphasia, consistent with TIAs in the same distribution. Magnetic resonance imaging (MRI) revealed a stroke in the left MCA distribution, and magnetic resonance angiography (MRA) showed high-grade bilateral stenosis. Her exam was remarkable for expressive aphasia. She was referred by neurology for angiography and treatment.

Four-vessel selective cerebral angiography was performed using a 4F Berenstein catheter. This revealed a critical left MCA stenosis in the most proximal segment (M1; Figure 46.8A) and a normal right MCA (in contradiction to the MRA findings). There were no collaterals from the vertebral artery, indicating an absence of the left posterior communicating artery.

Intervention was performed with a 6F multipurpose coronary guiding catheter placed into the distal extracranial left internal carotid artery (ICA) just below the base of the skull. Using digital subtraction angiography with road mapping, a hydrophilic coronary guidewire (Whisper™ wire) was advanced across the critical stenosis in the left MCA. The lesion was dilated with a 2.0 × 15 mm coronary balloon at 10 atmospheres (atm). Angiography revealed an excellent balloon result, so the guidewire was removed and angiography was repeated. Because of a small dissection at the site of the lesion (Figure 46.8B), we attempted to advance a coronary stent; however, this would not traverse the bony intracranial portion of the ICA and the procedure was terminated. The patient's aphasia improved but did not resolve completely by the morning after the procedure, and she was discharged on ASA and clopidogrel.

**CASE 46.4** This 63-year-old female patient was referred by her neurologist because of recurrent episodes of dizziness, weakness, and diplopia 10 days after suffering a posterior circulation stroke. Her exam was consistent with a cerebellar stroke (unable to stand, diplopia, and weakness). MRI
showed pontine and basal ganglia infarctions with ischemia in the visual cortex. MRA revealed high-grade stenosis of the basilar artery.

After premedication with aspirin and a clopidogrel loading dose of 300 mg, vertebrobasilar angiography was performed with a 6F headhunter catheter, demonstrating critical stenosis of the mid-basilar artery (Figure 46.9) with a stenosis in the V_{3} segment (intracranial portion) of the left vertebral artery.

Intervention was performed with a 6F Soft-tipped (Envoy, Cordis Corp, Miami, FL) guiding catheter and a hydrophilic coronary wire (Choice PT floppy). A Rapid Transit catheter (Cordis) was advanced distal to the lesion over the hydrophilic wire, which was exchanged for a balanced middleweight (BMW, Abbott) coronary guidewire. The basilar artery stenosis was dilated with a 3.0 mm \times 15 mm coronary balloon at 8 atm. Post-PTA angiography demonstrated 20% residual stenosis (Figure 46.9B). Stenting was not performed because of the risk of embolizing or “snow-plowing” atheromatous debris into the pontine branches that arise from the basilar artery at the stenosis. The patient had no subsequent events and remained asymptomatic at 2-year follow-up.

Illustrative Points

Intracranial intervention, both elective and emergency, is a field in its early development where collaboration between neurology, neuroradiology, and cardiology is important. These cases illustrate how patients with recurrent focal symptoms may benefit from angiography and intervention even if the duplex examination shows no cervical carotid stenosis. Lesions of the aorto-ostial common carotid artery and the intracranial carotid or vertebral arteries can be missed by carotid duplex examination.

CTA and MRA may also under- or overestimate the percent diameter stenosis, so invasive digital subtraction angiography remains the gold standard. Stenting is performed in a provisional manner because (i) many intracranial lesions are not stentable with current devices because of tortuosity in the target vessel, and (ii) side-branch occlusion of the small branches, especially of MCA (lenticulostriate arteries) and the basilar artery (pontine perforators), can lead to a major stroke, which may be more likely with stents than with PTA alone.

AORTIC ARCH AND CERVICAL VESSELS

Extracranial Carotid Artery Intervention

The majority of patients with internal carotid atherosclerotic narrowing are asymptomatic. The annual risk of stroke is between 1% and 4.3% for asymptomatic patients with \( \geq 50\% \) stenosis of the carotid artery.\textsuperscript{47,48} If there is plaque ulceration, the risk of stroke, in asymptomatic patients, increases to 7.5% per year. Symptomatic patients have a worse prognosis as compared to asymptomatic patients.
A transient ischemic attack (TIA), defined in the past as a neurologic event lasting <24 hours, predicted a 15% risk of stroke at 1 month and a 30% risk of TIA, stroke or death within 3 months.49·50

Large randomized trials begun in the 1990s demonstrated superiority of carotid endarterectomy (CEA) versus antiplatelet therapy (aspirin) for stroke prevention in both symptomatic and asymptomatic patients.51-54 Symptomatic patients have much more to gain from revascularization than do asymptomatic patients. This places a premium on reducing perioperative stroke and death to less than 3% in asymptomatic patients who are likely to live for 5 years. For symptomatic patients there was greater benefit with increasing severity of the stenosis above 50% diameter stenosis. However, in asymptomatic patients, the benefit was equal for moderate (60% to 79%) or severe (80% to 99%) lesions.55 There is a paradox, however, for very tight lesions, or near-occlusions, defined in the European Carotid Surgery Trial (ECST) as a severe stenosis with evidence of reduced flow in the distal carotid artery and evidence of narrowing of the poststenotic carotid artery. These patients did not benefit from CEA.53·56

Carotid artery stenting with embolic protection devices began with registry trials in the late 1990s in patients considered to be at increased risk for CEA57-65 (Table 46.1). The Stenting and Angioplasty with Protection in Patients at High

![Figure 46.9](image)

**Table 46.1** Features that Increase the Risk of Carotid Endarterectomy (CEA)

<table>
<thead>
<tr>
<th>Anatomic Criteria</th>
<th>Medical Comorbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>High cervical or intrathoracic lesion</td>
<td>Age ≥ 80 y</td>
</tr>
<tr>
<td>Prior radical neck surgery or radiation</td>
<td>Class III/IV congestive heart failure</td>
</tr>
<tr>
<td>Contralateral carotid artery occlusion</td>
<td>Class III/IV angina pectoris</td>
</tr>
<tr>
<td>Prior ipsilateral CEA</td>
<td>Left main coronary disease</td>
</tr>
<tr>
<td>Contralateral laryngeal nerve palsy</td>
<td>Multivessel coronary artery disease</td>
</tr>
<tr>
<td>Tracheostoma</td>
<td>Planned surgery (&lt;30 days)</td>
</tr>
<tr>
<td></td>
<td>LV ejection fraction ≤ 30%</td>
</tr>
<tr>
<td></td>
<td>Recent (≤30 d) myocardial infarction</td>
</tr>
<tr>
<td></td>
<td>Severe lung disease</td>
</tr>
<tr>
<td></td>
<td>Severe renal disease</td>
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</table>
risk for Endarterectomy (SAPPHIRE) trial is the only randomized multicenter trial comparing CEA and CAS in patients at increased risk for surgery. The 1-year primary endpoint for CEA was 20.1% and 12.2% for CAS (ARR 7.9%, 95% CI: 16.4% to 0.7%, \( P = 0.004 \) for noninferiority). Multiple registry trials to obtain FDA approval for CAS systems have shown continued improvement in outcomes with increasing experience (Figure 46.10). Currently, CAS is the preferred therapy for high surgical risk patients who require revascularization to prevent stroke and who have suitable anatomy for CAS (Table 46.2).

Four large randomized controlled trials have recently compared CAS to CEA in usual or average surgical risk patients. Three European trials [SPACE, EVA-3S, and ICSS] enrolled symptomatic patients with inexperienced CAS operators and who had no requirement for embolic protection devices (EPD). The largest randomized trial to compare CEA to CAS was the Carotid Revascularization Endarterectomy and Stenting Trial (CREST), which was based in the United States and Canada. CREST required stent operators to qualify by experience to gain entry into the trial, required that EPDs be used, and enrolled both symptomatic and asymptomatic patients. CREST enrolled 2,502 average surgical risk symptomatic (53%) and asymptomatic (47%) patients. Patients were followed out up to 4 years without any difference in the rates of the primary endpoint between CAS (7.2%) and CEA (6.8%) with a hazard ratio of 1.11 (95% CI: 0.81 to 1.51; \( P = 0.51 \)).

**Table 46.2** Features that Increase the Risk of Carotid Stenting (CAS)

<table>
<thead>
<tr>
<th>Co-Morbidities</th>
<th>Anatomic Features</th>
<th>Procedural Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥80 y</td>
<td>Complex aortic arch</td>
<td>Operator inexperience</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>Tortuosity</td>
<td>No emboli protection device</td>
</tr>
<tr>
<td>Decreased cerebral reserve</td>
<td>Calcification</td>
<td>Time delay from symptom onset</td>
</tr>
<tr>
<td>Hypercoagulable state</td>
<td>Intraluminal thrombus</td>
<td>Open cell stents</td>
</tr>
<tr>
<td>Severe renal disease</td>
<td>Echo lucent plaque</td>
<td>Vascular access difficulty</td>
</tr>
<tr>
<td>Increased bleeding risk</td>
<td></td>
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</tbody>
</table>
was an excess of minor strokes with CAS (4.1%) as compared to CEA (2.3%), but there was no difference in major strokes (CAS 0.9% versus CEA 0.7%). The CEA group had twice as many MIs (2.3%) as compared to CAS (1.1%). Cranial nerve palsy occurred in 4.8% of the CEA patients. There was an age effect with younger patients (<69 years) doing better with CAS and older patients doing better with CEA. The recent multisociety guideline document has endorsed CAS as Level I indication for usual-risk symptomatic patients.71

**CASE 46.5** This 80-year-old woman presented with right hemispheric TIAs manifested by left-sided weakness. She had a history of hyperlipidemia, three-vessel coronary artery disease, a permanent pacemaker, and prior coronary stenting. At the time of evaluation she had stable angina with exertion. Her physical examination was remarkable for a loud right carotid bruit and a normal neurologic exam. A carotid duplex examination revealed 80% to 99% stenosis of the right internal carotid artery (ICA) and 40% to 59% stenosis of the left ICA. Carotid angiography confirmed a severe (90%) right ICA stenosis (Figure 46.11A) and a mild (50%) left ICA stenosis. Vertebral angiography was unremarkable. She was referred for carotid angioplasty and stenting. Because of her age, she was considered as high-risk for CEA, and with a >70% symptomatic stenosis, she met Medicare appropriateness criteria for CAS.

