Vascular Access for the General Nephrologist

Nephrology Research and Clinical Developments
VASCULAR ACCESS
FOR THE GENERAL NEPHOLOGIST
Nephrology Research and Clinical Developments

Additional books in this series can be found on Nova’s website under the Series tab.

Additional e-books in this series can be found on Nova’s website under the e-book tab.
VASCULAR ACCESS
FOR THE GENERAL NEPHROLOGIST

MICAH R. CHAN,
ALEXANDER S. YEVZLIN
AND
ARIF ASIF
EDITORS
Dedicated to my wife, Paola,
the brains and beauty of the family.

Alexander S. Yevzlin, M.D.

Dedicated to my parents Daniel and Hally Chan,
my wife, sons and brothers.

Micah Chan
## Contents

### I. Access Creation

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Author(s)</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chapter I</td>
<td>Planning for Vascular Surgery - a Patient Centered Approach</td>
<td>Charmaine E. Lok, Cyndi Bhola, and Ingemar Davidson</td>
<td>3</td>
</tr>
<tr>
<td>Chapter II</td>
<td>The Arterial and Venous System as They Apply to Vascular Access</td>
<td>Bharat Sachdeva</td>
<td>19</td>
</tr>
<tr>
<td>Chapter III</td>
<td>Vascular Mapping Prior to Access Creation</td>
<td>Vandana Dua Niyyar</td>
<td>31</td>
</tr>
<tr>
<td>Chapter IV</td>
<td>Sites and Types of Avfs</td>
<td>Rick Mishler and Alex Yevzlin</td>
<td>41</td>
</tr>
<tr>
<td>Chapter V</td>
<td>Creation of Arteriovenous Fistulas by Nephrologists</td>
<td>Shouwen Wang and Andrew Cortez</td>
<td>51</td>
</tr>
<tr>
<td>Chapter VI</td>
<td>Secondary Arteriovenous Fistula</td>
<td>David Levine and Surendra Shenoy</td>
<td>67</td>
</tr>
</tbody>
</table>

### II. Vascular Access Care

<p>| Chapter VII | The Role of the General Nephrologist in Vascular Access Care | Kenneth Abreo and Karina Sulaiman | 81   |</p>
<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Authors</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>IX</td>
<td>The Role of Physical Examination of HD Access for the General Nephrologist</td>
<td>Loay Salman</td>
<td>107</td>
</tr>
<tr>
<td>X</td>
<td>Options for Patients with Hand Pain and Nerve Injuries Related to Dialysis Access</td>
<td>Arif Asif</td>
<td>115</td>
</tr>
<tr>
<td>XI</td>
<td>Renal and Vascular Ultrasonography for General Nephrologists</td>
<td>Lauren F. Alexander, Heidi R. Umphrey, Carl A. Abts, Mark E. Lockhart, Michelle L. Robbin</td>
<td>121</td>
</tr>
<tr>
<td>XII</td>
<td>Role of Nurses and Technicians in Vascular Access Care</td>
<td>Donna Merrill</td>
<td>145</td>
</tr>
<tr>
<td>XIII</td>
<td>Medications and Vascular Access Patency</td>
<td>Paul G. Schmitz, Adarsha Shrestha, Farnaz Mohammadi and Kevin J. Martin</td>
<td>151</td>
</tr>
<tr>
<td></td>
<td><strong>III. ARTERIOVENOUS FISTULAE</strong></td>
<td></td>
<td>171</td>
</tr>
<tr>
<td>XIV</td>
<td>Basics of AVF Maturation</td>
<td>Aris Urbanes</td>
<td>173</td>
</tr>
<tr>
<td>XV</td>
<td>Peripheral Arterial Disease and Vascular Access</td>
<td>Vikram Chhokar</td>
<td>185</td>
</tr>
<tr>
<td>XVI</td>
<td>AVF Outcomes in the “Fistula First” Era</td>
<td>Tushar J. Vachharajani</td>
<td>193</td>
</tr>
<tr>
<td></td>
<td><strong>IV. ARTERIOVENOUS GRAFT</strong></td>
<td></td>
<td>205</td>
</tr>
<tr>
<td>XVII</td>
<td>Arteriovenous Graft Stenosis and Thrombosis</td>
<td>Antoine Samaha</td>
<td>207</td>
</tr>
<tr>
<td>XVIII</td>
<td>Pseudo-Aneurysms in Dialysis Access</td>
<td>Karn Gupta</td>
<td>221</td>
</tr>
<tr>
<td></td>
<td><strong>V. CENTRAL VENOUS CATHETERS</strong></td>
<td></td>
<td>227</td>
</tr>
<tr>
<td>XIX</td>
<td>Tunneled Hemodialysis Catheters – Infection and Dysfunction</td>
<td>Hemender Vats and Micah Chan</td>
<td>229</td>
</tr>
</tbody>
</table>
Chapter XX  Central Venous Stenosis in Dialysis Patients
Micah R. Chan  243

Chapter XXI  Catheter Locks for Prevention of Infection and Maintenance of Access Viability
Sanjeev Shah  259

Chapter XXII  Catheter Surface Coatings – Do They Make a Difference?
Vandana Dua Niyyar and Alexander Yevzlin  267

Chapter XXIII  A General Nephrologist’s Approach to a Poorly Functioning Catheter
Roman Shingarev and Alexander S. Yevzlin  277

VI. HEMODIALYSIS VASCULAR ACCESS INTERVENTIONS  289

Chapter XXIV  Venous Angioplasty
George M. Nassar  291

Chapter XXV  Endovascular Stents for Dialysis Access
Ivan D. Maya  307

Chapter XXVI  Peritoneal Dialysis Catheter Management
Karthik Ramani and Kenneth Abreo  313

Chapter XXVII  Complications of Hemodialysis Procedures
Jamie Ross  329

VII. HEMODIALYSIS ACCESS DYSFUNCTION AND TRANSLATIONAL RESEARCH  343

Chapter XXVIII  Future Directions in Vascular Access Clinical Science
Alexander Yevzlin and Brad C. Astor  345

Chapter XXIX  What the General Nephrologist Needs to Know about Neointimal Hyperplasia
Timmy Lee and Charmaine Lok  363

Chapter XXX  Catheter Design: Does It Make a Difference?
Stephen R. Ash  385

Index  411
I. ACCESS CREATION
Chapter I

Planning for Vascular Surgery - A Patient Centered Approach

Charmaine E. Lok,1,2 Cyndi Bhola2 and Ingemar Davidson2

1Faculty of Medicine, University of Toronto, Toronto, Canada
2Nephrology, University Health Network-Toronto General Hospital, Toronto, Canada
2Department of Surgery, University of Texas Southwestern Medical Center, TX, US

Abstract

Patient focused dialysis modality and access selection requires a coordinated teamwork approach that emphasizes chronic kidney disease care to be a continuum of care.

Individualized and detailed patient history and examination are the mainstays of dialysis modality and access selection. Preoperative vessel mapping by duplex doppler ultrasonography can be a useful supplementary investigation to the history and physical examination to determine the optimal dialysis access type and site. Dialysis access modality and choice considers many patient factors that can be aided by a clinical risk score, asking key clinical questions, surgical expert opinion, and a multidisciplinary approach to individualized patient care. In many situations, a lifelong access utilization strategy prioritizes peritoneal dialysis as the first dialysis modality followed by appropriately planned hemodialysis. The goal of an integrated patient focused approach is to achieve complication-free access to help patients achieve their life goals on and off dialysis.

Introduction

The world population is experiencing an exponential growth of individuals with end stage renal disease (ESRD) requiring renal replacement therapy (RRT). In North America, there were over 600,000 ESRD patients in 2010 [1, 2.] The care of these ESRD patients consumed
approximately 7% of the United States Medicare budget of around $30 billion in total costs [1]. There are three primary options for renal replacement therapy: renal transplantation, hemodialysis (HD) and peritoneal dialysis (PD). Worldwide, HD (89%) is more common than PD (11%) [1-3]. However, the use and distribution of these modalities vary globally. For example, PD provided dialysis to 80% of patients in Mexico and Hong Kong compared with only 5% in Japan, Bangladesh and Luxemborg [4]. In North America, transplantation rates have remained stable with the majority of patients (approximately 80%) receiving HD as the preferred dialytic modality [2-5].

Indeed, early on in the past decade, North America has witnessed decreased utilization of PD, increased use of arteriovenous grafts (AV-grafts) and central venous catheter (CVCs) and decreased use of arteriovenous fistulas (AVFs) [6-7]. Many studies have shown that this practice pattern has contributed to increased morbidity and mortality as well as soaring healthcare costs [8-11]. In the wake of low AVF utilization [12] and recent National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF K-DOQI) recommendations [13], the Centers for Medicare and Medicaid Services (CMS) launched a National Vascular Access Improvement Initiative in 2003 emphasizing a “Fistula First” approach, to increase the use of AVFs in HD patients with the goal of exceeding a prevalent rate of at least 40% [14]. This goal has recently been raised to more than 66%. [15] While the intention of such an initiative is to cost-effectively improve patient outcomes on a population basis, the selection of dialysis access must, by necessity, be patient focused to achieve the desired outcome due to the individuality of patient life circumstances, health characteristics, and local care provider practice patterns. A sound long-term dialysis access is carefully designed to maximize patient quality of life, limit complications, improve survival and thereby will be cost-effective [16].

Thus, rather than emphasizing the doctrine of one modality fitting all, patient centered access planning is the preferred model. Decision-making requires input from the multidisciplinary team, including the vascular access nurse or nurse educator, nephrologist(s), surgeon(s), the patient and family members. The process includes timely patient referral to nephrologists and surgeons, patient education, with diligent follow-up by appropriate investigations and interventions in preparation for the desired dialysis access.

A Patient Focused Approach to Dialysis Access Selection

Dialysis access planning should start in chronic kidney disease (CKD) stage IV (glomerular filtration rate (GFR) 15-30 ml/min), when education about CKD and modalities of RRT should be discussed. The rate of decline of GFR over time is perhaps the best predictive guide to timely referral and access placement [17]. Recently, a prediction model was developed [18] and the use of proteinuria may help estimate the progression of CKD to ESRD. The components required for patient focused access planning are:

1) Timely and appropriate referral;
2) Education;
3) Patient history and physical exam;
4) Supportive investigations.
Timely and Appropriate Referral

Timely referral to a nephrologist and access surgeon for CKD management and surgical evaluation, respectively, increases the likelihood for placing a native vein AVF and reduces the likelihood of temporary CVC placement [14-19]. Therefore, when GFR approaches 30 ml/min, (CKD Stage 4), patient education about CKD, its potential progression to require RRT and dialysis access must begin. Appropriate referral for preemptive kidney transplantation and dialysis access must consider the patient’s “readiness” to accept their CKD diagnosis and its consequences, and the patient’s rate of CKD progression. When a patient is in denial or when their rate of renal decline is variable, one strategy is to empirically refer the patient for a surgical consult at a fixed level of GFR e.g. 15 ml/min. This strategy ensures that patients receive a surgical opinion that can be used by the multidisciplinary team for planning, reinforces the patient’s CKD reality, and may open the dialogue to consider peritoneal dialysis as a first access option, particularly if the patient is at high risk of AVF failure and may need multiple subsequent interventions to facilitate the access’ maturation and use for dialysis. Such a strategy allows for access education, consideration, and planning in patients who have relatively stable or “non-progressive” CKD whose renal function may suddenly deteriorate with an unexpected acute medical event.

Education

Each member of the multidisciplinary team must coordinate educational efforts so that the patient receives non-conflicting and clear information about their CKD, modality options, and the associated access. When the patient and their family members are active participants in the decision making process, adherence greatly improves [20-21].

A key element to emphasize in education of hemodialysis vascular access is to preserve veins by protecting them against veno-punctures, intravenous lines, central venous catheterizations and pacemaker insertions on the side of the planned future HD vascular access. For example, when venous access is required, only the dorsal aspect of the hand should be used. Peripherally inserted central catheters “PICC lines” should be avoided in patients with a potential future dialysis need, and should be considered absolutely contraindicated in patients with stage 4-5 CKD. Patients already undergoing HD can have blood draws done during their HD session to preserve veins.