After pretreatment with aspirin (81 mg/day) and clopidogrel (75 mg/day) for at least a week prior to the procedure, she was brought to the catheterization laboratory. Right common femoral access was obtained, and she was administered 5,000 Units of intra-arterial heparin. A 5F Vitek catheter was placed into the innominate artery and advanced over an extra stiff 0.035 inch Glidewire (Terumo) into the right common carotid artery, and then over the Glidewire it was placed into the right external carotid artery. The Glidewire was exchanged for an extra stiff 0.035 inch Amplatz exchange wire, and a 6F Shuttle sheath (Cook) was advanced into the right common carotid artery.

**Figure 46.11**

A. A lateral digital subtraction angiogram of the common carotid artery and its branches demonstrates minor plaquing in the common carotid just before the bifurcation and critical stenosis of the right internal carotid artery 1.0 cm beyond the bifurcation. B. After stenting, there is still 10% to 20% residual stenosis in the internal carotid artery. Aggressive dilating and trying to achieve a perfect result is not recommended because of the risk of distal embolization and stroke.
common carotid artery. Her activated clotting time (ACT) was 275 seconds.

An angiographic roadmap was made using digital subtraction and a 12 inch image intensifier. AP and Lateral views were obtained of the common carotid bifurcation and the right cerebral circulation. The right internal carotid artery lesion was crossed with an AngioGuard distal protection device (Cordis), and the lesion was predilated with a 4.0 × 30 mm balloon. During the inflation, the patient developed transient bradycardia and hypotension, which resolved after balloon deflation. Prior to stent deployment she was pretreated with 1.0 mg of atropine. A 9.0 × 40 mm self-expanding nitinol stent was then deployed across the carotid bifurcation. The stent was postdilated to 8 atm with a 5.0 × 20 mm balloon, and the patient again developed bradycardia and hypotension that required treatment with neosynephrine and 250 mL of saline intravenously. The distal protection device was retrieved, and final angiography was performed, including AP and lateral views of the cerebral circulation. There was <30% residual stenosis at the angioplasty site (Figure 46.11B).

After the procedure, she again developed transient hypotension that responded to volume expansion, atropine, and neosynephrine. Oral midodrine was begun in the recovery room. Her neurological exam was normal; the patient was discharged the next morning and the midodrine was tapered over 4 days. She remained asymptomatic and had no evidence of restenosis at 1 year by carotid duplex examination.

Illustrative Points
For symptomatic (>50%) and asymptomatic (>70% to 80%) carotid stenosis there are seven CAS systems approved for use by the FDA for high surgical risk patients and one CAS system, for usual surgical risk patients. The most recent multisocietal guideline document makes CAS the preferred treatment for selected high surgical risk patients and a Level 1 indication for symptomatic >50% diameter stenosis patients.

Self-expanding stents with embolic protection devices are preferred for the carotid bifurcation because of the risk of crushing associated with balloon expandable stents. These stents can be delivered through either a 6F sheath or an 8F guiding catheter. There seems to be no evidence favoring one type of stent over another—closed-cell versus open-cell or stainless steel versus nitinol. There are no data supporting the use of “tapered” stents over nontapered stents in the carotid artery. The choice of delivery mode depends upon the operator’s preference and the presence or absence of tortuosity in the common carotid artery. The nonkinking 6F sheaths have an outer diameter approximately the same as that of an 8F guiding catheter, so the size of the access site hole is similar for both.

The emergence of proximal protection devices has raised the bar for embolic protection. Comparative studies demonstrate less evidence of cerebral embolism with proximal protection systems as compared to distal filters, but proximal protection systems increase the complexity of the case, while filters are very user friendly.

Unlike in coronary artery stenting, the goal is not a perfect angiographic result after carotid stenting. The main risk of this carotid intervention is distal embolization because of the large plaque burden, so great care is taken not to overdilate the carotid plaque any more than is necessary to achieve a <30% lesion. Many operators will prefer to avoid post-stent balloon expansion if possible. Using a technique of underdilation of self-expanding stents, a target lesion recanalization rate of <5% can be expected.

Hypotension and bradycardia with predilation of the carotid stenosis is a marker for hemodynamic instability with stent placement owing to stimulation of the carotid body. Hypotension occurring hours following carotid stenting may signify access site bleeding. This generally responds to volume expansion, although atropine and alpha agonists such as neosynephrine and midodrine are employed when volume expansion alone is not sufficient.

Vertebral Artery Intervention
Approximately 20% to 25% of ischemic strokes involve the posterior circulation and the vertebralbasilar system. The prognosis for patients with posterior circulation atherosclerotic disease is poor, with occlusion or thrombosis associated with 80% to 100% mortality. Medically refractory, symptomatic vertebral artery disease carries a 5% to 11% incidence of stroke or death at 1 year. Transient ischemic attacks owing to extracranial vertebral disease are associated with a stroke rate of 30% at 5 years.

Revascularization of the vertebral arteries is indicated only for symptomatic patients. Typical symptoms include vertebrobasilar insufficiency (VBI), namely, dizziness, ataxia, visual disturbances, confusion, or coma. When assessing a patient with significant stenosis of a vertebral artery, the interventionalist should always determine the patency of the contralateral vertebral artery, the dominance of the diseased vertebral artery, and the amount of blood supplied to the vertebrobasilar system by the carotid arteries.

Depending upon the location of the stenosis, treatment options for vertebral artery stenosis may include balloon angioplasty with or without stent placement and surgery involving transplantation of the vertebral arteries onto the carotid artery or bypass grafting from the subclavian to the vertebral artery.

Lesions located at the ostium (V0) or proximal (V1), mid (V2), or distal (V3) segments of the vertebral artery can be approached percutaneously. We prefer primary balloon-expandable stent placement for V0 and V1 lesions to scaffold the lesions and minimize elastic recoil. Lesions located more distally may be treated with balloon angioplasty with provisional balloon-expandable or self-expanding stents, depending upon the angiographic results and the tortuosity of the vessel. Lesions at the vertebrobasilar junction (V4) and in the basilar artery have a higher complication rate and are the most prone to dissection, occlusion, and perforation, and stroke.

We have recently reported the largest single-center series of vertebral artery intervention in 105 consecutive
symptomatic patients (112 arteries, 71% male). Technical and clinical success was achieved in 105 (100%) and 95 (90.5%) patients, respectively. One-year follow-up was obtained in 87 (82.9%) patients, of which 69 patients (79.3%) remained symptom-free. At 1 year, six patients (5.7%) had died and five patients (5%) had a posterior circulation stroke. Target vessel revascularization (TVR) occurred in 7.4% at 1 year. At a median follow-up of 29.1 months (IQR 12.8 to 50.9 months), 71.4% were alive, 13.1% underwent TVR, and 70.5% remained symptom-free. Our data demonstrate that vertebral stent placement in symptomatic patients in experienced hands can be accomplished with a very high success rate (100%), with few periprocedural complications, and is associated with durable symptom resolution. We concluded that stenting of atherosclerotic vertebral artery disease is a safe and effective treatment and should be considered first-line therapy for this disease.

**CASE 46.6** A 66-year-old man presented with recurrent episodes of dizziness (vertigo) that was orthostatic and associated with diplopia over a 2-month period. His history was remarkable for hyperlipidemia, systemic atherosclerosis, prior myocardial infarction, coronary artery bypass surgery, carotid stenting, and lower extremity percutaneous intervention. His physical examination revealed a right carotid bruit and a right supraclavicular bruit. His neurologic examination was normal. A color-flow Doppler examination of the carotid and vertebral vessels revealed no significant carotid stenosis and high velocities at the origin of both vertebral arteries consistent with stenosis with antegrade flow. He was referred for aortic arch and four-vessel selective cerebral angiography, and possible intervention.

He was pretreated with clopidogrel (75 mg/day) and aspirin (81 mg/day) for more than a week. Selective vertebral angiography was performed using digital subtraction with a 4F Berenstein catheter, which revealed (i) an 80% stenosis of the right vertebral artery, (ii) a left vertebral artery that ended in posterior inferior cerebellar artery (PICA), and (iii) non-critical carotid artery stenosis. There were no significant intracranial stenoses.

Right vertebral artery intervention was performed after administering 5,000 IU of heparin and by placing a 6F JR-4 coronary guiding catheter into the right subclavian artery. The right vertebral osium was gently engaged and baseline angiography was performed (Figure 46.12A). A 0.014 inch coronary guidewire [Balloon Middle Weight (BMW) Abbott] was advanced across the vertebral artery stenosis and positioned at the base of the skull. The patient’s ACT was 268 seconds. The lesion was primarily stented directly with a 4.0 × 12 mm balloon-expandable coronary stent deployed at 12 atm. Poststent angiography (Figure 46.12B) revealed no residual stenosis or dissection. He was discharged on aspirin (81 mg/day) and clopidogrel (75 mg/day for 30 days). The patient had complete resolution of his symptoms at 1-year follow-up.