Optimal outcomes, such as initiating HD with a functioning access is more likely when patients and their families receive high quality, individualized CKD education [19, 22, 23]. For example, in a nationwide study of >3000 patients, patients who received education about vascular access had an odds ratio of 2.06 for having an AVF or AV-graft placed compared with a CVC [23]. Patients who receive education about vascular access also had reduced anxiety about receiving their AVF [22]. This education must be supported by healthcare workers and administration alike within the hospital or dialysis facility, in order for it to be effective. Optimal patient outcomes and lowered costs will reinforce the effectiveness of comprehensive modality and access education.
Table 1. Factors Influencing Dialysis Modality Selection

Patient related.
- Patient education and motivation to learn about dialysis issues and options.
- Lifestyle, professional and educational factors.
- Socioeconomic factors e.g. available support systems.
- Co-morbidities and their severity.
- Stage of CKD.

Medical team related.
- Nephrologists’ education and training of PD and HD.
- Surgical experience and technical support.
- Resource availability for modalities.

Favoring HD.
- Patient limitations to learn the PD technique.
- PD training facility availability.
- Home environment e.g. Storage availability, inability to maintain hygienic conditions (e.g. untamed pets).
- Abdominal anatomy (e.g. colostomy).
- Extent of anatomical alteration and/or scarring from previous abdominal surgeries.
- Recurrent abdominal inflammatory events.
- Morbid obesity.
- Functional limitations.

Favoring PD.
- Degree of residual renal function.
- Desires active lifestyle.
- Employment time restraints.
- Unsuitable vessels for HD access, known HD access problems.
- Logistic difficulties (e.g transportation unavailable, prohibitive distance to HD facility).
- Strong support system.

History

A pertinent patient history and physical examination (H/P) are by far the most important first steps in determining the course of action, both prior to access placement and when evaluating an established access with problems. It is the foundation for the optimal dialysis modality selection and site of access placement [20, 21] for each patient. This pertinent history can be categorized broadly in terms of the patient’s:

1) Past medical history;
2) Current active medical issues;
3) Specific access focused history.

A patient’s past medical history will provide necessary details regarding the eligibility of a patient for PD or HD. For example, surgeries affecting the peritoneum, such as a colostomy will contraindicate a patient for PD. Important medical and non-medical factors that may
affect a patient’s ability to perform PD are listed in Table 1. Other medical history may help guide the nephrologist and surgeon regarding the most appropriate HD vascular access for a patient who is ineligible for PD or who is best suited for HD. For example, significant cardiovascular disease, as indicated by a history of a myocardial infarction, cardiac revascularization or established peripheral vascular disease are indicators of poor vessel integrity. When considering the appropriate HD access, such diseased vessels may not respond appropriately e.g., by dilating, in order for a fistula to mature. This may lead the clinician to further investigate the integrity of these vessels by dynamic vessel mapping (below) and may impact the HD access choice. Recently a clinical score has been developed and validated that may help risk stratify patients who may be at increased risk of their fistula failing [24] ; use of such a score is based on key elements determined from a well-conducted patient history. An example of how this fistula failure to mature (FTM) Risk Score “FTM Risk Score” can be used is illustrated in Figure 1.

Determining details of the patient’s current medical status and social situation is critical for access planning. For example, several social factors may suggest PD might be suboptimal (Table 1). If these factors cannot be overcome, a PD catheter access would be excluded as an access option. The medical status and life circumstances of the patient must be carefully considered when planning dialysis access. For example, the patient should survive longer than it would take for the access to be created and successfully used for dialysis. A familiar situation is the one where the potential HD patient is elderly, with a limited life expectancy. In this circumstance, a relatively short-term HD access, such as a synthetic AV-graft, can be established and used quickly instead of creating an AVF. Such a strategy would simultaneously achieve the goal of avoiding the complications of catheters and the inconvenience and cost of the potential interventions required to facilitate fistula maturation.

Case: 67 year old African American woman with ESRD due to hypertension requires a dialysis access. She has uremic symptoms (anorexia, nausea, vomiting and pruritis) but wishes to avoid a central venous catheter. She is obese, has established peripheral vascular disease with claudication pain, and has glucose intolerance. She still has residual renal function but her eGFR is 9 ml/min. Based on her FTM Risk Score (her score is 8), the likelihood of her fistula failing is close to 70%. This patient may benefit from a synthetic graft for hemodialysis or a PD catheter for peritoneal dialysis.

Figure 1. Risk Score.

An ‘HD access-focused’ history is unique and required in planning dialysis access. Such a history will shed light on potential complications that may occur, such as failure of an AVF to mature or AV-graft associated steal syndrome, and will navigate the surgeon to either
preemptive intervention or consideration of an alternate access. This “vessel focused” history includes determining the type and nature of past access procedures (especially CVCs, PICC lines and pacemakers), past accesses (interventions required to facilitate or maintain its patency and reason(s) for loss), breast and axillary dissection surgery, chest radiation and emergency vascular cut-downs. Furthermore, a parallel “PD-focused” history should be pursued to help inform the choice of dialysis access. Factors that may affect the peritoneum, such as the presence of significant inflammatory bowel or diverticular disease and prior abdominal surgeries require interrogation, especially when PD is a serious consideration.

Physical Examination

The focused physical exam includes a detailed inspection of the neck, chest, abdomen and extremities. The examination must take into consideration the significance of previous chest and abdominal surgeries (for PD), pacemakers, presence of edema and collateral vein formation suggesting central vein pathology. The vascular examination must assess both the arterial as well as the venous system [20, 21].

<table>
<thead>
<tr>
<th>Table 2. Minimal vascular requirements for successful AVF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Absence of central vein obstruction.</td>
</tr>
<tr>
<td>2. Segmental blood pressure differential of less than 20 mm Hg</td>
</tr>
<tr>
<td>3. Lack of segmental stenosis of artery or vein.</td>
</tr>
<tr>
<td>4. Anastomosis luminal diameter of at least 2.5 mm.</td>
</tr>
<tr>
<td>5. Straight vein cannulation segment of at least 2.0 cm.</td>
</tr>
<tr>
<td>6. Vein cannulation segment less than 5 mm below skin surface.</td>
</tr>
<tr>
<td>7. Matured vein (or synthetic graft) diameter of at least 6 mm.</td>
</tr>
<tr>
<td>8. Flow Rate of 500-600 ml/min or more.</td>
</tr>
<tr>
<td>9. .</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3. Key physical exam findings indicative of access dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Swelling within the face, chest wall, shoulder, breast or neck may be indicative of high venous pressure suggestive of central stenosis (e.g. superior vena cava or innominate vein). Collateral veins may also be evident on physical exam.</td>
</tr>
<tr>
<td>• Localized edema is indicative of potential infection or venous outflow impairment e.g. isolated forearm edema suggests a stenosis in the main draining vein.</td>
</tr>
<tr>
<td>• Palpably increased access pulsation: May be predictive of venous anastomotic stenosis and/or stenosis in the access body.</td>
</tr>
<tr>
<td>• Palpation may detect fibrotic stenotic lesions e.g. a “step” can be felt at the anastomosis.</td>
</tr>
<tr>
<td>• An overly strong (water hammer) pulse may be detected upstream to a stenotic lesion. The access downstream to the stenosis may collapse on arm elevation.</td>
</tr>
<tr>
<td>• High bruit pitch and/or short diastolic component may indicate stenosis; recall bruit should be heard throughout systole and diastole.</td>
</tr>
<tr>
<td>• Reduction in bruit intensity following arm elevation is indicative of arterial inflow abnormalities limiting flow.</td>
</tr>
</tbody>
</table>
• Prolonged bleeding time after needle withdrawal of > 10 minutes or a change from current baseline with no change in anticoagulation: This should be measured and documented as a potential indicator for AV-graft or AVF stenosis and requires evaluation.

Table 4. Main Features Addressed by Duplex Doppler Vascular Examination

**Arterial System.**
- Artery size from the axilla to hand including the palmar arch.
- Dual arteries in upper arm, i.e. high bifurcation.
- Degree of arterial wall calcification.
- Arterial stenotic lesions.
- Blood flow at defined segments.

**Venous System.**
- Detailed venous anatomy in arm and leg as needed.
- Vein size mapping from wrist to axilla.
- Vein patency and presence or lack of stenosis.
- Patency and flow pattern of subclavian vein.
- Presence of diving venous branch at antecubital fossa.

*Note: A (radial) artery diameter of 2 mm or less is unlikely to mature and therefore, fail from inadequate fistula flow (less than 500 ml/min). Likewise, an AV anastomosis diameter of 2.5 mm or less is likely to yield inadequate flow rate.*

For HD vascular access, a detailed vascular exam requires a relaxed patient in a comfortable environment. A cold room will cause vessel vasoconstriction and potentially underestimate the size of available vessels. The use of an upper arm tourniquet or warming the extremity (e.g. with hot water) followed by asking the patient to close and open their fists, will help augment vessels for assessment. The arterial assessment should include evaluation of pulse quality, segmental blood pressure, and the Allen test. The venous system comprises a detailed inspection and palpation for vessel integrity, caliber and size. Duplex ultrasound (DU) may be used to clarify or confirm concerns of vessel integrity and/or may be used to better define surgical and interventional anatomy (below). The minimal vascular requirements for a successful AVF are listed in Table 2.

Once the HD access is created, it should be routinely monitored by physical examination. The presence of a palpable thrill, pulse quality, and appearance of the overlying skin (i.e. redness, edema, skin quality) are essential components of the examination. See Table 3.

**Supportive Investigations**

Duplex ultrasonography (DU) is a standard non-invasive outpatient diagnostic test that may be used to supplement the findings of a prior H/P and help confirm decisions regarding the optimal dialysis access. DU combines conventional B-Mode (black and white brightness)
ultrasound imaging with doppler imaging (color and spectral analysis). Thus, it has potential to provide important information on both the dimensional anatomy of the vessels and blood flow characteristics. It should be performed in cases where there is a H/P of any of the following:

1) Extremity swelling.
2) Prominent/collateral veins on extremity.
3) Size differential between extremities.
4) History of CVC, PICCs or pacemakers.
5) Previous access surgeries at, below or above the planned site.
6) Previous surgeries on the access-planned arm, neck or chest.
7) Complicated and/or previously failed access.

DU is particularly useful in the obese patient, but may not always add much to a careful and experienced physical exam (below). Indeed, the quality of the DU examination is operator dependent; ideally, the surgeon should perform the DU or be present to direct the sequence of examination steps and mark the skin, documenting vessel size, intended surgery sites, and anatomical variations [20, 21]. The specific features assessed during DU are listed in Table 4.

Since the findings of DU should be considered amongst other variables determined by the H/P, caution should be given to using size criteria alone to determine vessel eligibility for the desired access. Such a narrow focus may lead to missing other important features of the vessel, including vessel quality (calcifications, distensibility), and prior vessel injury that may contribute to intimal hyperplasia and failure. Imaging must document full compressibility and patency of all vessels examined with absence of any luminal defects and or thrombosis. Outcomes are expected to be superior when DU involves maneuvers to assess the vessel’s distensibility with its response directly observed by the surgeon performing the access surgery [29, 30].

The value of preoperative vessel mapping has ranged from harmful (leading to delays in access creation and greater failures) [31], equivocal (similar outcomes to physical exam) [32, 33], and superior with improved fistulas outcomes [14]. Given the mix of potential outcomes [34], a cost analysis might provide guidance regarding the use of DU but has yet to be conducted.

An abbreviated DU strategy of venous and arterial vessel assessment for access planning follows. A more detailed assessment on DU can be found in Chapter 11 of this textbook.

**A) Stepwise Strategy in the Duplex Ultrasound Evaluation**

Both arms are examined with the patient in the sitting or supine position, starting with the non-dominant arm in a dependent, relaxed position with the elbow slightly flexed and forearm supinated. To dilate veins, use an upper arm tourniquet and/or ask the patient to make hand fists over a soft ball. Apply pre-warmed body temperature conducting gel.