**Figure 46.12** A. Selective injection of contrast into the right vertebral artery through a 6F guiding catheter demonstrating ostial stenosis. B. Poststenting, there is excellent filling of the vertebral artery and no residual ostial stenosis.
Illustrative Points

The vertebral arteries arise from the right and left subclavian arteries very near to the internal mammary arteries. They converge to form the basilar artery, which supplies the brainstem (pons, medulla, and midbrain), cerebellum, and posterior cerebral arteries (supplying the visual cortex). The posterior communicating arteries may also supply collaterals to the middle and anterior cerebral arteries in patients with critical carotid artery stenosis.

In order for a patient to have neurologically symptomatic ischemia from vertebral or subclavian stenosis, both vertebral arteries or the basilar artery itself must be involved unless one artery ends before it reaches the basilar, as in this case. Because the diagnosis of posterior circulation ischemia is complex and highly variable, we consult our neurology colleagues for their opinion and support, prior to intervention.

Because the posterior circulation is a dual system, to relieve the vertebral ischemia, only one artery needs to be treated. The surgical treatment of symptomatic vertebral artery stenosis has a high complication and failure rate, requires excision and reimplantation of the vertebral artery, and is feasible only for ostial lesions.

Stenting the vertebral artery can be accomplished from arm (radial/brachial) or femoral access using coronary equipment. We try to obtain nonselective angiograms, without actually engaging the vertebral artery, to avoid trauma to the ostium. We often use 4F or 5F diagnostic catheters to engage the vertebral artery if that becomes necessary. It has not been our practice to routinely use embolic protection systems when stenting vertebral arteries, although there may be reasons to consider doing so.

Subclavian and Innominate Artery Angioplasty

The prevalence of significant subclavian artery stenosis has been found to be approximately 2% in the general population and 7% in patients with risk factors for atherosclerotic disease (one-third had established peripheral vascular disease) in a recent large study. The stenosis is usually located in the proximal portion of the vessel, before the origin of the vertebral and internal mammary arteries and tends to be focal. The left subclavian artery is involved more frequently than the right. Although atherosclerotic disease is by far the most common cause of subclavian artery stenosis, unusual conditions such as Takayasu’s arteritis, fibromuscular dysplasia, giant cell arteritis, radiation-induced occlusive disease, and the thoracic outlet syndrome may affect this vessel and cause significant stenosis. The clinical manifestations of subclavian artery stenosis include upper extremity ischemic symptoms with arm claudication related to exercise or from embolization to the digits. Subclavian steal syndrome occurs as a result of flow reversal in the vertebral artery, leading to symptoms of vertebrobasilar insufficiency. In the coronary-subclavian steal syndrome, there is coronary ischemia owing to reversal of flow in an internal mammary graft as a result of a proximal subclavian stenosis.

Several surgical techniques have been used including carotid-subclavian bypass and axillo-axillary bypass. Since all of them carry significant morbidity and mortality, percutaneous revascularization with stenting has become the standard of care. A comparison of surgical studies and percutaneous trials demonstrated similar outcomes with fewer complications and lower morbidity for PTA.89

We have reported the Ochsner experience of treating 170 patients with primary stent placement in 177 subclavian innominate (S/I A) arteries. The indications for revascularization included arm ischemia (57%), subclavian steal syndrome (37%), coronary-subclavian steal syndrome (21%), and planned coronary bypass surgery with the involved internal mammary artery (8%). We were successful in 98.3% (174/177) arteries; the success rate was 99.4% for stenotic lesions (155/156) and 90.5% for occlusions (19/21). There were no procedure-related deaths but there was one stroke (0.6%, 1/170). Follow-up was done in 151 (89%) patients at 35.2 ± 30.8 months, which revealed a TVR rate of 13% (23/177). Catheter-based revascularization with stents for symptomatic S/I A lesions is safe and effective with excellent patency rates and sustained symptom resolution over 3 years of follow-up. Percutaneous primary stent therapy is the preferred method of revascularization in patients with suitable anatomy.

CASE 46.7 This 66-year-old woman presented with a chief complaint of left arm claudication and aching when she used her left hand. She also complained that when she used her left arm, for example, when washing dishes, the room would “spin around her.” She had a history of hypertension, hyperlipidemia, and diabetes mellitus. Her blood pressure was 180/90 mmHg in the right arm and 130/60 mmHg in the left arm. Her left radial pulse was weak.

Duplex scanning revealed reversal of flow in the left vertebral artery. Angiography of the left subclavian artery revealed 90% stenosis of the left subclavian artery proximal to the left internal mammary artery (Figure 46.13A). The vertebral vessel filled via the right vertebral artery in a retrograde manner.

The patient was brought to the catheterization laboratory on aspirin (81 mg/day), and right common femoral access was obtained with a 6F sheath. After 5,000 IU of heparin was administered, a 4F Judkins R-4 angiographic catheter was engaged in the ostium of the left subclavian artery. The lesion was crossed with a 0.035 inch steerable guidewire (Wholey wire) which was advanced into the axillary artery. The 4F catheter was advanced across the lesion and the soft Whooley wire was exchanged for a 0.035 inch Amplatz extra-stiff exchange-length wire. Next, the angiographic catheter and short arterial sheath were removed and a 6F shuttle sheath was advanced to the proximal left subclavian artery. The ACT was 257 seconds. The systolic translesional gradient was measured to be 50 mmHg. The stenosis was predilated using a 6 × 20 mm balloon. A 6 × 17 mm balloon-expandable stent was then advanced across the lesion and deployed at 12 atm. A second 7 × 17 mm balloon-expandable stent was deployed at the ostium at 16 atm. Final angiography was performed...
A. Critical stenosis in the left subclavian artery which supplies both the left vertebral (underfilled) and left internal mammary arteries as well as supplying the axillary artery. There is ostial disease in the subclavian artery as well. B. After placing tandem balloon-expandable Palmaz stents in the left subclavian artery, there is normalization of flow to the left vertebral and left axillary arteries. The left vertebral artery has a 50% ostial stenosis, which was not treated.

Figure 46.13

The pressure gradient across the lesion was eliminated.

Illustrative Points

There is no indication to treat an asymptomatic subclavian stenosis, unless coronary bypass grafting with an internal mammary artery (IMA) is planned. The presence of retrograde vertebral flow, detected by duplex ultrasound, is not sufficient to make the diagnosis of subclavian steal syndrome in the absence of specific symptoms.

Subclavian artery stenosis can present with arm claudication, critical arm ischemia, embolic disease to the digits, or the subclavian steal syndrome. In patients with prior left IMA-to-coronary artery bypass surgery, angina may be the presenting symptom of significant left subclavian stenosis. Subclavian/innominate stenosis is easily discovered by the simple technique of measuring blood pressure in both arms and noting reduced distal pulses on examination. This patient’s symptoms and examination were consistent with the proximal left subclavian stenosis that was found.

The operator has a choice of access sites (radial/brachial versus femoral) and a choice between a 6F shuttle sheath and an 8F guiding catheter if larger (≥8 mm) stents are to be delivered. For ostial lesions, we prefer guiding catheters to sheaths. Some complex lesions may be more easily approachable from the arm. We have not routinely used embolic protection systems in the vertebral artery to protect the posterior circulation from embolization, but it is something to consider. The same technique is used to perform aorto-ostial stenting of the carotid and innominate arteries. Balloon-expandable stents are preferred in this location because of their ability to be precisely positioned at the ostium without compromise of important side branches, although self-expanding stents are used in non-ostial, more distal, lesions.

Coarctation of the Aorta

Patients with long-standing coarctation of the aorta have an increased risk for development of coronary artery disease, aortic dissection, and pseudo-aneurysm formation. The treatment of native coarctation of the aorta has traditionally been surgical. Although this procedure is effective in relieving the gradient and eliminating the symptoms, the incidence of restenosis and aneurysm formation is not negligible ranging from 5% to as high as 50%. Percutaneous catheter-based procedures have emerged as a feasible alternative to surgical treatment in selected patients. Several studies have shown that balloon angioplasty/stenting can be carried out with a high technical success and a low complication rate. Whether angioplasty/stenting or surgery is the treatment of choice for native coarctation of the aorta remains controversial, but most experts agree that balloon angioplasty is a better treatment option for recurrent coarctation after surgery. The use of stents to minimize the elastic recoil, improve the immediate hemodynamic results, and possibly decrease the recurrence of coarctation has been investigated, even though the experience is limited.

CASE 46.8

This 70-year-old woman presented with severe hypertension despite multiple medications and asymptomatic two-vessel coronary artery disease. Her examination was remarkable for a systolic bruit between her scapulae, a 50 mmHg gradient between her arm and leg blood pressures, and weak but symmetrical pulses in her lower extremities. She was referred for catheter intervention rather than surgery because of her age and concomitant coronary disease. Following femoral artery (6F) and vein (4F) access,
5,000 IU heparin was administered. The coarctation was crossed with a floppy-tipped guidewire and multipurpose catheter. Aortography revealed an 80% stenosis in the aorta just distal to the left subclavian artery with post-stenotic dilatation (Figure 46.14A) and 60 mmHg systolic gradient across the coarctation. Intravascular ultrasound demonstrated the aorta diameter proximal and distal to the coarctation to be 18 and 25 mm, respectively. Using an extra-stiff 0.035 inch guidewire, the multipurpose catheter was exchanged for a long 12F sheath, which was advanced across the coarctation. A transvenous pacemaker was placed in the RV, and asynchronous rapid ventricular pacing was employed at 180 bpm during balloon inflations. This successfully stopped forward flow in the aorta. Using the sheath to protect the stent across the lesion, the coarctation was stented directly with a 12 × 36 mm stent mounted on a 16 × 40 mm balloon (Figure 46.14B). Angiography revealed underdilation of the stenosis with a persistent gradient of 18 mmHg, so a larger 20 × 40 mm balloon was used to postdilate the balloon-expandable stent. Angiography (Figure 46.14C), IVUS, and pressure gradients all confirmed correction of the coarctation.