**Venous System**

*The antecubital (AC) superficial venous anatomy* (median cubital vein (MCV), cephalic vein (CV), basilic vein (BV)) and their continuation proximally up in the arm and distally down the forearm must first be visualized. Although much variation exists, there is a typical
venous anatomy pattern where the CV and the BV are connected by the MCV, depicted in Figure 2. Uniformly, a diving vein (vena communicantes) at the AC level connects the superficial system to the deep brachial (concomitant) veins. In cases of inadequate forearm anatomy for a wrist AVF, this is the ideal site for the vein anastomosis forearm loop with a synthetic graft, providing three or more outflow veins. This will allow upper arm veins to mature and dilate making future upper arm access (i.e. basilic vein transposition, brachio-cephalic AVF and upper arm synthetic graft) successful.

The cephalic vein (at the forearm) is then followed from the antecubital fossa to the wrist. At the wrist, a minimum vein diameter of 2.5-3.0 mm is desirable. The presence of the cephalic vein dorsal branch (usually within 5-6 cm from the wrist joint) is optimal for an end “patch” cephalic vein to side radial artery anastomosis [21]. In contrast, duplicate cephalic veins or other anatomical findings (i.e. multiple branching) might make future AVF maturation and/or successful dialysis needle cannulation less likely.

The cephalic vein (in the upper arm) is next assessed moving proximally to the shoulder. Often, 4-6 cm above the antecubital fossa, a lateral branch of the CV from the forearm joins the upper arm CV. This branch is important when considering an upper arm brachial artery to cephalic vein AVF, since this lateral branch may need to be divided or could be used (depending on size, location and distance to the brachial artery). Sometimes a brachiocephalic AVF at the elbow site may be created using the bifurcation of the diving vena communicantes as a vein “patch” anastomosis to the side brachial artery. An AVF at the antecubital fossa is a reasonable second choice when suitable vascular anatomy at the wrist is lacking.

The basilic vein is identified either at the antecubital fossa by following the median cubital vein (MCV) into the BV or by finding it more proximally, closer to the axilla. Because of its deep location, the BV is usually untouched by venipunctures (except for PICC lines). When considering a basilic vein transposition (BVT), it is optimal to assess the entire BV length from AC to the axilla. The BV usually bifurcates 4-5 cm above the AC (sometimes into 3-4 branches), of which one branch becomes the main forearm BV. Sometimes the BV is missing or joins the brachial veins at the mid upper arm level. Although transposing a brachial vein, as a continuation in such a case is feasible, this may not be the most optimal vessel sparing option. A more distal synthetic graft (i.e. a forearm loop graft) will make upper arm veins enlarge for future use and preserve vessels. Surgeons must be selective when choosing the upper arm BVT procedure, since a synthetic graft may produce equal or better outcome than a borderline BV [35].

The basilic vein in the forearm is typically larger (3-5 mm) and may be suitable for transposition.

Although an AVF can be made between the distal basilic vein and the ulnar artery at the wrist, the awkward position makes needle cannulation practically difficult. Thus, transposition of the forearm basilic vein in a straight or loop configuration to the distal radial artery at the wrist or to the brachial or radial artery at the AC fossa, respectively, may be feasible. The loop configuration is chosen when the wrist arteries are deemed inadequate.
Arterial System

For the creation of upper arm accesses, the subclavian, axillary, brachial, radial and ulnar arteries are assessed for patency and breaches of integrity, such as vascular calcifications or stenosis. Systolic pressures are also measured at the brachial (upper arm), ulnar and radial sites (forearm); pulse volume recording (PVR) waveforms are obtained at both levels, bilaterally. Any pressure gradient of greater than 15 mmHg found upon comparison between the two arm pressures is considered hemodynamically significant and merits further investigation to assess the brachiocephalic and subclavian arteries (i.e. arteriogram).

The importance of evaluating the arterial system should not be underestimated. For example, if a severely calcified or small (<2.0-2.5 mm) radial artery is seen on DU, an AVF created with such a vessel would be at high risk of failure because of poor distensibility and insufficient inflow, respectively. Also, the ulnar artery should be evaluated when creating a radiocephalic AVF as a small or absent ulnar artery may increase the risk of steal syndrome.

The Allen test [26] can be performed during DU to confirm findings found by physical exam. A photoplethysmography probe is used to obtain the baseline thumb arterial flow doppler signal without any compression maneuvers. The signals are then obtained repeatedly while manually compressing the radial artery first, the ulnar artery next, and then both arteries together. If the doppler signal demonstrates a significant reduction in the amplitude when the dominant artery is compressed i.e. both palmar arches do not communicate (Figure 2), this should serve as a warning of risk of hand ischemia after access placement.

B) Angiogram

If the physical exam or DU assessment raises concerns where confirmation or clarification of vascular anatomy is warranted, invasive imaging using contrast dye or CO2 angiography is warranted [36 37]. See Chapters 2 and 3 for further details.
Putting It into Practice: A Team Approach

The above strategies and decision-making processes requires a coordinated teamwork approach which encompasses a “continuum of care” model for CKD. The dialysis access strategy should be considered a “life strategy” whereby the appropriate access is the one that aligns the modality for renal replacement therapy (dialysis or transplant) to help each patient achieve their life goals safely. This concept relies on clear, timely, and effective communication between the patient and their family, and key team members. As such, a dialysis access short and long term plan should be updated on a regular basis. With a proactive approach future anticipated access problems can be addressed with the overall goal to avoid access complications, dialysis interruptions, temporary central venous catheter use and associated morbidity.

While this approach strives for the best practice option for each patient, the actual treatment modality may be quite different, sometimes dictated by complex, and/or uncontrollable circumstances. For example, peritoneal dialysis may be deemed the best option for an elderly patient; however, the individual may reside by themselves in a rural area and the required assistance by a homecare nurse may not be available. Aside from logistical concerns, culture, tradition and religious beliefs may greatly affect the decision making process in treating the CKD patient.

An open mind and flexibility to allow the optimal vascular access for the patient is required if hemodialysis is chosen as the modality. Generally the outcome of functioning native AVF are superior to that of AV-grafts. However, the increasing number of AVFs unsuitable for dialysis has resulted in more patients needing long-term catheter dialysis access and exposure to their serious complications. A patient focused approach will ask four basic questions to help guide the placement of the most appropriate dialysis access. They aim to explore the patient’s medical conditions, available access anatomy, feasibility for each modality and their corresponding access, in the context of their individual life experiences, circumstances and goals, for optimal access planning and success (Figure 3 [38]).

1) What is the timeframe available for access creation and functional use? One must consider what stage of CKD the patient is in: Is the patient pre-dialysis with stable or rapidly progressing kidney failure? In other words, is there time to place a fistula that
will mature and function in time for dialysis initiation? Depending on their risk of fistula failure, will there be time for facilitatory interventions and/or creation of another fistula if it fails? Is the patient already on dialysis? If so, will the fistula mature quickly enough to avoid prolonged catheter exposure or would a synthetic graft be more appropriate?

2) *What is the patient’s overall life expectancy?* Is the patient young with residual renal function who might benefit from peritoneal dialysis or is the patient elderly with serious competing comorbidity? In the later situation, it would be unjust to subject a patient to fistula creation whereby the time required for fistula maturation may be longer than the patient’s expected survival. Here, placement of a graft may provide safe dialysis without the exposure to catheter use and risk of infection/sepsis. Each patient’s life circumstances must be considered when deciding on dialysis modality and its access. If a young patient were not an immediate transplant candidate, an ideal situation might be to initiate PD when the patient has residual renal function. This would preserve renal function for a longer duration and impact patient survival for the first several years after dialysis initiation [39-45]. Concurrently, the patient would be evaluated for a kidney transplant, which may occur pre-emptive to PD technique failure. Patients who receive a kidney transplant while on PD have better long and short-term transplant outcomes compared to those patients who are on HD immediately prior to kidney transplant [46, 47]. Alternatively, a fistula could be created prior to PD failure. Such pre-emptive fistula creation would allow ample time for maturation and for creative access options such as two-stage surgical procedures to optimize access outcomes. Clearly, individualized variations to this ideal are a given but an effort to consider PD as a primary option when appropriate is important.

3) *Has the patient had previous failed accesses?* This information would provide insight into the patient’s likelihood of future access success, potential need for intervention and catheter exposure. The patient’s prior experience with their access may impact on their future access choice and/or dialysis modality.

4) *What is the patient’s likelihood of fistula failure?* A functioning fistula should always be the first consideration; however the risks and benefits must be weighed for each patient. The likelihood of failure is an estimate that combines information gathered clinically using history and physical (with or without assistance from the FTM Risk Score) and from evaluation of vessels (with or without pre-operative vessel mapping). These 4 questions are merely a guideline to encourage an open minded and thorough approach to access planning with the patient’s specific physiology and unique life-circumstances as focal considerations.

## Conclusion

Proper modality and access planning involves an individualized patient strategy which is required to prevent serious uremic complications, improve patient outcomes and quality of life in a cost-effective way [48]. It is dependent on appropriately timed, integrated, open-minded multidisciplinary education, coordination, input, and intervention. The different dialysis modalities and access types must not be seen as competitive but rather
complementary where over the modality and access’ lifetime, maximal complication free utilization is the overall goal.

References


Radović M., Jemcov, T. Primary arteriovenous fistula patency is dependent of venous distensibility, not inflammatory, procoagulant markers or vascular functional parameters 2011; A. S. N. oral presentation, Philadelphia, P. A.
Planning for Vascular Surgery – A Patient Centered Approach


Chapter II

The Arterial and Venous System as They Apply to Vascular Access

*Bharat Sachdeva*
L. S. U. Health Sciences Center, Shreveport, LA, US

Keywords: Vascular Access, Dialysis, Anatomy, Artery, Vein, Fistula, Graft

Introduction

Mortality and morbidity in a hemodialysis patient is significantly affected by the kind of vascular access. [1]. Nephrologists have the challenge to not only establish a working Arterio-Venous (AV) fistula for their patients, but also to monitor the access for any complications. Preoperative vessel mapping increases the placement rates for AVF [2] and combination of Physical Exam, Ultrasound and Venography to establish the adequacy of vessels prior to surgical procedure can help minimize a high primary fistula failure rate [3]. An Interventionist involved in management of dialysis access problems; will need a comprehensive knowledge of not only the normal anatomy but also be aware of anatomical variants known to exist in vascular anatomy. In this chapter we will review pertinent anatomy relevant to dialysis access creation and management.

Basic Anatomy Arteries/Vein

Arterial and venous walls contain three concentric layers (*tunicae*). The vessels adapt to their different circulatory tasks by differing in the structure of these layers. The inner coat, tunica intima, consists of a single layer of endothelial cells applied to a thin connective tissue
layer, the basement membrane. The middle coat (tunica media) contains primarily smooth muscle, elastic tissue fibers and collagen. The outer coat (tunica adventitia) embeds the vessel in its surroundings and consists mainly of connective tissue along with nerve and vessel capillaries. Stenosis in Venous system usually involves the intimal layer and angioplasty may cause tear/rupture in plaques.

Veins are characterized by comparatively thin wall in comparison to arteries of similar size. Pressure inside the veins approaches zero, close to the heart and vessel lumen may be held patent by tethering of veins to connective tissue fasciae. Amount of muscle in veins is considerably less compared to arteries but veins have ability of vasoconstriction in response to vessel injury, sometimes seen as spasm after balloon inflation.

Most veins have “valves” to maintain blood flow in one direction. Valves have a lining of endothelial cells with collagen and elastic fiber providing support. Semilunar in shape, they are attached by the convex edges to the vessel wall. Most commonly two or three valves lie opposite to each other. During antegrade flow the valve is approximated against the vessel wall. If flow gets retrograde, one way valve close and blood fills an expanded region of the vein. On Venography this may give a “knotted appearance” to the distended vein. One of the options available to a surgeon creating AV fistula is a proximal radial artery to native vein (cephalic/basilic) in distal forearm, a retrograde flowing access created by disrupting the venous valve using a vessel probe. [4, 5]

**Vascular System of Upper Extremity**

Venous drainage of the Upper Extremity is divided into the superficial and deep venous system separated by the deep fascia. While dialysis access procedure utilizes primarily the superficial veins in the forearm, both superficial and deep veins can be used for AV access in upper arm.

The superficial veins of the upper extremity are the digital, metacarpal, cephalic, basilic and median vein. Digital and Metacarpal veins form dorsal venous plexus on dorsal surface of the hand and should be accessed for all blood draw in chronic kidney disease (CKD) patients to preserve the superficial cephalic, basilic and median vein for future AV access [6]. Located distally, an injury to the veins at this location would not jeopardize future access options. Injury to cephalic vein, medial cubital vein or the basilic vein in forearm/upper arm will eliminate use of the vein for fistula creation in future.

*The cephalic vein* (Figure 1) starts at the dorso-lateral aspect of wrist (snuff-box), the vein winds around the lateral end of forearm to run on the ventral surface of the forearm. Cephalic vein at “snuff-box” runs close to radial artery and “snuff-box” fistula will be the most distal anastomosis of radial artery and cephalic vein. The cephalic vein then passes over the ventral surface of the elbow where it connects with the median cubital vein (Communicating vein between the cephalic and basilic on the ventral surface of elbow).

Cephalic vein diameters of < 1.6 mm have been associated with A/V fistula failure [7], while good patency rates were obtained in patients with A/V fistulas that were created with minimum diameter of the cephalic vein at the wrist > 2-2.5mm. [2, 8]

The cephalic vein (Figure 2) then ascends in front of the elbow in the groove between the Brachioradialis and the Biceps brachii muscle. It pierces the coracoclavicular fascia at
shoulder, crosses the axillary artery, and ends in the axillary vein just below the clavicle to form the subclavian vein. The cephalic arch (Figure 4) is the final 3-5cm of the cephalic vein before it joins the axillary vein to form the subclavian vein. The cephalic arch is a common site for stenosis seen in as many as 39% of upper arm cephalic vein fistulae. [9] High turbulence and shear stress related to the curve, higher number of valves in this region of the vein just distal to the orifice of axillary vein and external compression by the fascia and muscles as the vein traverses medially to join axillary vein; are proposed as the mechanisms causing the vein to develop stenosis in this segment. [10]

Sometimes cephalic vein communicates with the external jugular vein by a branch which ascends in front of the clavicle and joins the internal/external jugular vein.

The basilic vein (Figure 1) starts dorso-medial surface of the wrist, curves around the ulnar surface of forearm to come on the ventral forearm. It runs on the medial aspect of the forearm to elbow where it is joined by the median cubital vein (Joins the basilic vein to the cephalic vein). It then runs upward along the medial border of the Biceps brachii, perforates the deep fascia a little below the middle of the upper arm (Figure 2) and ascending on the medial side of the brachial artery to the lower border of the Teres major, is joined by brachial vein to continue onward as the axillary vein.

Figure 1. Forearm Veins: A-Cephalic Vein, B-Basilic Vein, C- median antibrachial vein.

Figure 2. Upper Arm Veins: A-Cephalic Vein, B-Brachial Veins, C-Basilic Vein.
Communicating branches to the deep veins are used to create a variant of elbow fistula; the Gracz fistula [11, 12]. The perforating vein, originating from various sites of the venous triangle in the elbow region, (media cubital vein, cephalic and basilic vein) is anastomosed to the brachial or the proximal radial artery. The perforating vein can dilate and remodel only to a limited extent, thus interposing a natural constriction between the artery and vein.

Forearm basilic vein can be used with transposition for AV fistula when the cephalic in forearm is inadequate for fistula creation. [13] In upper arm the vein runs deep to the deep fascia and has to be superficialized for cannulation. [14] In upto 17% of patients basilic vein drains into the brachial vein close to the elbow and a single, unpaired brachial vein runs the length of the arm. Failure to recognize this variation will result in inadvertent ligation excision of the single brachial vein in upper arm with subsequent arm swelling. [15, 16]

The accessory Cephalic vein starts at the dorsal surface of the hand, drains upwards on the dorsal surface of the forearm (Lower 2/3) and then curves proximally towards the ventral aspect of the hand near the elbow to join the cephalic vein. In some cases the accessory cephalic springs from the cephalic above the wrist and joins it again higher up. A large branch may connect the basilic and cephalic veins on the back of the forearm. The median antibrachial vein (Figure 1) drains the venous plexus on the volar surface of the hand. It ascends on the ulnar side of the front of the forearm and ends by joining the basilic vein or the median basilic vein.

The deep veins follow the course of the arteries, are generally arranged in pairs, and are situated one on either side of the corresponding artery, and connected at intervals by short transverse branches. Since most of the venous flow from the upper limb is returned by superficial veins, the deep veins are relatively small. Deep volar venous arches in the hand drain into the radial vein, running with the radial and ulnar arteries, they join near the elbow as paired brachial veins.

The brachial veins (Figure 2) drain as a pair around brachial artery, medial vein frequently joins basilic vein to form axillary vein. Axillary vein (Figure 3) ascends to the outer border of the first rib where it becomes the subclavian (Figure 4). Axillary vein is joined by brachial vein distally and near the termination by the cephalic vein. The subclavian vein (Figure 4) extends from the outer border of the first rib to the sternal end of the clavicle, where it joins the internal jugular to form the innominate vein (Figure 4). At its junction with the internal jugular, the left subclavian vein receives the thoracic duct, and the right subclavian vein the right lymphatic duct. The Right Innominate Vein (2.5 cm. in length) joins with the left innominate vein (Figure 4) (6 cm. in length) close to the right border of the sternum and forms the superior vena cava (SVC) (Figure 4). SVC descends from its origin to join the right atrium at the level of the third right costal cartilage in front and the seventh thoracic vertebra behind.

Vertebral veins drain into innominate close to its origin, and, lower down, the internal mammary and inferior thyroid veins, empty into innominate vein. Stenosis of subclavian vein with an AVF access on ipsilateral arm will present as arm swelling, whereas stenosis of Innominate may cause facial/breast swelling along with ipsilateral arm swelling. Persistent left SVC (PLVC) can be seen in 0.3% of patients, left innominate vein drains directly into right atrium. [17]

Also draining into the SVC is the azygos vein. The azygos vein is derived from a venous system that originates in the dorsal wall of the lower abdomen and is the system into which the intercostal veins drain.
It is important to recognize because it may be quite large and prominent with SVC/IVC stenosis. The azygos runs up the posterior part of the mediastinum, to the right of the aorta and thoracic vertebrae. It curves forward over the root of the right lung and opens into the superior vena cava just before it drains into right atrium.

**Anatomy Neck Veins**

The side of the neck presents a somewhat quadrilateral outline, subdivided into two large triangles by Sternocleidomastoid, which passes obliquely across the neck, from the sternum
and clavicle below, to the mastoid process and occipital bone above. The triangular space in front of this muscle is called the anterior triangle of the neck, and that behind it, the posterior triangle of the neck.

The *internal jugular vein* collects the blood from the brain, from the superficial parts of the face and from the neck. It runs down the side of the neck in a vertical direction, lying at first lateral to the internal carotid artery, and then lateral to the common carotid, and at the root of the neck unites with the subclavian vein to form the innominate vein. At the sternoclavicular joint the internal jugular vein passes between the sternal and clavicular heads of the sternocleidomastoid (the site where the jugular venous pressure is assessed and central venous access commonly obtained).

Significant variation is seen in position of internal jugular in relation to common carotid artery. In majority of patients (54%), internal jugular vein overlies the common carotid artery [18]. Ultrasound guided cannulation of internal jugular vein can help prevent inadvertent cannulation of carotid artery [19]. Right internal jugular vein is placed at a little distance from the common carotid artery, and crosses the first part of the subclavian artery, while the left internal jugular vein usually overlaps the common carotid artery. The left internal jugular vein has 3 natural curves, at junction of internal jugular with innominate vein; curve around aortic arch and at the junction with SVC. Catheter placed in the right internal jugular vein have significantly less dysfunction compared to left internal jugular vein catheters (6.6 *versus* 19.5%; *P* <0.001) [20].

*External jugular vein* receives the greater part of the blood from the exterior of the cranium and the deep parts of the face. It commences within parotid gland, on a level with the angle of the mandible, and runs perpendicularly down the neck, in the direction of a line drawn from the angle of the mandible to the middle of the clavicle at the posterior border of the Sternocleidomastoideus. In its course it crosses the Sternocleidomastoideus obliquely, and in the subclavian triangle perforates the deep fascia, and ends in the subclavian vein. The external jugular vein varies in size, bearing an inverse proportion to the other veins of the neck, it is occasionally double.

**Arteries Of The Upper Extremity**

Preoperative evaluation of the arterial system would ensure adequacy of the arteries to sustain a fistula and also help prevent ischemic complications to the hand. Duplex ultrasonography criteria for adequate arterial anatomy includes:

1. Patent palmar arch;
2. Arterial inflow diameter > 1.6 mm;
3. Symmetric upper extremity blood pressures (discrepancy < 20 mm Hg). [2, 6, 21]

Arterial supply hand is divided into superficial (fed primarily by the ulnar artery) and deep (formed by continuation of the radial artery) palmar arch. The two systems combined provide extensive collateral circulation to the digits of the hand. Integrity of palmar arch (Figure 7) should be confirmed prior to all AVF placements by performing Allen test. [22]
The Arterial and Venous System as They Apply to Vascular Access

Figure 5. Upper arm Artery: Brachial Artery and Axillary artery.

Figure 6. Forearm Arteries: A-Radial Artery, B- Ulnar Artery, C- Common Interosseous artery.

Figure 7. Forearm Arterial System: A-Radial Artery, B-Ulnar Artery, C- Palmar Arch.
Bharat Sachdeva

Figure 8. High Bifurcation of Brachial Artery: A-Brachial, B-Ulnar, C-Ulnar Artery.

Radial Artery (Figure 6) begins about 1 cm distal to the bend of elbow and descends along the lateral side of the forearm to the wrist. It is palpable superficially at the anatomical snuffbox. It then curls posteriorly to laterally to form the deep palmar arch along with the deep branches of the ulnar artery. Radial artery arises proximally in upper arm in about 1/5 cases; usually, from the axillary (23%) or beginning of the brachial artery (64%) [23, 24]. Named the brachioradial artery (Figure 8), it runs superficial to the median nerve along the arm and passes anterior to the bicipital aponeurosis in 1/3 cases [24].

Ulnar Artery (Figure 6) is the largest terminal branch of the brachial artery. It begins just distal to the elbow and reaches the medial side of the forearm; midway between elbow and wrist. It crosses the wrist and then continues across the palm as the superficial palmar arch. Similar to radial artery, the ulnar artery may arise proximal to the elbow from the brachial artery or from the axillary artery [24].

Brachial Artery (Figure 5) is continuation of the axillary beyond the upper 1/3 of the arm and ends just below the elbow joint. At first, it is medial to the humerus but gradually spirals to the anterior until it lies midway between the humeral epicondyles. The artery is superficial, covered anteriorly only by skin and superficial/deep fascia. Frequently, the brachial artery may divide more proximally than usual into radial and ulnar branches. Axillary Artery (Figure 5) begins at the first rib’s outer border and ends at the upper 1/3 of the arm; where it becomes the brachial artery. The artery is quite superficial in the axilla, covered only by skin and the fascia.

Vascular System of the Lower Extremity

Femoral Artery (Figure 10) is a continuation of the external Iliac artery (Figure 9), begins at inguinal ligament (common femoral artery), midway between the anterior superior iliac spine and pubic symphysis. It then descends along the anteromedial part of the thigh in the femoral triangle and becomes popliteal artery. Behind the inguinal canal the artery lies in the lateral compartment of the femoral sheath that houses femoral vein in the middle and lymphatics in the medial canal. Just below the inguinal ligament the common femoral gives
off the profunda femoris branch and continues down as the superficial femoral artery; used as inflow for thigh AV access.

Popliteal Artery (Figure 10) is not usually used for inflow for dialysis access, knowledge of the artery is vital in cases with symptoms of claudication. Stenosis of the popliteal artery is frequently seen in peripheral vascular disease and may worsen flow to distal limb. Popliteal artery starts as a continuation of the femoral artery, descends laterally to the intercondylar fossa (Knee). It divides into the anterior and posterior tibial arteries.