**Illustrative Points**

Coarctation of the aorta usually presents with hypertension proximal to the coarctation and symptoms related to hypertension. In some patients with long-standing coarctation, congestive heart failure can result in chronic pressure overload. When treating coarctation of the aorta with endovascular techniques, cross-sectional imaging with IVUS or CTA is critical to size the aorta and to avoid overdilation that can lead to serious dissection, rupture, or even death. Typically balloons are sized according to the proximal reference diameter, not the poststenotic dilated segment diameter.

Self-expanding stents tend to migrate into the distal ectatic aorta rather than remain in the narrowed coarctation, so balloon-expandable stents are recommended. The use of rapid ventricular pacing effectively stops the cardiac output for a few moments to allow proper placement of the stent without distal migration during systole. At these very large diameters, considerable shortening of the balloon-expandable stent occurs, so careful positioning is important. Restenotic, post-surgical coarctations are less likely to develop aortic dissection and rupture with balloon angioplasty than are native coarctations.

**Thoracic Aneurysm Repair**

The prevalence of thoracic aneurysms in the United States is difficult to determine because of under-reporting of these aneurysms in mortality statistics. In Sweden, in a stable urban population with an autopsy rate of 83%, the incidence of thoracic aortic aneurysm between 1958 and 1985 was 489 per
100,000 autopsies in 65-year-old men and 670 per 100,000 autopsies in 80-year-olds.\textsuperscript{100}

The prognosis of patients with large thoracic aneurysms left untreated is poor. For untreated aneurysms, rupture is the most common cause of death.\textsuperscript{101,102} Aneurysms larger than 5.5 cm in the ascending aorta and larger than 6.0 cm in the aortic arch or descending aorta should undergo surgical intervention. Because of the high prevalence of cardiovascular disease and the advanced age of this patient population, surgical treatment carries a significant mortality, which can be as high as 12\% when the procedure is performed electively, or as high as 50\% when the procedure is performed emergently. Similarly, stroke and spinal cord injury are frequent complications of surgical treatment.\textsuperscript{101}

Although the experience is still limited, endovascular stent grafts appear to be a promising alternative to surgery for the treatment of thoracic aortic aneurysms in selected patients.\textsuperscript{103-105}

**CASE 46.9** This 58-year-old Hispanic man was referred from South America for treatment of an asymptomatic 6 cm saccular descending thoracic aneurysm (Figure 46.15A). He was treated by endovascular means using a femoral cut down and a self-expanding nitinol endoluminal graft during a procedure that lasted under an hour. Following deployment of the graft, there was still a bulge of graft material into the aneurysm owing to lack of external support for the graft; however, there was no evidence of leaking (Figure 46.15B).

**Illustrative Points**

Although this is a very promising and exciting area for endovascular intervention, nonsurgical treatment of these aneurysms is still in its infancy. Because standard surgical repair carries with it a high morbidity and mortality as stated above, investigators are anxiously awaiting the development of an endovascular solution to this problem. Of note, the most likely cause of this type of saccular aneurysm of the thoracic aorta is infection, especially salmonellosis, not atherosclerosis.

**VIS CERAL AND RENAL INTERVENTION**

**Chronic Mesenteric Ischemia**

Mesenteric artery stenosis is relatively common with a prevalence of 17\% in patients older than 70 years of age.\textsuperscript{106} Despite the prevalence of this condition, chronic mesenteric ischemia is an uncommon cause of chronic abdominal pain with a reported prevalence of approximately 1 case per 100,000 population.\textsuperscript{107} This is because symptoms do not usually occur until at least two of the three mesenteric vessels are compromised. The mesenteric circulation consists of three arteries: the celiac trunk, the superior mesenteric artery (SMA), and the inferior mesenteric artery (IMA). The stomach and upper half of the duodenum compose the foregut and are supplied by the celiac trunk. The lower half of the duodenum, jejunum, ileum, cecum appendix, ascending colon, and proximal two-thirds of the transverse colon compose the midgut and are supplied by the SMA. The lower third of the transverse colon, sigmoid colon, descending colon, rectum, and the upper part of the anal canal compose the hindgut and are supplied by the IMA.

![Figure 46.15](image)
Not only is there significant communication among these three vessels but there is also significant collateral flow to the mesenteric circulation from other aortic branches such as the lumbar intercostal, middle sacral, mammary, and internal iliac (hypogastric) arteries. Because of this, the clinical syndrome of chronic mesenteric ischemia usually develops as a result of critical stenosis or occlusion of at least two of the three vessels, celiac artery, SMA, and IMA. Over 90% of the cases of chronic mesenteric ischemia occur owing to atherosclerosis, usually extensions of aortic atheroma rather than intrinsic disease of the mesenteric branches.

Abdominal pain is the most frequent symptom, with some series reporting this manifestation in up to 100% of the patients. The discomfort is food-related and typically occurs after food is taken, and may eventually result in food fear. Other symptoms include weight loss, diarrhea, nausea, vomiting, and constipation. The abdominal pain is usually postprandial and cramping, localized in the epigastrium or mid abdomen. Over 80% of the patients note the relationship of pain to food intake. A significant percentage of patients may have concomitant coronary or peripheral vascular disease.

The traditional treatment for chronic mesenteric ischemia has been surgical. Because stenosis of the mesenteric branches is frequently focal, limited to the ostium and/or the very proximal portion of the vessel, percutaneous, catheter-based techniques of revascularization have been explored and appear to be a feasible alternative to surgery in selected patients. An analysis of 11 published studies comprising 126 patients treated with balloon angioplasty revealed a mean initial technical success of 86% (range: 38% to 100%). After exclusion of technical failures, the clinical success rate (resolution of symptoms) was 90%. At a follow-up of up to 101 months, the primary and secondary clinical success were 76% and 92%, respectively. Major complications occurred in 6% of patients, and the 30-day mortality was 3%.

Endovascular stenting of the mesenteric branches appears to be safe and effective in selected patients. We recently reported the results of 61 patients with chronic mesenteric ischemia treated with endovascular stent placement, including 81 mesenteric arteries (47 celiac, 24 SMA, 8 IMA, 1 vein graft, and 1 common hepatic artery). Angiographic success (residual stenosis), clinical success (angiographic success without in-hospital death or need for surgery), and symptom relief were obtained in 98%, 97%, and 91% of the patients, respectively. At a mean follow-up of 35 ± 23 months, 11 patients died. Anatomical follow-up was obtained in 88% of the patients with CT angiography, ultrasound, or ultrasound, revealing a restenosis (>50% diameter stenosis) rate of 26% per vessel and 43% per patient; however, only 10 patients (17%) developed recurrence of symptoms and were successfully treated with a second percutaneous intervention. Although experience is still limited, catheter-based techniques of revascularization, such as balloon angioplasty with or without stenting, appear to be a promising alternative to surgical intervention in selected patients with chronic mesenteric ischemia.

CASE 46.10 This 32-year-old woman had a 9-month history of postprandial mid-epigastric pain with a 50 pound weight loss and bloating. She denied anorexia; however, she had stopped eating to avoid the recurrence of pain. On examination, she was cachectic, weighing only 110 lb, and appeared chronically ill. She had an epigastric bruit and diminished abdominal pain. An extensive GI work-up was negative, including upper and lower endoscopy; small bowel follow-through; CT scan of the abdomen; ultrasound of the gallbladder, liver, and spleen; complete blood count; and serum chemistries. She denied cardiac symptoms and had quit smoking 2 years ago.

She was referred for abdominal aortography and selective celiac and mesenteric angiography while on chronic aspirin (81 mg). Right brachial artery access was obtained, a 4F sheath was placed, and 2,000 IU heparin was administered. Using a 4F multipurpose catheter, angiography was performed in the AP and lateral views. The SMA and IMA were found occluded. Figure 46.16A demonstrates high-grade stenosis of the celiac trunk. The sheath was upsized to 6F, an additional 3,000 IU heparin was administered, and a 6F multipurpose guide was used to engage the celiac artery. The lesion was crossed with a 0.014 inch guide wire (Sport wire, Guidant) and was directly stented with a 6 X 28 mm balloon-expandable stent and postdilated with a 7 mm balloon at 12 atm. Final angiography (Figure 46.16B) demonstrated no residual stenosis. The gradient reduced from 60 to <5 mmHg. The patient's symptoms were immediately relieved, and 2 months later she had regained 20 lb.

CASE 46.11 This 49-year-old woman had a history of chronic postprandial abdominal pain with a 40 lb weight loss. Abdominal CT scan done by her primary care physician revealed occlusion of the celiac and IMA, with 99% stenosis in the SMA.

Using a 6F multipurpose guiding catheter and a BMW coronary guide wire, the lesion was predilated with a 3.0 mm coronary balloon. It was then stented with a 4.0 × 25 mm coronary stent and postdilated with a 5.0 × 20 mm balloon. Final angiography (Figure 46.17B) revealed no residual stenosis. The patient had dinner that evening and ate food without abdominal distress for the first time in months.