Figure 9. Aortogram: A-Aorta, B-Common Iliac artery, C-External Iliac artery, D- Internal Iliac artery (Hypogastric Artery).

Figure 10. Lower Extremity Arterial System: A- Common femoral artery, B- Perforating artery, C- Superficial Femoral artery, D- Popliteal artery.

Anterior Tibial Artery descends anterior/lateral to the tibia, to lie anterior to tibia and lies midway between the maleoli continuing on the dorsum of the foot as the arteria dosrsalis
Veins of the Lower Extremity

Great saphenous vein is the longest vein in body, starts as continuation of medial marginal vein and ascends up to join femoral vein 3 cm below the inguinal ligament. The femoral vein is a continuation of the popliteal vein. It extends from above the knee to the inguinal ligament. As the vein passes under the inguinal ligament, it lies medial to the femoral artery. The femoral vein continues as external iliac vein after passing under the inguinal ligament. The external iliac continues around the rim of the pelvis to join with the internal iliac (also referred to as the hypogastric vein) opposite the lumbosacral articulation to form the common iliac. The right and left common iliac veins converge and join to form the inferior vena cava at the level of the upper border of the fifth lumbar vertebra.

Femoral and saphenous veins can be transposed to be anastomosed to proximal or mid thigh superficial femoral vein. Transposed native vein fistula in thigh has significantly lower risk of infection compared to synthetic loop graft [25].

Conclusion

Hemodialysis vascular access and its associated problems represent an extremely important part of the management of the chronic dialysis patient. A great deal of morbidity can be saved by a through preoperative assessment/understanding of the anatomy. Planning for an access should start with a through physical examination, use of ultrasonography with duplex exam of arterial flow and Venography of central veins.

References


Chapter III

Vascular Mapping Prior to Access Creation

Vandana Dua Niyyar*
Emory University, Atlanta, GA, US

Abstract

The population of patients with end-stage renal disease (ESRD) in the United States is progressively increasing, with hemodialysis (HD) as the major mode of renal replacement therapy. The National Kidney Foundation’s Dialysis Outcomes and Quality Initiative and the Fistula First Initiative recommend increasing the use of arteriovenous fistulae (AVF) in both incident and prevalent hemodialysis patients. The use of pre-operative vascular mapping to assess the presence of suitable vessels among both pre-dialysis chronic kidney disease (CKD) and ESRD patients on HD has been shown to increase the AVF placement rate. This chapter aims to review the literature on vascular mapping, including the various techniques (physical examination, ultrasonography and angiography); their advantages and disadvantages and whether it helps to maximize the AVF creation rate as well as increase functional AVF in the HD population.

Introduction

The population of patients with end-stage renal disease (ESRD) in the United States is progressively increasing, with hemodialysis (HD) as the major mode of renal replacement therapy [1]. Of the three types of hemodialysis vascular access, arteriovenous fistulae (AVF) have higher patency rates [2], lower infection rates [3] and lower overall costs [1] than either grafts or catheters. Consequently, the National Kidney Foundation’s Dialysis Outcomes and Quality Initiative recommends that AVF be placed in 50% of all incident and 40% of all prevalent dialysis patients [4]. The Fistula First Initiative, jointly formed by CMS and

*Emory University, Division of Nephrology, Woodruff Memorial Research Building, Rm 338, 1639 Pierce Drive, Atlanta, GA 30322.
the ESRD has complemented this goal by aiming to have 66% of prevalent hemodialysis patients dialyzing with an AVF, via specific change concepts to promote AVF placement and maintenance [5].

However, the majority of patients initiate hemodialysis with a central venous catheter (CVC) as their primary access [6, 7], despite these recommendations. Frequent phlebotomies, peripherally inserted central catheters (PICC) lines [8] and a high prevalence of co-morbid conditions including diabetes, obesity and vascular disease [9] in this high-risk population may negatively impact the vasculature. This may, in part, contribute to early AVF dysfunction and the high rate (20%-50%) of primary failure that precludes their successful use for dialysis [7].

Thus, for both pre-dialysis CKD and ESRD patients on hemodialysis, pre-operative vascular mapping is recommended prior to AVF creation. This article aims to review the literature regarding pre-operative vascular mapping and whether it promotes AVF creation and increases AVF use.

The Techniques

Vascular mapping includes assessment of both arterial and venous systems prior to access placement. One of 3 techniques may be used: physical examination, ultrasonography and angiography.

Physical Examination

A simple bedside assessment may be done to evaluate the patency of the arterial and the venous systems.

Arterial evaluation includes documentation of bilaterally equal strong pulses and differential blood pressure measurements in both extremities. The Allen’s test should be performed prior to creation of any forearm AVF to assess the patency of the palmar arch. For the venous examination, a tourniquet is placed at the upper extremity and the veins are inspected to assess the diameter, the length of a straight venous segment suitable for cannulation and the distance of the vein from the skin surface [10]. Though an upper extremity physical examination can be valuable; used alone, it is often inadequate, particularly in obese patients or those with a history of prior vascular access and may need to be supplemented with additional techniques, such as ultrasonography [11]. In a cohort of 116 patients, vein quality was considered good in patients with adequate cephalic vein visibility, poor with hardly visualized veins, and absent when no veins could be found by physical examination.

Duplex sonography was then was performed in patients in whom veins were not visible clinically and venography was reserved for those patients who did not have adequate veins on both physical examination and ultrasound. Preoperatively, clinically examined veins could be found in only 54 of 116 patients (46.5%), and poor clinically visible or clinically absent veins were found in 62 patients (53.5%). Among these 62 patients, duplex sonography established good veins in 48 patients (77%), and only 14 patients (23%) required venography [11].
Ultra声 Examination

Ultrasonography is an excellent tool that provides an objective and non-invasive assessment of the venous and arterial systems prior to fistula creation. The preoperative criteria currently used to support successful AVF maturation include a minimal venous diameter of 2.5 mm and a minimal arterial diameter of 2.0 mm in the upper extremities. [12]. The technique for vessel ultrasonographic imaging is meticulously detailed in prior publications and the salient points are as follows [7, 13, 14]. The patient’s arm is positioned comfortably, at approximately 45° from the body and the forearm is evaluated first. Evaluation of the upper extremity arteries includes measurement of arterial wall thickness, the internal diameter, arterial flow and the presence of calcifications and/or other abnormalities. Both ulnar and radial arterial diameters are evaluated; and if they are less than 2.0 mm in diameter, the arteries are not suitable for forearm AVF creation and the brachial artery is then assessed.

Similarly, in order to visualize the venous system, the entire upper extremity is evaluated, starting from the cephalic vein in the forearm to the cephalic, basilic and axillary veins in the upper arm. A tourniquet is sequentially placed at the mid-forearm, antecubital area and at the upper arm and the cephalic, basilic and brachial vein diameters are measured throughout their course up to their insertion into the subclavian or axillary veins. However, a limitation of ultrasonography is that it offers only indirect evaluation of central venous vasculature, which is assessed for stenosis or thrombosis by analysis of the waveform for changes in respiratory phasicity and transmitted cardiac pulsatility. Thus, particularly among patients with a history of central venous catheter use, additional techniques may be needed.

In a study designed to evaluate the impact of DOQI (Kidney Dialysis Outcome and Quality Initiative) guidelines, including the routine use of pre-operative venous mapping, the authors reported a significant increase in the use of autogenous AVF (5% to 68%) [15]. In another prospective evaluation to assess the effect of pre-operative vessel mapping by ultrasonography, pre-operative mapping resulted in a change in the planned procedure in 31% of the patients, and the AVF placement rate increased from 32% to 58%. Unsuccessful surgical explorations decreased from 11% to 0% [13]. Based on these promising initial data, the authors extended their intervention and reported the results over a 17-month period. The proportion of fistulas placed increased from 34% in the historical controls to 64% with pre-operative vascular mapping. Not only that, their intervention resulted in essentially doubling the proportion of patients dialyzing with a fistula (from 16% to 34%). [16]

Angiography

Vascular mapping can also be conducted via radiocontrast administration [10, 17], though it is primarily the veins that are evaluated with this technique. A peripheral vein on the dorsum of the hand is cannulated and the arm is then placed in the anatomic position. Sequential tourniquets are then applied - one at the elbow and the other at the axilla. Low iso-osmolar contrast diluted with normal saline is injected through the cannula and images are obtained throughout the course of the veins using calibrated fluoroscopy. The lower tourniquet may be removed once the forearm is examined, to allow contrast to pass into the
upper arm. The criteria used to determine suitability of veins for AVF placement are the same as those for ultrasonography [12]: vein diameters of at least 2.5 mm, a 6 cm long straight cannulation segment and patent draining and central veins.

Angiography offers the advantage of direct imaging of the central veins, and is often employed in patients with a history of long-term central venous catheter use. Nevertheless, administration of radiocontrast material does expose the patient to the risk of potential nephrotoxicity. Recent data have shown that small doses of low iso-osmolar contrast agent for venous mapping may be safe in patients with stages 4 and 5 CKD [18, 19]. In a prospective dataset, 25 consecutive patients were evaluated for contrast nephropathy after venograms utilizing 10-20 ml of contrast. Of the 21 patients who had pre- and post procedure GFR measurements, there were no differences in the two measurements [19]. In another study evaluating the safety of low-dose contrast for endovascular salvage, a total of 65 procedures on 34 patients were performed over 2 years. The authors reported the incidence of contrast-induced nephropathy as 4% at 2 days and 4.7% at 1 week. All patients returned to baseline renal function at 2 weeks and none required dialysis. The authors concluded that fistulas could be salvaged with low dose contrast in advanced CKD [18]. However, larger studies with long-term follow-up are needed prior to establishing the safety of contrast in this high-risk population.

A prospective analysis involving an organized program by an interventional nephrology team for tunneled catheter assigned patients included vascular access education and vascular mapping using angiography. [20] The patients were divided into two groups – those who had never had a prior AV access and those who had at least one previous AV access. After vascular mapping, 97% of patients in the first group and 90% of the patients in the second group had adequate veins for AVF creation. Overall, they had a remarkable success rate with 77% of the tunneled catheter consigned patients achieving functional AVF and 5% receiving AVG.

**Conclusion and Future Directions**

It has now been inconclusively shown that pre-operative vessel mapping increases AVF creation [12, 13, 15, 21-24], though there is limited and conflicting evidence regarding the effect of vessel mapping on AVF maturation [16, 25]. It is important to distinguish an increase in AVF creation from an increase in mature, functional fistulae. In a key study demonstrating the benefit of pre-operative ultrasonography, the authors conducted an historical cohort study, comparing primary failure rates and patency rates of AVF before and after institution of ultrasonographic assessment of the upper extremity vasculature [12]. The protocol resulted in a significant increase in the creation and use of AVF, with a reduction in early AVF failure rates and an increase in cumulative AVF patency. Other researchers have observed similar results after implementation of the various techniques for pre-operative evaluation, including physical examination, ultrasonography, angiography or a combination thereof, as well as institution of a comprehensive multi-pronged approach to maximize AVF placement [13, 15, 16, 21-24].

Though it would be presumed that a pre-operative strategy to identify suitable vessels for AVF creation would translate into decreased early failure rates and an increased
proportion of prevalent patients dialyzing with an AVF, it may not always be the case. In one such study, routine pre-operative vascular mapping resulted in a marked increase in AVF creation and an increased maturation rate for forearm AVF, but it did not improve the maturation of upper arm AVF [16]. In another study, though the implementation of pre-operative ultrasonography and angiography increased AVF creation, it had the unintended consequence of decreasing the AVF maturation rate from 73% to 57% [25]. This decline was attributed to a change in practice patterns, with more complicated surgeries being performed in the study group as compared to the historical controls. Moreover, they did not routinely perform ultrasonography in all patients and reserved the technique for those patients in whom physical examination was inadequate to identify suitable vessels for AVF placement. A synopsis of the evidence in this field is summarized in Table 1, with the caveat that all the studies demonstrating a benefit of pre-operative mapping are not randomized. In most cases, the primary outcome of previous studies has been AVF creation, rather than AVF maturation, or usability, and only three of the twelve previous studies report favorable outcomes related to venous mapping and AVF maturation. Incidentally, it must also be noted that a majority of these studies were published in tandem with promotion of AVF creation by major national initiatives [26].