Illustrative Points
These are two classic cases of chronic mesenteric ischemia. The diagnosis is usually missed in the early stages because of the myriad causes of abdominal pain. Profound weight loss with postprandial abdominal pain is hallmark of this condition. Conversely, the absence of significant weight loss should make you doubt the diagnosis of mesenteric ischemia. Symptoms do not usually occur unless there is stenosis or occlusion of two or more of the three vessels (Celiac, SMA, IMA).
The traditional management of this condition has been surgical; however, owing to their ostial nature, atherosclerotic lesions, much like renal artery stenosis, lend themselves to an endovascular approach. Furthermore, by the time the diagnosis is made, the patients usually become cachectic and are not ideal candidates for surgery. Owing to the natural caudal orientation of the mesenteric vessels, approaching the mesenteric arteries from the arm (brachial/radial) is attractive. They can be treated also from the femoral access, but advancing stents around sharp bends can be a challenge.

Figure 46.16  
A. Angiography of the celiac artery demonstrating high-grade stenosis of the mid-celiac before intervention.  
B. After stenting, there is no residual stenosis. The stent is placed in such a way that several millimeters of stent extend into the aorta since this is an ostial lesion.

Figure 46.17  
A. Angiography reveals subtotal occlusion of the origin of the superior mesenteric artery (SMA). The celiac and inferior mesenteric are occluded (not shown).  
B. Poststenting, there is normal flow and no residual stenosis.
Renal Artery Intervention

Renal artery stenosis (RAS) is common in patients with known coronary or peripheral atherosclerotic disease (Table 46.3). In one study of 196 patients undergoing cardiac catheterization for presumptive coronary artery disease, the prevalence of significant (>50%) renal artery disease was 18%, and when coronary artery disease was confirmed in 152 patients, the prevalence was 22%. Because of such high prevalence of renal artery disease in patients with other atherosclerotic diseases, screening renal angiography is performed at the time of cardiac catheterization in patients undergoing cardiac catheterization for atherosclerotic coronary disease and who would be candidates for renal intervention if a significant stenosis is found.

Significant hemodynamic obstruction of the renal blood flow causes renal ischemia, which is manifested by stimulation of the renin-angiotensin system with attendant vasoconstriction, volume overload, and eventual ischemic nephropathy. The clinical manifestations of atherosclerotic RAS are (i) renovascular hypertension, (ii) ischemic nephropathy, and (iii) cardiac destabilization syndromes with heart failure or unstable angina. Duplex ultrasound in a skilled technician’s hands and CTA/MRA are the best imaging options. Plasma renin assays and radionuclide renograms are not helpful screening tools.

Catheter-based therapy for hemodynamically significant RAS has largely replaced surgical revascularization in patients with suitable anatomy. A recent survey of Medicare patients suggests that renal surgery decreased by almost half in the year 2000, while catheter-based therapy increased 2.4 times.

The primary issue becomes one of appropriate utilization of revascularization with renal stent placement, including patient selection, screening strategies for RAS, and the risk of procedure-related complications. The two ends of the spectrum are represented on one extreme by the patient who is failing medical therapy and benefits from a renal stent placement and on the other extreme by the patient with mild to moderate RAS but who does not improve after renal stent therapy. The overall procedural success rates for renal stenting are very high (98%, 95% CI: 95% to 100%), the overall complication rates are acceptable (11%, 95% CI: 6% to 16%), and the serious complication rates are low.

### Table 46.3 Predictors of Increased Risk for Atherosclerotic Renal Artery Stenosis

<table>
<thead>
<tr>
<th>Predictors</th>
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<tbody>
<tr>
<td>Onset of hypertension ≥55 y</td>
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<tr>
<td>Malignant, accelerated, or resistant hypertension</td>
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<tr>
<td>Unexplained renal dysfunction</td>
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<tr>
<td>Development of azotemia with an ACE inhibitor or ARB medication</td>
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<tr>
<td>Unexplained size discrepancy of ≥1.5 cm between kidneys</td>
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<tr>
<td>Cardiac disturbance syndrome (flash pulmonary edema)</td>
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<tr>
<td>Peripheral arterial disease (Abdominal Aortic Aneurysm or ABI &lt;0.9)</td>
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<tr>
<td>Multivessel coronary artery disease</td>
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### Illustrative Points

Fibromuscular dysplasia (FMD) is commonly found in young adults, especially women, but the condition can persist into later life. This interesting case illustrates a combination of two lesions: atherosclerotic renal artery ostial stenosis and FMD of the mid-renal artery. The angiographic appearance of a corrugated vessel is diagnostic of FMD, and the renal artery is the most common location of this abnormality. In a patient with FMD who is hypertensive despite medical therapy, balloon angioplasty is indicated, and the patient will usually respond to balloon angioplasty without the need for stenting. Ostial renal artery stenosis owing to atherosclerosis does not respond very well to balloon angioplasty, owing to recoil, and does require primary stenting.

### CASE 46.12

This 77-year-old female with known coronary artery disease and stable angina had a history of long-standing hypertension and diastolic dysfunction. Despite three anti-hypertensive medications, her blood pressure was 200/95 mmHg. Her physical examination and laboratory data were normal. A color flow duplex examination suggested significant unilateral right renal artery stenosis.

Renal angiography showed fibromuscular dysplasia of the mid-right renal artery and ostial atherosclerosis narrowing (Figure 46.18A). Balloon angioplasty was performed with a 5.0 × 20 mm balloon. The ostium was treated with a balloon-expandable stent (Figure 46.18B). The patient was discharged the next morning on only one antihypertensive medication with a blood pressure of 145/70 mmHg.

### CASE 46.13

This 73-year-old man was admitted for non-ST elevation myocardial infarction complicated by uncontrolled hypertension with a blood pressure of 179/96 mmHg on four medications including IV nitroglycerine. He had been treated for congestive heart failure, with repeated hospital admissions, over the past 12 months. He underwent coronary artery bypass surgery 12 years previously. There were no audible abdominal bruits. His renal function was mildly abnormal with a creatinine level of 1.4 mg/dL. Because he was unstable, noninvasive studies were deferred, and he underwent urgent coronary and renal angiography.
A. Renal angiogram of a patient with both atherosclerotic ostial stenosis and fibromuscular dysplasia. The typical appearance of fibromuscular dysplasia (arrow) is a corrugation of the vessel. This is diagnostic of fibromuscular dysplasia, but not of renovascular hypertension.

B. The corrugated appearance of the vessel does not change after balloon angioplasty; however, the ostial lesion has been successfully stented. Stenting of the fibromuscular disease is reserved for persistent hypertension after balloon angioplasty.

He was taking chronic aspirin 81 mg daily and was loaded with 300 mg of clopidogrel.

He was taken to the catheterization laboratory and right femoral artery access was obtained with a 6F sheath. He was anticoagulated with 5,000 IU of heparin. Coronary and bypass graft angiography did not reveal any treatable culprit lesions. His ejection fraction was 35% with inferior hypokinesis. Nonselective screening renal angiogram was obtained along with an abdominal aortogram (Figure 46.19A). This demonstrated severe bilateral aorto-ostial renal artery stenosis. Using a 4F internal mammary artery diagnostic catheter, telescoped through a 55 cm 6F hockey stick guide, the renal arteries were atraumatically engaged. Both the right and the left renal arteries were stented with balloon-expandable stents (6 × 18 mm for both) over 0.014 inch wire systems. The right renal stent was postdilated with a 7.0 mm balloon, and the left renal stent with an 8.0 mm balloon. Final angiography revealed no significant stenosis (Figure 46.19B). The patient remains asymptomatic without recurrent hospitalizations and on diuretics and metoprolol 5 years after renal stenting.

A. Bilateral aorto-ostial renal artery stenosis (arrows) as demonstrated by cineangiography at the time of cardiac catheterization. Notice the diffuse atherosclerotic involvement of the infrarenal aorta.

B. Aortogram of the same patient immediately after bilateral stent implantation.
**Illustrative Points**

This case illustrates cardiac destabilization owing to severe bilateral RAS. It also illustrates how the lesions of renal artery stenosis often comprise aortic plaque that encroaches upon the renal ostia rather than plaque originating in the renal arteries themselves. It may be noticed how diseased the abdominal aorta is in this patient. For this reason, we recommend very careful cannulation of the renal arteries using a 4 to 6F diagnostic catheter rather than a guiding catheter to avoid the risk of atheroembolism.

Furthermore, as this case also illustrates, the teaching point is that even though this patient presented with an acute coronary syndrome, the clues of poorly controlled hypertension on multiple medications, history of recurrent heart failure episodes, and mildly abnormal renal function all pointed to the fact that he likely had renovascular disease. The key is to be able to recognize these patients and to be able to treat their problems.

**CASE 46.14**

This 71-year-old woman presented with an exacerbation of chronic heart failure and a hypertensive crisis. She had a history of prior coronary interventions; poorly controlled hypertension on a beta blocker, lasix 40 mg per day, and an angiotensin converting enzyme (ACE) inhibitor; and dyslipidemia. Her blood pressure in the right arm was 188/108 mmHg, respiratory rate 18 per minute, and her pulse rate was 68 beats per minute. Her radial pulses were 2+ bilaterally, and the Allen’s test was normal. Her physical examination was remarkable for bibasilar crackles and 2+ edema of feet and ankles. Initial laboratory results demonstrated a serum creatinine of 1.7 mg/dL and an estimated glomerular filtration rate of 46 cc/minutes. An abdominal duplex ultrasound examination ruled out obstructive nephropathy but suggested a critical narrowing of the right renal artery.