Table 1. Effect of pre-operative vascular mapping on vascular access outcomes

<table>
<thead>
<tr>
<th>Author</th>
<th>Technique</th>
<th>AVF Creation rate.</th>
<th>Percentage of Usable AVF.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silva (1998).</td>
<td>US</td>
<td>14% (pre) to 63% (post).</td>
<td>8% (pre) to 64% (post).</td>
</tr>
<tr>
<td>Robbin (2000).</td>
<td>US</td>
<td>32% (pre) to 58% (post).</td>
<td>Not reported.</td>
</tr>
<tr>
<td>Ascher (2000).</td>
<td>US + DOQI</td>
<td>5% (pre) to 68% (post).</td>
<td>Not reported.</td>
</tr>
<tr>
<td>Allon (2001).</td>
<td>US</td>
<td>34% (pre) to 64% (post).</td>
<td>16% (pre) to 34% (post).</td>
</tr>
<tr>
<td>Gibson (2001).</td>
<td>US + Institutional Policy change.</td>
<td>11% (pre) to 95% (post).</td>
<td>Not reported.</td>
</tr>
<tr>
<td>Dalman (2002).</td>
<td>US</td>
<td>35% (pre) to 85% (post).</td>
<td>Not reported.</td>
</tr>
<tr>
<td>Fullerton (2002).</td>
<td>US + DOQI in Gp 1.</td>
<td>23% (Gp 1) to 39% (Gp 2).</td>
<td>79% (Gp 1) to 71% (Gp 2).</td>
</tr>
<tr>
<td>Huber (2002).</td>
<td>US + Angiography.</td>
<td>90%.</td>
<td>71%</td>
</tr>
<tr>
<td>Patel (2003).</td>
<td>Physical examination + US + Angiography.</td>
<td>61% (pre) to 73% (post).</td>
<td>73% (pre) to 57% (post).</td>
</tr>
<tr>
<td>Wells (2005).</td>
<td>Physical examination (73%); US (27%).</td>
<td>100% (physical examination) to 76.5% (US).</td>
<td>Not reported.</td>
</tr>
<tr>
<td>Elsharawy (2006).</td>
<td>Physical examination (26%); Angiography (74%).</td>
<td>95%</td>
<td>Not reported.</td>
</tr>
</tbody>
</table>

Figure 1. US vascular mapping: Brachial artery at elbow, diameter 0.52 cm.

Figure 2. US vascular mapping: Radial artery at wrist, diameter 0.35 cm.

Figure 3. US vascular mapping: Ulnar artery at wrist, diameter 0.25 cm.
Figure 4. US vascular mapping: Cephalic Vein at wrist, diameter 0.30 cm.

Figure 5. US vascular mapping: Cephalic Vein above elbow, diameter 0.33 cm.

Figure 6. US vascular mapping: Basilic Vein above elbow, diameter 0.49 cm.
With regards to the technique, so far no randomized studies have compared the various techniques for AVF vascular mapping. Nonetheless, each technique has advantages in certain clinical settings. A detailed and focused physical examination alone may suffice by using clearly defined criteria and careful clinical examination. In a European analysis of 145 consecutive patients referred for vascular access surgery, 106 patients (73%) proceeded to vascular access surgery on the basis of clinical examination alone, with favorable (77%) subsequent patency results [28]. However, because an increasing proportion of the HD population in the United States has multiple co-morbidities which may affect the vasculature, as well as a high prevalence of central venous catheter use, physical examination alone may be insufficient in the vast majority of these patients. However, in a retrospective comparison of two surgical practices, pre-operative duplex ultrasonography resulted in an unexpected decrease in AVF creation when compared to physical examination [27]. The authors attributed this to be a consequence of under-estimation of cephalic vein size by ultrasonography. On the other hand, a large number of studies support the use of ultrasonography to increase AVF creation, as detailed in Table 1, as it has the advantage of providing noninvasive assessment of both venous and arterial systems, as well as indirect assessment of central venous patency, without exposure to radiation or potentially nephrotoxic contrast. Angiography offers the advantage of direct imaging of the central veins, and is often employed in patients with a history of long-term central venous catheter use. Nevertheless, administration of radiocontrast material does expose the patient to the risk of potential nephrotoxicity. Though recent data have shown that small doses of low iso-osmolar contrast agent for venous mapping or fistula salvage may be safe in patients with stages 4 and 5 CKD [18, 19], larger studies with long-term follow-up are needed prior to establishing the safety of contrast in this high-risk population.

Currently, there is no evidence to support one vessel mapping technique over another; the technique used should be individualized to the patient, with careful consideration of the advantages and disadvantages of each method. The use of ultrasonography in patients with poorly defined vessels on physical examination may expedite placement of fistulae by early referral for surgery [28]. Though minimal vessel diameter criteria have been established for ultrasonography [12], these clearly have limitations, as shown by the poor AVF maturation rates reported in the DAC study. Thus, perhaps additional variables including resistive indices, internal vessel diameter, and blood flow before and after reactive hyperemia might be considered in order to maximize AVF placement and maturation [14, 29, 30]. Indeed, a combination of techniques, as detailed in a prospective algorithm, was successful in creating a native AVF in an overwhelming majority of patients presenting for a new hemodialysis access [24]. Prospective studies are needed to further delineate the impact of these measures on the creation of mature, functional AVF. Future research should focus on prospective, randomized controlled trials to evaluate the efficacy of pre-operative mapping techniques on the creation, maturation and patency of AVF.
References


Chapter IV

Sites and Types of AVFs

Rick Mishler and Alex Yevzlin
University of Arizona, University of Wisconsin School of Medicine and Public Health, Madison, WI, US

Introduction

Since the initial development of hemodialysis, vascular access has been considered to be the Achilles’ heel of this life saving therapy [1]. This is the case because in order to provide access to the circulating blood, reliable vascular access is necessary in every patient. In the early years, venous-venous cannulation was used in order to achieve this goal. Venous cannulation of the upper extremity as well as the lower extremity was preferred. Cannulation of a distal vein of an extremity with return of blood to a venous cannulation placed proximal to a lightly inflated blood pressure cuff also was utilized [2]. Faced with significant challenges in achieving the requisite blood flow to achieve adequate dialytic therapy, four physicians from the Bronx Veterans Administration Hospital developed a novel procedure that was designed to provide arterial flow with rotating venous cannulation points: The arteriovenous fistula (AVF). Michael Brescia, James Cimino, Kenneth Appel and Baruch Hurwich published their seminal description of the radial-cephalic fistula that was created using a side to side anastomosis between the distal radial artery and cephalic vein (Figure 1) [3]. Despite numerous advances in dialysis technology in the intervening 45 years, autologous arteriovenous fistulae remain the standard for hemodialysis vascular access [4].

After this initial foray into vascular access, many nephrologists turned their focus away from actively managing this crucial component of dialytic therapy, deferring to the expertise of their surgical and interventional colleagues. The past ten years have witnessed a renewed interest on the part of general nephrologists in becoming key decision makers in planning and selecting their patients’ access choice. The purpose of this chapter is to describe the common sites at which autologous fistulae can be constructed and the types of autologous accesses that are currently available to general nephrologists for their dialysis patients.
Figure 1: side of vein to side of artery anastomosis.

Table 1. Requirements for AVF to adequately support dialytic therapy

1. Adequate cardiac output to produce flow of blood.
2. Continuous and preferably disease free arterial circuit from left ventricle to arteriovenous anastomosis.
3. Connection between artery and vein (anastomosis).
4. Segment of vein which can be easily, repeatedly cannulated.
   - Minimum 6 cm length straight segment.
   - 6 mm in diameter.
   - 6 mm or less below skin surface.
5. Continuous and preferably disease free venous circuit from arteriovenous anastomosis to the right ventricle.

Arteriovenous Fistulae (AVF) Fundamentals

The term “fistula” in common medical usage refers to a non-physiologic connection between an organ, vessel, or intestine and another structure. This connection may occur as a result of a pathologic process or be created intentionally. In the case of dialysis access, the surgically created connection is between an artery and a vein. In its most elementary description, an AVF is a closed pump-driven system; the heart provides a source of the blood flow via the arterial vessels and the veins provide the areas for cannulation and subsequent blood return to the heart. In order for an AVF to function adequately, there are several necessary conditions that must be met (Table 1).
Figure 2. End to vein to side of artery anastomosis.

Figure 3. Upper arm cephalic and basilic veins.

Figure 4. Proximal radial artery source for AVF creation.
Among these requirements, many believe that the most important segment during dialysis therapy is the venous portion which is used several times per week for cannulation. Klaus Konner states that “the anastomosis is just a tool” that establishes a stable connection between the artery and vein which allows the access system to work, rather than an end in itself as some may believe. This connection can be achieved using a variety of surgical techniques but results in essentially two configurations. The more common is the end to side anastomosis. In this application, the end of the vein is connected to the side of the artery (Figure 2). The original but less commonly used configuration published by Brescia and Cimino [3] is a side to side anastomosis where the side of the vein is anastomosed to the side of the artery (Figure 1a). In current use, the distal segment of the vein is usually ligated especially in the wrist AVF to prevent distal venous hypertension (Figure 1b).

When considering AVF creation for a patient, it is important to think like a nephrologist: assume nothing and focus on dialysis delivery as the primary endpoint. A complete history and physical which includes previous vascular accesses as well as ultrasonic vessel mapping is mandatory in all patients [5]. Pertinent questions to be answered when choosing a site for AVF creation are whether or not there will be adequate blood flow in the access from the chosen artery and whether or not the chosen vein will permit regular reliable cannulation. When accessing sites for potential vascular access creation, both of these questions must be answered in the affirmative.

AVF Possibilités

Let us now consider the possible sites for AV fistula creation. Since the venous portion of the fistula is that which is most clinically relevant to dialysis and thus to a general nephrologist, this discussion will explore fistula creation from the perspective of the vein rather than the arterial source. In the upper extremity, there are two major superficial venous systems: the cephalic and basilic veins which run from the distal upper extremity to the axilla where they join to form the axillary vein. (Figure 3) Branches of these veins are often present in the antecubital fossa and may be referred to as median cubital veins. These may be useful for AVF creation in selected patients. A paired deep venous system also exists: the radial, ulnar and brachial veins. This deep system is located near the same named artery and is connected to the superficial system via the communicating or perforating veins. These deep systems may be used for AVF creation in extreme cases when the patient has exhausted more conventional sites for access creation. Because the cephalic vein is most often used for dialysis access, it will be considered initially.

Cephalic Vein

The cephalic vein usually is located on the superficial, ventral-lateral aspect of the upper extremity and generally is not located near major sensory and motor nerves which might be injured by repeated cannulation with dialysis needles. The radial artery in the forearm and the brachial artery in the upper arm are available for anastomosis to form an AV fistula in many different areas. According to NKF-K/DOQI 2006, the preferred AVF is to be
constructed from the distal radial artery and distal cephalic vein. This is sometimes referred to as a “wrist” fistula. Should a distal AVF not be possible, the next choice is the brachial artery-cephalic vein AVF creation [6]. Traditionally, the anastomosis is located above the elbow.

So, are there only two sites that are suitable for construction of a cephalic vein fistula? Not according to Dr. Konner. Dr. Konner describes the mid-forearm region as the “gap” between the wrist and the forearm below the antecubital fossa [7]. In this area, the radial artery may be available along most of its length for primary or secondary AVF creation. Additional dissection and elevation of the artery may be necessary in some areas due to its deeper location. Even the most proximal portions of the radial artery may also be suitable for use (Figure 4). Although, located in a deeper position than the radial artery, the ulnar artery may be used as a source for an AVF. While not commonly used for AVF construction, a cephalic vein-ulnar artery AVF may serve some patients well (Figure 5).

Figure 5. Cephalic vein-Ulnar artery AVF.

Figure 6. Postoperative Radial artery-basilic vein avf.
Figure 7. Radial artery-basilic vein AVF 8 weeks post op and ready for use.

Figure 8. Basilic vein in situ prior to transposition (Courtesy of Shouwen Wang, MD, PhD).

Figure 9. Transposed basilic vein 8 weeks post op.
Basilic Vein

Next we turn to the basilic vein. The basilic vein originates in the distal forearm at the back of the hand. The vein usually courses along the medial aspect or posterior-medial aspect of the distal arm. In the forearm the vein may either be anastomosed to the ulnar artery or with mobilization, the vein may be fed from the radial artery [8] (Figures 6 and 7). Near the elbow, the basilic vein is joined by the median cubital vein. In the upper portion of the arm, the vein enters the brachial fascia and joins the radial vein to form the axillary vein. Due to the basilic vein’s medial location in the forearm and medial as well as deep location in the upper arm, usually this vein requires transposition prior to use for dialysis. Without transposition, these veins do not offer an easy position for cannulation or positioning during the dialysis treatment. Another factor to keep in mind is that in the upper arm, the basilic vein may overlay the deeper brachial artery and median nerve. Usually the medial cutaneous nerve of the forearm is located near or wrapped around the basilic vein. An essential part of the transposition procedure is careful dissection of this nerve from around the vein. The nerve is left in its native position while the vein is moved to the more superficial-lateral aspect of the arm. Despite the necessity for more complicated surgeries, the basilic vein often is a useful vascular access conduit for dialysis patients [9] (Figures 8 and 9).

AVF in the Lower Extremities

Fistulae creation in the legs is uncommon in comparison to the upper extremities. For that matter, use of synthetic graft material is much more common than autologous AVF creation in the lower extremities. An example of this type of autologous access is the superficial femoral artery-common femoral vein transposition in the thigh. This procedure is technically
challenging and the risk of distal ischemia is significant as compared to upper extremity accesses. However, with proper planning, patient selection and use of intraoperative measures to reduce ischemia, adequate outcomes have been achieved [10].

**Deep Venous AVF**

The two-stage brachial artery-brachial vein autologous fistula has been espoused by some as a viable alternative for hemodialysis access in certain patients. As with any venous transposition, the transposed brachial artery-brachial vein fistula is technically challenging and at best would be reserved for very select patients [11]. Other groups have demonstrated that if performed as a single stage procedure, this transposition is associated with inferior patency rates when compared to the basilic vein transposition fistula and AV grafts [12]. Given these contradictory findings, it seems that this procedure should not be performed frequently.

**Elevation of AVF**

Due to considerations of body habitus, many obese patients are not thought to be candidates for autologous fistulas. Dr. Konner has reported identical outcomes for AVF creation in diabetic and non-diabetic patients with elbow AVF being more common in the diabetic group [13]. In order to address the difficulty of AVF use in diabetes, fistula elevation procedures (FEP) have been proposed as a potential solution. This technique is equally useful in either the forearm or upper arm. Commonly the FEP involves mobilizing the venous conduit, approximation of the subcutaneous tissue beneath the conduit such that the vein is held in a more superficial position and closure of the skin in the usual fashion. Given that is a rather simple procedure that enhances fistula utilization, it may be helpful in some obese patients [14].

**Conclusion**

Data suggest that it should be possible to create autologous arteriovenous fistulae in the vast majority of CKD and dialysis patients. Given an adequate multi-disciplinary preoperative evaluation, intraoperative will and skill and adequate postoperative evaluations and therapy, this goal can be met. There are many sites from which to choose when considering access possibilities. The idea that after a failed distal radial-cephalic AVF the next choice should be an upper arm AVF is an antiquated concept; multiple mid forearm options may exist. The most important factor regarding vascular access is for nephrologists to become knowledgeable about and stay involved in all aspects of access planning, including access site choice.
References


Chapter V

Creation of Arteriovenous Fistulas by Nephrologists

Shouwen Wang* and Andrew Cortez
Ambulatory Surgery Center, Arizona Kidney Disease and Hypertension Center, Phoenix, AZ, US

Introduction

Vascular access has been the Achilles heel for hemodialysis since the inception of this life-saving therapy. [1, 2] Arteriovenous fistulas (AVF) have become the preferred access type for hemodialysis since their first reported use in 1966. [3] Benefits of AVF include better dialysis efficiency, longevity, reliability, and lower complication rates. [4] The efforts to increase fistula prevalence in dialysis patients have been hindered by various factors, including fragmented care because patients struggle navigating various specialties for their dialysis access care needs.

Dialysis access care typically involves the services of nephrologists, surgical specialists, and interventional radiologists. Unfortunately, vascular access is a low priority to many subspecialists who are not involved in the delivery of dialysis therapy per se. The recent emergence of Interventional Nephrology has generated a greater focus on the maintenance of established arteriovenous access in outpatient settings, but fistula creation remains largely the task of traditionally trained surgical specialists. Creation of arteriovenous hemodialysis access by trained Nephrologists is widely practiced throughout the world. With the desire to improve AVF prevalence, leading experts have been advocating fistula creation by trained nephrologists in the United States. [5, 6]

In this chapter, the historical roles and current practices of nephrologists in hemodialysis access creations around the world are briefly reviewed and clinical aspects of training Interventional Nephrologists to become access surgeons in the United States are discussed. In

* Address correspondence to: Shouwen Wang, M.D., Ph.D., AKDH-ASC. 3320 N 2nd St, Phoenix, AZ 85012. Tel: 602-200-8288; Fax: 602-200-8549. E-mail: swang@akdhc.com.
addition, we present a “one-stop” comprehensive dialysis access care model based on an outpatient practice in which Interventional Nephrologists and Nephrologist Access Surgeons provide specialized comprehensive dialysis access care.

**Historical Contributions of Nephrologists to Dialysis Access Creation**

Since the advent of hemodialysis, nephrologists have made major contributions to dialysis access care. [7] These contributions are exemplified by the invention of the Scribner Shunt, the design and application of Brescia-Cimino arteriovenous fistulas, and the design and use of long-term Stanley Catheters for chronic maintenance dialysis. [7]

Hemodialysis therapy was pioneered in the 1940s by Dr. Willem Kolff, [7] but ESRD was still fatal before 1960 because of unreliable vascular access. The invention of the Scribner arteriovenous shunt in 1960 by Dr. Belding H. Scribner and colleagues from the University of Washington made long-term maintenance hemodialysis possible. [8, 9] This external Scribner shunt established a radial artery to cephalic vein bypass with silastic-teflon cannulae that were used to access the circulation during dialysis. [8-10] The first patient had his shunt placed on March 9, 1960 and survived 11 years on hemodialysis. This became the landmark case in maintenance hemodialysis. [11] The Scribner shunt became widely accepted in the following years. Based on the reliability of this vascular access, Dr. Scribner conceptualized and helped establish the first community based outpatient hemodialysis center, the Seattle Artificial Kidney Center, in 1962. [11] This model of hemodialysis-centered care is widely followed today.

An alternative vascular access for hemodialysis in the early years was simple venipuncture as reported by Drs. James Cimino and Michael Brescia from the Bronx Veterans Administrations Hospital in New York in 1962. [12] In their subsequent seminal report, these physicians described constructing radial-cephalic arteriovenous fistulas for chronic hemodialysis. [3] Even though the fistula surgeries were performed by a surgeon, Dr. Kenneth Appel, the concept and much of the developmental work in animals were carried out by these Nephrologists (personal communication from Dr. Brescia 2008). Cannulating dilated veins after arteriovenous fistula creation remains the standard for hemodialysis access today. The configuration of radial-cephalic arteriovenous fistulas still bears the names of these two Nephrologists --- Drs. Cimino and Brescia.

Dr. Stanley Shaldon, a European Nephrologist, pioneered the use of the percutaneously inserted, indwelling hemodialysis catheter in 1961. [13] Despite the recent contributions of the KDOQI/NKF vascular access guidelines and the Fistula First Breakthrough Initiative, catheters continue to play an essential role in hemodialysis vascular access.
Current Practice of Nephrologists Creating AVF around the World

While Nephrologists made seminal contributions to dialysis vascular access development and practice, most of the initially reported surgical work was performed by their surgical colleagues. [3, 8] Because of the increasing complexity of access related issues, Nephrologists delegated the responsibility of vascular access to their surgical colleagues (Table 1). For many years, vascular access was regarded as an exclusively surgical issue. [7] However, dialysis access surgeries were generally of low priority for many surgeons. The desire to bring optimal care to their dialysis patients led many Nephrologists around the world to create arteriovenous fistulas. With the encouragement and assistance of their talented surgical colleagues, these Nephrologists honed their surgical skills specifically in dialysis access creations.

Renowned German nephrologist, Dr. Klaus Konner, performed thousands of dialysis access surgeries. He published extensively, served on various international panels of dialysis access, disseminated fistula creation techniques and philosophy through publications and lectures. [14, 15] He is a proponent of perforating vein fistulas in the elbow region, which is a non-traditional approach. [16, 17] He visited the Ambulatory Surgery Center of Arizona Kidney Disease and Hypertension Center (AKDHC-ASC) in Phoenix and shared his knowledge and surgical techniques on several occasions.

Fistula creation by Nephrologists is widely practiced in other European countries. [18] According to reports, over 80% of permanent dialysis accesses were created by Nephrologists in Italy. [2, 18-20] In Poland, Nephrologists create fistulas and perform fistula revision surgeries, including superficializing fistula veins in obese patients. [21, 22] Nephrologists from Macedonia have extensive experience with vascular access procedures, including over three thousand arteriovenous fistulas. [23]

According to DOPPS data, nephrologists created 25% of the fistulas in Japan. [2] Dr. Modi from India displayed his poster of 179 fistula constructions at the 2008 ASN Annual Meeting. [24] In China, nephrologists have also been creating arteriovenous fistulas for many years based on the authors’ personal communications with colleagues.

Table 1. Physicians involved in dialysis access creations

<table>
<thead>
<tr>
<th>Physicians:</th>
<th>Comments:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular surgeons.</td>
<td>Expertise in vascular work.</td>
</tr>
<tr>
<td>Cardiovascular surgeons.</td>
<td>Expertise in vascular work.</td>
</tr>
<tr>
<td>Transplant surgeons.</td>
<td>Expertise in vascular work and kidney care.</td>
</tr>
<tr>
<td>General surgeons.</td>
<td>Interest and expertise in dialysis access.</td>
</tr>
<tr>
<td>Urologists.</td>
<td>Close relationship with nephrologists.</td>
</tr>
<tr>
<td>Other Surgeons.</td>
<td>Training and interest in dialysis access.</td>
</tr>
<tr>
<td>Nephrologists.</td>
<td>Close connection with CKD/ESRD patients.</td>
</tr>
<tr>
<td></td>
<td>Need proper surgical training.</td>
</tr>
</tbody>
</table>
Dr. Peter Ivanovich of Northwestern University in Chicago is a distinguished academic Nephrologist with a special interest in dialysis access creation. He trained with Dr. Belding Scribner during his Nephrology fellowship and helped placing Scribner Shunts. He later became proficient in using a stapling technique to create radial artery to cephalic vein fistulas through end-to-end anastomosis. [25] He has not only created fistulas for his patients but also taught his expertise to other physicians, including surgeons.

In Arizona, four Nephrologist Access Surgeons of AKDHC have created approximately 3000 arteriovenous fistulas for the patients in their practice. [26-28] To our knowledge, AKDHC Nephrologist Access Surgeons are among the few Nephrologists actively practicing fistula creations in the United States. Two other Nephrologists in the United States have received training, but their opportunity to practice fistula creation has been hindered by various factors. [29]

**Clinical Outcomes of AVF Created by Nephrologists**

Failure of fistula maturation is common and reports vary from 18 to 53%. [29] Surgical training and experience in this field has emerged as a major factor influencing outcomes. [30-33] The question arises: can Nephrologists do equal or better in terms of fistula outcomes?