She was brought to the catheterization suite with a plan to open the right renal artery stenosis. In order to maximize the safety of this procedure, a radial artery approach was chosen, use of radiographic contrast was limited, and embolic protection was used. A 5F right radial artery sheath was put in place. An exchange-length 0.035 inch J-wire was advanced to the aorta, the 5F sheath was removed, and a 125 cm 4F multipurpose diagnostic catheter, which had been inserted through a 100 cm 6F multipurpose guiding catheter, was advanced into the radial artery using a sheathless technique. The wire and catheters were advanced into the descending aorta and 5,000 IU of heparin was administered.

The right renal artery was selectively engaged with the 4F multipurpose catheter, and baseline angiography was performed (Figure 46.20A). The 6F guide catheter was advanced over the 4F diagnostic catheter to engage the right renal artery. The diagnostic catheter was removed, and the lesion was crossed with a filterwire (Boston Scientific). The filterwire was deployed to predilate the lesion with a 5 × 18 mm balloon at 12 atm. The balloon was removed, and a 5.5 × 18 mm balloon-expandable stent was deployed at 12 atm (Figure 46.20B). The filterwire was retrieved and final angiography was performed (Figure 46.20C).

The catheters were removed, and local hemostasis at the wrist was obtained. There was a significant amount of debris captured in the filter. A total of 33 cc of iodinated contrast was used. Prior to her discharge the patient became normotensive on the same medications she had been on before the procedure, her lungs cleared, her peripheral edema improved, and her serum creatinine improved to 1.4 mg/dL.

**Illustrative Points**

This case illustrates the role of unilateral renal artery stenosis in patients with hypertensive crisis and acute volume overload. The presumption is that long-term hypertension and nephrosclerosis have damaged the contralateral patent renal artery. Opening the obstructed kidney brings more functional nephrons online and reduces production of renin.

Radial access for renal artery intervention is a good technique to avoid femoral or brachial artery vascular complications, but occasionally requires longer catheters (125 cm 6F guiding catheters and 150 cm length balloon and stent catheters). In this case, the conventional 100 cm guide catheter and 135 cm length balloon and stent catheters were long enough to reach her renal artery. To reduce the size of the radial artery entry site, we often use a sheathless technique of telescoping a 4F catheter through a 6F guide catheter.

The risk of atheroemboli complicating renal artery intervention may be much more common than previously suspected. Hence, embolic protection devices should be considered for patients with impaired renal function and who have suitable anatomy. There may also be a role for aggressive platelet inhibition in protecting the renal microcirculation, though we require more data to confirm this.

**LOWER EXTREMITY PERIPHERAL VASCULAR DISEASE**

**Aorto-Iliac Intervention**

Revascularization options for patients with infrarenal aortic and iliac obstructive atherosclerotic disease include aorto-iliac and aorto-femoral bypass procedures, which are associated with 74% to 95% 5-year patency rates, comparable, but not superior to, those of percutaneous therapies.120,121 Endovascular treatment for infrarenal aortic disease can be performed with lower morbidity than that of open surgery and with better durability than that of extra-anatomic bypass; there are, however, no randomized controlled trial data to compare these therapies.

For common iliac bifurcation lesions, kissing balloon-expandable stents have become the preferred option.122 In
one series of 48 patients all stents were placed successfully and there were no major complications. All of the patients experienced symptomatic improvement, and the 2-year patency rate was 87%.

Iliac artery stenting demands a very important skill set in terms of managing vascular access site complications and obtaining vascular access. In patients with aorto-iliac stenotic or occlusive lesions, iliac intervention might be indicated when obtaining vascular access for angiography/intervention or in order to place an intra-aortic counterpulsation balloon.

The TransAtlantic Inter-Society Consensus (TASC) document describes characteristic lesion morphology for ideal (Type A) and unfavorable (Type D) iliac lesions. Surgical and percutaneous treatment of TASC type B and C lesions have been compared in a nonrandomized observational study. There was no difference in limb salvage or patient survival at 5 years, but vessel patency was found to be reduced in limbs with poor run-off treated with stents as compared to those treated with surgery. Based on these and other trial data, current recommendations favor endovascular procedures for TASC A and B lesions, and for selected C lesions. TASC D lesions generally will be considered surgical candidates, but with newer technology (e.g., reentry devices, covered stent grafts) they are increasingly being considered for endovascular therapy on a case-by-case basis.
In a comparison study of the different interventional approaches to iliac disease, the immediate postprocedure results of a randomized trial of PTA comparing provisional stent placement (stent placement for unsatisfactory balloon angioplasty results) to primary stent placement in iliac arteries demonstrated that pressure gradients across the lesions after primary stent placement (5.8 ± 4.7 mmHg) were significantly lower than after PTA alone (8.9 ± 6.8 mmHg), but not after provisional stent placement (5.9 ± 3.6 mmHg). The primary clinical success rate, defined as an improvement of at least one clinical grade category, was not different for the primary stent group (81%) as compared to the PTA plus provisional stent group (80%). By using provisional stenting, the authors avoided stent placement in 63% of the lesions, and still achieved an equivalent acute hemodynamic result as compared to primary stent placement. At a mean follow-up of 5.6 years, there was no difference in repeat interventions between the two groups with a target vessel revascularization (TLR) of 18% in the primary stent group versus 20% in the provisional stent group. This approach is reasonable in relatively short, non-occlusive lesions but has not been tested in more complex subsets.

When trials with long-term outcomes are combined, 873 patients had an iliac stent acute procedural success of above 90%, with 3 ± 1 year primary patency rates of 74% to 87% and secondary patency rates of 84% to 95%, which compare favorably with reported patency rates for surgical treatment. The 30-day mortality risk was 0.5%, much lower than the 4% weighted mortality risk for aorto-femoral bypass. Variables correlating with poor outcomes after iliac stent placement include occlusions rather than stenoses, longer lesions, female gender, and external iliac stent placement. Occlusions of the iliac arteries may be approached with a success rate of 90%, a serious complication rate of 1.4%, and a 3-year primary patency rate of 78% with a secondary patency rate of 86%. The current ACC/AHA Class-I guideline recommendation is for primary stent placement in the iliac arteries (level of evidence B for common iliac arteries and C for external iliac arteries).

There has been debate on whether stent architecture or composition (i.e., nitinol versus stainless steel) has any effect on restenosis rates. The recently completed CRISP trial failed to show any difference in outcomes between nitinol (SMART, Cordis, Miami Lakes, FL) and elgiloy alloy of stainless steel (Wallstent, Boston Scientific Corp., Watertown, MA) iliac artery stents at 1 year.

**CASE 46.15** This 77-year-old hypertensive man complained of bilateral lower extremity fatigue with exercise, and could walk less than 100 feet before having to stop. He also complained of bilateral calf claudication. Resting relieved his symptoms. His examination was remarkable for diminished bilateral femoral and lower extremity pulses. His ankle-brachial index (ABI) was 0.5 bilaterally. Angiography revealed severe bilateral common iliac stenoses with extensive collaterals (Figure 46.21A).

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**Figure 46.21**  
A. Severe bilateral common iliac stenosis with collaterals from the inferior mesenteric artery (IMA) and lumbar arteries to the right internal iliac artery.  
B. Poststenting angiogram with balloon-expandable stents. Notice the absence of collaterals and persistent filling of the right internal iliac artery.
Bilateral common femoral artery access was obtained, and the iliac stenoses were crossed with 0.035 inch hydrophilic guidewires. Two 35 cm long 6F sheaths were advanced across the lesions bilaterally and the hydrophilic wires were exchanged for extra-stiff Amplatz wires. The sheaths were pulled back, and both common iliac arteries were dilated simultaneously with 7 × 40 mm balloons. Kissing balloon-expandable stents were then deployed (7 × 40 mm) simultaneously. The patient’s symptoms completely resolved, and his ABI following the procedure rose to 0.8 bilaterally.

**Illustrative Points**

This case is an example of how revascularization has changed over 20 years. At one time this man would have undergone a major abdominal operation with aorto-femoral bypass, but now he can very well be treated in less than an hour with kissing stents and go home the next morning. This case also highlights the necessity for cardiologists to possess the knowledge and skill to perform iliac intervention to preserve access for peripheral, renal, and coronary intervention.

**Femoral–Popliteal Intervention**

Atherosclerotic occlusive disease is 3 to 5 times more common in the femoral–popliteal arteries than in the iliac artery. The femoral–popliteal arteries are 3 times more likely to be occluded than to be stenotic, a distribution that is reversed in the aorto-iliac system.

Revascularization with surgery or percutaneous transluminal angioplasty is indicated for relief of vocational or lifestyle-limiting claudication in patients who have failed exercise and pharmacologic therapy. Medical therapy, intervention, and surgery have been compared in several trials in symptomatic patients with femoral–popliteal disease. A meta-analysis comparing PTA to exercise therapy in patients with intermittent claudication reported similar quality-of-life outcomes at 3 and 6 months, while the functional capacity (ABI) improved more with endovascular therapy than with exercise.

Cost-effectiveness and quality-of-life outcomes favor the performance of percutaneous therapy whenever feasible as a more effective treatment than exercise alone. A matched cohort study of 526 patients with intermittent claudication found significant advantages for a revascularization strategy (surgery or PTA) as compared to medical therapy. Revascularization was more effective than medical therapy for improvement in physical function, bodily pain, and walking distance. Patients with the maximum improvement in their ABI results also had the best clinical improvement indicating that the degree of revascularization was related to a successful outcome. If one estimates that the 5-year patency will be 230%, then percutaneous therapy will be more cost effective than surgery.

Balloon angioplasty alone of short occlusions (<5cm) and/or stenoses yield better results than yielded by treatment of long stenoses (>10 cm) and occlusions. The presence of patent runoff vessels correlates with long-term benefits, reflected in the improved outcome in patients with milder symptoms. Significant residual stenosis after angioplasty correlates with a poor long-term outcome, and absence of diabetes correlates with an improved patency rate. A meta-analysis has demonstrated a better patency at 3 years for stents as compared to balloon angioplasty in the most severely affected patients—those with occlusions and critical limb ischemia.

One strategy is to perform PTA followed by provisional “bailout” stenting only if the balloon angioplasty is not successful. Primary stenting with self-expanding stents is superior to provisional stent placement for femoral–popliteal lesions of longer length (7 to 10 cm), in terms of restenosis, improvement in ABI, and longer walking distance. At 2-year follow-up, the benefit for primary stenting remains statistically significant, but the restenosis rate for femoral–popliteal stents rises to about 50%. In more discrete femoral lesions (mean 4.5 cm), a strategy of “balloon first with stent only for bailout” is as good as routine stenting. The difference in outcomes for short versus long lesions, even though stenting is equally good for long and short lesions, exists because longer lesions are more prone to restenosis after PTA alone. As a result, stents improve outcomes in longer lesions, and a strategy of provisional PTA with bailout stenting is preferable for more discrete femoral lesions.

The expectation that “debulking” atherosclerotic plaque would improve the primary patency for femoral–popliteal lesions has not been realized. Adjunctive therapies such as atherectomy, cryotherapy, and the cutting balloon therapy have little data to support their use. In randomized trials, laser angioplasty was not superior to conventional percutaneous transluminal angioplasty and/or stent placement in the superficial femoral artery (SFA). Given the substantial additional expense for such devices, more evidence is needed to support their efficacy before widespread adoption could be justified.

Initial attempts at transferring the benefits of drug elution seen in the coronaries for both balloons and stents to the femoral–popliteal arteries have failed. Recently, a randomized trial (Cook, Bloomington, IN) using a paclitaxel-coated nitinol stent without polymer coating versus bare-metal nitinol stent has demonstrated efficacy and improved patency for the drug-eluting stent. Primary patency at 12 months was achieved in 83% of subjects receiving the DES versus 67% of those receiving angioplasty with provisional stenting (P < 0.01). This trial resulted in an FDA panel recommendation to approve this stent.

Two randomized trials comparing a paclitaxel-eluting balloon to a noncoated balloon in de novo SFA lesions have demonstrated promising results. In THUNDER the target lesion revascularization was significantly lower in the drug-eluting balloon group at 6 and 24 months as compared to the noncoated balloon group (4% versus 29% at 6 months, P < 0.001; 15% versus 52% at 24 months, P < 0.001). In the
Femoral Paclitaxel (FemPac) trial, target lesion revascularization occurred in 7% in the paclitaxel-coated balloon (PCB) group as compared with 33% of the control group ($P = 0.045$) at 6 months. This difference was maintained at 18 months.

**CASE 46.16**  A 79-year-old woman who was wheelchair bound with multiple sclerosis was referred for an ischemic, nonhealing ulcer in her right lower extremity, the limb she was using to transfer from wheelchair to bed. She did not complain of rest pain in the limb. She was scheduled for amputation, but wanted a second opinion. Her ABI was 0.4, and she had faint Doppler signals in both tibial arteries. Angiography revealed an SFA occlusion with patent tibial vessels. She was scheduled for SFA recanalization for limb salvage.

Left common femoral artery access was obtained with a 6F sheath. A 4F internal mammary artery (IMA) diagnostic catheter was advanced to the terminal aorta, and the ostium of the right common iliac artery was selectively engaged. An extra-stiff, angled glide wire was advanced to the right common femoral artery, and the IMA catheter was advanced over the Glidewire. An exchange-length extra-stiff Amplatz wire was advanced into the right SFA, and the IMA catheter and short 6F sheath were exchanged for a Crossover sheath (Boston Scientific), which was placed in the right common femoral artery. Anticoagulation was achieved with 5,000 IU of heparin and confirmed with ACT testing.

Angiography was performed revealing an occlusion of the right SFA (Figure 46.22). The lesion was crossed with a 4F glide catheter and an angled extra-stiff Glidewire. After the initial balloon dilation failed to restore flow, three self-expanding nitinol stents were deployed in a staggered manner and postdilated with a $6 \times 100$ mm balloon at 8 atm. This restored normal flow to the lower extremity and foot. Within several weeks substantial healing of her ulcer had occurred and we were able to salvage her limb.

**Illustrative Points**

Most patients with femoral–popliteal disease present with claudication. Because this patient was wheelchair bound, she was asymptomatic with severe lower extremity ischemia (ABI $\leq 0.4$). With trauma, she developed a nonhealing ulcer. The decision to amputate is always a difficult one. In this case, the patient was using her right leg to transfer from wheelchair to bed, which placed a priority on limb salvage. The longer stents used require close follow-up with duplex ultrasound for possible restenosis. She was treated with aggressive risk factor modification and long-term aspirin therapy.

**Tibial–Peroneal Intervention**

The indication for infrapopliteal angioplasty is critical limb ischemia manifested by (i) ischemic rest pain, (ii) ischemic

![Figure 46.22](image-url)
nonhealing ulceration, and/or (iii) gangrene. However, severe claudication limits walking, and infrapopliteal angioplasty to improve run-off following femoral–popliteal PTA has been advocated by some.

The adaptation of coronary equipment has improved the results of tibioperoneal intervention. Current procedural success rates for below-knee intervention in limb salvage patients range from 60% for occlusions to >90% for more ideal lesions. Limb salvage rates at 2 to 5 years are 80% to 90% with modern endovascular techniques.

Optimal treatment of tibioperoneal disease requires appropriate patient and lesion selection for treatment. Focal stenoses have the best outcomes, and occlusions ≥6 cm in length have better outcomes than observed for longer lesions. Strategically, straight-line, pulsatile flow to the foot is the goal of therapy in patients with CLI. Success is determined more by relief of rest pain, healing of ulcers, and avoiding amputation than by long-term vessel patency. When trying to treat ischemic ulcers, the basic principle is that it takes more oxygenated blood flow to heal a wound than to maintain tissue integrity.

Encouraging results for balloon-expandable, coronary, drug-eluting stents in tibial vessels have been reported. The largest series, a nonrandomized comparison of tibioperoneal bail-out stenting in 58 patients [29 bare-metal stents and 29 sirolimus (Cypher, Cordis, Miami Lakes, FL) eluting stents] demonstrated a marked reduction in restenosis at 6 months, from 55% in bare-metal stents to 4% (P < 0.001) in the drug-eluting stents. The PARADISE study reported on a prospective cohort of 106 patients with critical limb ischemia treated with infrapopliteal drug-eluting stents. The amputation rate at 3 years was only 6%. While these results are encouraging, more rigorous comparisons and longer follow-up are required, especially concerning the late thrombosis risk seen in the coronary application of drug-eluting stents.

CASE 46.17

This 65-year-old man with a 100-pack-year smoking history presented with a painful foot and a nonhealing ulcer on the second digit of his left lower extremity. He had a history of severe coronary artery disease and peripheral vascular disease, and had undergone bilateral femoral–popliteal angioplasty 7 years earlier for lifestyle-limiting claudication. At that time, he had a severe (>70%) stenosis of his left tibioperoneal trunk, but this was not treated. His ABI was 0.4 on the left and 0.8 on the right.

Right common femoral access was obtained with a 4F sheath, and a 4F pigtail catheter was advanced over a 0.035 inch J-wire to the infrarenal aorta. Aortography and lower extremity run-off were performed, with non-ionic contrast injected at 8 cc/second for a total of 10 seconds, using stepping-table digital subtraction angiography. Next, contralateral access was obtained with a 4F IMA catheter placed at the terminal aorta, and this selectively engaged the left common iliac artery. An extra-stiff angled Glidewire was advanced to the left common femoral artery. After the IMA catheter was advanced over the Glidewire to the left common femoral artery, the Glidewire was removed. An exchange-length extra-stiff Amplatz 0.035 inch wire was advanced into the left SFA, and the IMA catheter and short 4F sheath were exchanged for a 6F Crossover sheath, which was advanced over the Amplatz wire to the left common femoral artery. Selective left leg angiography demonstrated single-vessel (peroneal artery) below-knee run-off with a critical stenosis in the tibioperoneal trunk and occlusion of the posterior and anterior tibial vessels (Figure 46.23A). A 6F multipurpose (100 cm) coronary guiding catheter was advanced over the Amplatz wire to the left popliteal artery. The tibioperoneal stenosis was crossed with a 0.014 inch coronary guidewire and dilated with a 3.0 × 20 mm coronary balloon at 8 atm. There was significant recoil and inadequate PTA result, so provisional stenting with a 3.0 × 8 mm coronary balloon-expandable stent was performed (Figure 46.23B). The final angiogram revealed an excellent result (Figure 46.23C). The patient was discharged on aspirin, clopidogrel, and antibiotics, and advised follow-up in the wound clinic at weekly intervals until his ulcer healed completely. His ABI improved to 0.75 on the left.

Illustrative Points

The indication for tibioperoneal angioplasty is critical limb ischemia, defined as rest pain, nonhealing ischemic ulcers, or gangrene. Critical limb ischemia requires stenosis or occlusion of all three infrapopliteal vessels, and very often multiple levels of disease in the iliac and femoral arteries.

Below-knee intervention is not routinely offered to patients with claudication, as illustrated by this man’s course 7 years ago. The goal of revascularization in patients with critical limb ischemia is to provide pulsatile flow to the foot. The introduction of low-profile coronary systems into the periphery has to a great extent facilitated infrapopliteal intervention. A strategy of provisional stenting rather than primary stenting with antiplatelet therapy is the current standard of care. While surgical therapy is an option, an “angioplasty first” strategy seems prudent at this time. The important goal here is to heal the ulcer. The role of drug-eluting stents in this location, though promising, has not been defined.

PERCUTANEOUS TREATMENT OF ACCESS SITE COMPLICATIONS

Access site complications are the most common complication of percutaneous intervention and include dissection, thrombosis, abrupt occlusion, rupture, bleeding, and pseudoaneurysm formation. The most serious of these complications, retroperitoneal bleeding and acute limb ischemia, are also life-threatening. The following cases will illustrate how these complications can be managed percutaneously. It should be borne in mind, however, that in the hands of an inexperienced operator, these treatments may not be
Figure 46.23
A. Single-vessel peroneal patency with high-grade stenosis in the tibioperoneal trunk. B. Owing to a suboptimal percutaneous transluminal angioplasty (PTA) result, a balloon-expandable stent is deployed. C. Completion angiogram showing excellent result. Digital subtraction angiography (DSA) is a very useful technique when performing tibial intervention.

technically possible. Therefore, vascular surgery consultation may be prudent and necessary.

CASE 46.18
This 64-year-old woman underwent uncomplicated percutaneous coronary intervention (PCI) from the left common femoral artery (CFA) after a failed attempt to obtain right CFA access owing to inability to pass the 0.035 inch guidewire up the external iliac artery. Four hours later, she was noted to be hypotensive and diaphoretic. Examination revealed a pulse of 90 bpm, cool clammy extremities, and right lower-quadrant fullness, guarding, and tenderness. The left CFA access site was unremarkable. A clinical diagnosis of retroperitoneal hemorrhage was made, and manual compression was applied to her right groin. Her ACT was normal, and she had not received IIb/IIIa inhibitors. She was on aspirin and had been fully loaded with clopidogrel. She was urgently taken back to the catheterization laboratory for angiography and intervention.

Left CFA access was obtained and a 6F sheath was put in place. A 4F IMA catheter was advanced to the terminal aorta and the right common iliac artery was selectively engaged. Angiography revealed contrast extravasation (bleeding) at the right external iliac/common femoral artery junction, which was the location of the previously aborted access site (Figure 46.24A). An extra-stiff Amplatz 0.035 inch guidewire was advanced into the right SFA, and a 6F Crossover sheath was inserted. A 6 × 40 mm balloon was inflated to 4 atm to tamponade the bleeding. Contrast injections confirmed hemostasis achieved by the inflated balloon. After serial balloon inflations of up to 5 minutes each, the bleeding continued. A 7 × 30 mm Wallgraft (Boston Scientific) was deployed across the bleeding site in the distal external iliac and common femoral arteries (Figure 46.24B). Angiography demonstrated cessation of bleeding (Figure 46.24C). The patient was treated with clopidogrel and aspirin for 6 months. There were no sequelae.

Illustrative Points
This case demonstrates the preferred approach to manage serious, hemodynamically significant vascular access bleeding. The diagnosis of retroperitoneal bleeding is a clinical one and usually does not require CT scanning. “Ramee’s Triad” of ipsilateral lower-quadrant fullness, tenderness, and guarding in a patient with hypotension after femoral artery access
Section VIII Clinical Profiles

A. Site of bleeding is identified (arrow) by using digital subtraction angiography (DSA). A small amount of visible extravascular bleeding correlates with severe, life-threatening hemorrhage.

B. Deployment of a Wallgraft just above the femoral head.

C. Site of bleeding (arrow) is no longer visible after Wallgraft deployment.

Is diagnostic of retroperitoneal bleeding. The initial management of the patient includes manual compression over the common femoral artery puncture site and evaluation of the patient's anticoagulation status (ACT, PT if on warfarin, and platelet count).

How can you tell if the bleeding has stopped? That is the critical question! A CT scan does not give you this information. Duplex scanning also cannot tell the difference between continued bleeding and a pseudo-aneurysm, or contained bleeding. In the hypotensive patient, we recommend returning the patient to the angiography suite to determine the bleeding site, and then control the bleeding.

CASE 46.19 The patient is a 60-year-old man with a previous aorto-bifemoral bypass (AFB) grafting who had diagnostic angiography at a community hospital with manual compression for hemostasis of the CFA. He was transferred to our center for intervention. On presentation, he complained of a cold, painful right lower extremity that started after the diagnostic angiogram 3 days earlier. On examination, he had ecchymosis without hematoma over the right groin, and absent femoral pulse. A Doppler exam showed monophasic signals in the feet. A duplex ultrasound confirmed our suspicion that the right limb of his aorto-bifemoral graft has been occluded. Angiography was performed from the left brachial artery with a diagnostic catheter (Figure 46.25A) demonstrating occlusion of the proximal right limb of the AFB graft.

The occlusion was traversed with an extra-stiff angled Glidewire and a 4F multipurpose catheter. An exchange-length Platinum Plus coronary wire was placed in the distal profunda femoris; the 4F multipurpose catheter was exchanged for a 6F multipurpose coronary guiding catheter, and mechanical thrombectomy (Angiojet) was performed. Figure 46.25B demonstrates the high-grade residual stenosis that remains at the CFA and in the graft itself after thrombus removal. These lesions were dilated and stented resulting in
normalization of the pulse in the lower extremity and relief of the ischemia (Figure 46.25C).

**Illustrative Points**

This patient suffered an iatrogenic complication related to manual compression following an angiogram. While this complication may not be preventable, it is treatable by either mechanical thrombectomy (as in this case) or surgical thrombectomy with or without patch angioplasty or bypass. When acute limb ischemia happens after a catheter-based procedure, there is usually an underlying vascular stenosis that becomes occluded during the procedure or during hemostasis. Unless this stenosis is relieved, recurrent thrombosis will occur.

**CASE 46.20** A 60-year-old man underwent PCI followed by suture device closure of the common femoral access site. Forty-eight hours later, he returned with complaints of right lower extremity weakness and claudication. His pulses had been normal pre-PCI, and his CFA was angiographically normal before the closure device was used. Post PCI, his pulses were noted in the medical record to be diminished but palpable.

On examination, his right common femoral and tibial pulses were absent. Color flow Doppler demonstrated subtotal occlusion of the right common femoral artery.

The patient underwent emergency angiography via the left common femoral artery using a 4F IMA diagnostic catheter (Figure 46.26A). The lumen was narrowed and irregular with a filling defect. This appearance may suggest dissection or suturing of the posterior wall to the anterior wall of the lumen. The lesion was crossed with difficulty with an angled hydrophilic 0.035 inch Glideewire, and the 4F IMA catheter was advanced across the lesion over the Glideewire. The Glideewire was replaced with a 0.035 inch Amplatz extra-stiff guidewire, and a 6F Crossover sheath was advanced to the right common iliac artery. A 6 × 20 mm PTA balloon catheter was advanced across the stenosis. Despite multiple balloon inflations, the angiographic appearance never changed. Therefore an 8 × 29 mm self-expanding Wallstent was deployed, and positioned so that it would be below the inguinal ligament. The Wallstent was dilated to 14 atm with the 6 mm balloon, and angiography demonstrated no residual stenosis (Figure 46.26B). Hemostasis was obtained with manual compression in the left CFA.

**Illustrative Points**

The importance of postprocedure evaluation of the peripheral pulses again cannot be underestimated. When dealing with access closure device complications one must keep in mind that in addition to dissection and thrombosis, there is also the possibility of suturing of the posterior wall (as in this case) or
intravascular deployment of collagen. Initial attempts at PTA alone were appropriate, but when that fails stent placement is indicated. Repeat access in this patient’s stented right CFA was still possible as the stents cells were large enough to accommodate a vascular sheath. The surgical alternative, open repair of the vessel, is associated with significant acute morbidity and late scarring that makes repeat CFA access very difficult.

**Illustrative Points**

The pathology of access site bleeding and pseudo-aneurysm formation are the same: a hole in the artery caused by the sheath. Noninvasive ultrasound-guided thrombin injection has become the standard of care in treating PSA. Whether using duplex ultrasound or fluoroscopy, it is critical to ensure proper placement of the needle and to inject the thrombin very slowly to avoid intravascular injection and acute limb ischemia. In cases in which there is a risk of thrombin spreading out of the PSA, placing an occlusive balloon in the vessel will occlude the mouth of the PSA, prevent thrombin embolization outside the PSA, and facilitate thrombosis of the PSA. Compression with a US probe is no longer commonly done because it causes severe pain and is unreliable. Surgery is rarely needed and is reserved for refractory cases.
A. The angiographic appearance of a pseudo-aneurysm sac (outlined by arrows). The hole in the artery is between the sac and the common femoral artery.

B. Using roadmapping and fluoroscopy, a needle is inserted percutaneously into the pseudo-aneurysm sac. Once pulsatile flow is obtained, contrast is injected to confirm location, followed by very slow injection of thrombin, a tenth of a cc at a time.

C. Final angiography demonstrates closure of the hole in the common femoral artery and obliteration of the pseudo-aneurysm (arrow).

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