Vascular surgeons or other traditionally trained surgeons (Table 1) create arteriovenous fistulas with varying degree of success. Dr. William Jennings (general surgeon from the University of Oklahoma) has strived to create fistulas in all feasible patients. He reported an assisted fistula patency rate above 90% at one year, and has rarely used prosthetic grafts. [34, 35] The clinical outcomes of fistulas created by many other surgeons are far below what Dr. Jennings achieved. One large randomized controlled trial with 877 patients from nine major academic and community centers had only an approximately 50% usability rate. [36]

Understandably, the reported fistula outcomes constructed by Nephrologists also vary. In Dr. Konner’s report of 748 patients, the one year primary fistula patency rates were 67-85% and secondary patency rates were 84-98%. [16] There were variations in patency rates due to age, gender, and diabetes status of patients. During his six year study period between 1993 and 1998, prosthetic grafts were used in only a small percentage of the 243 revision surgeries, none as initial access. [16] These results are on par with the best and superior to most reported outcomes. Dr. Ravani and colleagues from Italy reported 197 consecutive fistula creations between 1995-2001, with primary fistula patency rate of 64% and secondary patency rate of 71%. [20] Also from Italy, Dr. Stanziale and colleagues reported greater than 80% primary patency rate of radial artery-cephalic vein fistulas at one year. [37] In the United States, Dr. Mishler documented his early fistula outcomes. Of the 100 fistulas he created, the assisted patency rate was 84% at an average follow-up of 286 ± 98 days. [28]

Bear in mind, the criteria for patency rates used in these report may vary, the patient populations are diverse, and many factors other than surgeons’ skills may influence fistula outcomes. Direct comparison is difficult. Nonetheless, well-trained Nephrologist Access Surgeons can achieve comparable or even more favorable outcomes.
Importantly, fistula creation by Nephrologists increases fistula prevalence. In Dr. Konner’s report, usable fistulas were achieved in over 90% of their patients. [16] Dr. Oncevski and colleagues from Macedonia documented fistula prevalence rates of greater than 90%. [23] Two dialysis centers in Italy published fistula prevalence rates of 92.5% and 96.1%. [38] There are many other examples around the world. Key to success is the dedicated effort of physicians and other health care providers, in which the barriers to optimal care are minimized.

Table 2. Dialysis access procedures beyond arteriovenous fistula creation

<table>
<thead>
<tr>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fistula revisions.</td>
</tr>
<tr>
<td>Basilic vein transposition (two stage techniques) and cephalic vein transposition.</td>
</tr>
<tr>
<td>Fistula vein superficialization (elevation, transposition, lipectomy).</td>
</tr>
<tr>
<td>Steal syndrome management (arterial angioplasty, banding to limit flow, etc.).</td>
</tr>
<tr>
<td>Surgical and endovascular management of occlusive cephalic arch lesions.</td>
</tr>
<tr>
<td>Fistula and graft aneurysm repairs.</td>
</tr>
<tr>
<td>Arteriovenous prosthetic graft placements.</td>
</tr>
<tr>
<td>Bridging grafts for fistula complications (aneurysms, occlusive lesions).</td>
</tr>
<tr>
<td>Endovascular interventions to promote fistula maturation and maintain patency.</td>
</tr>
<tr>
<td>Peritoneal dialysis catheter placement and management.</td>
</tr>
<tr>
<td>Terminal/extreme access creations (usually performed in hospitals).</td>
</tr>
</tbody>
</table>

Table 3. Desirable elements for successful access surgeons

<table>
<thead>
<tr>
<th>Element</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong interest in dialysis access care.</td>
</tr>
<tr>
<td>Understanding the need of each ESRD patient and viewing it as priority.</td>
</tr>
<tr>
<td>Knowledge of various dialysis access surgeries and options.</td>
</tr>
<tr>
<td>Meticulous surgical skills.</td>
</tr>
<tr>
<td>Creative when needed.</td>
</tr>
<tr>
<td>Endovascular interventional expertise (or proper referral when needed).</td>
</tr>
<tr>
<td>Knowledge and skills of managing dialysis access complications.</td>
</tr>
</tbody>
</table>

Proposing a Proper Name: Nephrologist Access Surgeon

Comprehensive dialysis access care is a specialized field and goes beyond fistula construction (Table 2). Special knowledge and skills are required for optimal dialysis access care. [4, 39] Surgeons are usually categorized based on their expertise. To distinguish surgeons’ expertise in dialysis access surgeries, it would be appropriate to call them “access surgeons”. [16]
Surgeons by definition are physicians who specialize in performing surgeries. Most Nephrologists doing vascular access surgeries are not initially trained in surgical specialties, but their subsequent training and experience equip them to perform these focused surgeries competently. Many reports show that dedicated and skilled Nephrologists achieve excellent outcomes in dialysis access surgeries. It matters less whether a physician begins postgraduate training as an internist or surgeon, what matters most are optimal services, dedication, experience with access creation, and good outcomes. To recognize the focused skills of these Nephrologists, an appropriate and descriptive title would be “Nephrologist Access Surgeon”. Nephrologists pioneered dialysis accesses, and well-trained Nephrologist Access Surgeons can play a crucial role in serving the ESRD population and advancing hemodialysis vascular access care.

**Desirable Elements for Successful Dialysis Access Surgeons**

The goal of access surgeries is to create a functional dialysis access. As mentioned earlier, evidence supports the assertion that the training and experience of surgeons in dialysis access surgeries affects outcomes. To optimize the likelihood of good outcomes, several important attributes define the ideal access surgeon (Table 3). These may be conceptually reduced to interest, knowledge, and skill.

At the forefront is strong interest in dialysis access care. It is hard to imagine quality and timely outcomes from a provider with low interest who views dialysis access procedures as sideline work. The need for meticulous surgical skill is intuitively obvious. It is also necessary to possess essential knowledge of various dialysis access procedures and be able to manage complications of dialysis accesses. In addition, interventional procedures may be required to promote fistula maturation and maintain access functionality. Understanding hemodialysis and the needs of dialysis patients is also a plus.

Creativity is needed in challenging patients. It takes both quality artery and quality vein to create a functional access for dialysis. The comorbid conditions associated with ESRD frequently result in repeated insults to arm veins (blood draws, venous cannulations, etc.) where damage and obliteration of these veins are common. Many patients also suffer from peripheral arterial diseases. These factors pose added challenges to successfully creating arteriovenous fistulas. Traditional access options may not be optimal or possible.

Qualified Nephrologist Access Surgeons with Interventional Nephrology background can integrate the dialysis access care services. With knowledge, dedication, experience, and skills, these access specialists can improve the overall access care for many patients.

**Training Nephrologist Access Surgeons**

There are some advantages when Nephrologists (especially Interventional Nephrologists) perform access surgeries. The main advantages are focused interest, better understanding of the needs of ESRSD patients, closer connection with ESRD patients, and valuable interventional skills to integrate the access care services. With the emergence of
Interventional Nephrology, many hurdles have been lowered. Nephrologists have been trained with extra skills in dialysis access maintenance care. Some of these Interventional Nephrologists are suited to training in fistula creations. [26]

There are also certain challenges a Nephrologist must confront to become an access surgeon (Table 4). The priority is competency in performing the intended surgeries. The needed surgical training depends on the background of each physician. For residents or fellows in the surgical specialties, greater than 25 fistula creations during training has been found to be associated with improved fistula patency. [33, 41] Even for trained surgeons, there is a learning curve for fistula creation. [42] Based on our limited experience, a typical Interventional Nephrologist requires about 50-100 cases as assistant and 50-100 cases as primary operator with supervision to become independent in fistula creations. For Interventional Nephrologists with prior comprehensive surgical training (such as the author SW), the training needed may be much shorter.

Table 4. Challenges and advantages for nephrologists performing access surgeries

<table>
<thead>
<tr>
<th>Challenges:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Proper surgical training (training opportunity may be limited).</td>
</tr>
<tr>
<td>• Basic surgical knowledge (such as wound healing, vascular biology).</td>
</tr>
<tr>
<td>• Steeper learning curve for those with little prior surgical experience.</td>
</tr>
<tr>
<td>• May need surgical backup for managing advanced access problems.</td>
</tr>
<tr>
<td>• May need further training if advanced procedures to be performed.</td>
</tr>
<tr>
<td>• Credentialing, insurance maybe hurdles.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Advantages:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Strong and undivided interest in dialysis access care.</td>
</tr>
<tr>
<td>• Closer relationship with kidney disease patients.</td>
</tr>
<tr>
<td>• Nephrology knowledge beneficial to understanding dialysis patients’ need.</td>
</tr>
<tr>
<td>• Endovascular interventional skills for post-creation care.</td>
</tr>
<tr>
<td>• Specialized dialysis access care may improve the quality of care.</td>
</tr>
<tr>
<td>• Outpatient surgeries under conscious sedation are safe and economical.</td>
</tr>
</tbody>
</table>

Besides surgical skills, additional knowledge related to dialysis access creation must be gained during the training. Availability of more experienced surgeons will be helpful to improve the clinical decisions of newly independent Nephrologist Access Surgeons. The more complex dialysis access procedures will not fall within every surgeon’s expertise and should be deferred to those best qualified. Vascular Surgeons are still indispensable in dialysis access care.

Several key issues need to be considered before fistula creation can be advocated: proper surgical training, medical liability insurance, reimbursement for surgeries, and credentialing. The training opportunities may be limited for various reasons. The liability insurance and reimbursement need to be secured. There may be resistance from the surgical establishment to credentialing Nephrologists in hospitals. The training and practice settings will likely be outpatient surgery centers or access centers, similar to Interventional Nephrology. [43]
Despite these challenges, Interventional Nephrologists can expand their skills to become Nephrologist Access Surgeons and help provide optimal care to their dialysis and pre-dialysis patients.

**A “One-Stop” Comprehensive Dialysis Access Care Model in Outpatient Settings**

As part of the AKDHC nephrology practice, AKDHC Surgery Center (AKDHC-ASC) is among the earliest outpatient dialysis access care centers in the United States. With a large patient population, the practice employed a talented vascular surgeon for dialysis access surgeries. In 2004, a senior Interventional Nephrologist, Dr. Rick Mishler, began assisting these surgeries and then was trained as primary operator. Dr. Mishler has now trained three other AKDHC Interventional Nephrologists in fistula surgery. Together, these Nephrologist Access Surgeons have created approximately 3000 fistulas.

**Table 5. A “one-stop” comprehensive dialysis access care model as outpatient**

Pre-operative care:

- CKD and dialysis education.
- Vessel mapping and vein preservation for CKD stage 4 and 5 patients.
- Dialysis access planning (dialysis modality, vascular access type, timing).

Dialysis access operative care:

- Focused effort to create new access to minimize hemodialysis catheters.
- Preemptive fistula creation in advanced CKD patients.
- Immediate pre-operative ultrasound vessel mapping for surgical planning.
- Arteriovenous fistula creation or prosthetic graft placement (fistula first).
- Peritoneal dialysis (PD) catheter placement.
- Post-operative follow-up, wound check.

Maturation care – ensure an usable dialysis access:

- Routine fistula ultrasound evaluation 4-6 weeks post creation.
- Endovascular or surgical interventions to promote maturation as needed.

Management of access complications:

- Thrombosis (thrombectomy), insufficient flow (angioplasty or revision).
- Management of steal syndrome, aneurysms, and other complications.
- Poor peritoneal catheter flow (repositioning) or infection.
The AKDHC surgery center has progressed to providing comprehensive dialysis access care: from education and access planning to advanced dialysis access procedures (Table 2, Table 5). Besides fistula creations (Figure 1), other access procedures include: basilic vein transposition (Figure 2), deep fistula vein superficialization (Figure 3), cephalic vein swing-down to basilic vein for occlusive cephalic arch lesions, fistula/graft banding for steal syndrome, fistula and graft aneurysm repairs (Figure 4), prosthetic graft placement, and surgical and vascular interventions to promote maturation and maintain patency, peritoneal catheter placement and maintenance (Table 2). [44-46] The services provided are so comprehensive that the access care needs of most of our patients can be met by this center --- thus the concept of “one-stop” dialysis access care. This model offers many advantages: comprehensive approach, priority specialized care, one-stop convenience, continuity of care, improved communication, reduced hassle for staff/physicians.

The experiences in this center and many others have proven that it is safe to perform these procedures using conscious sedation plus local anesthesia in the outpatient settings, even for patients considered high risks for general anesthesia. [47] The existence of a dedicated outpatient access center decreases hospitalization and missed outpatient dialysis treatments. [48]

Despite these advantages, there are limitations. The combined efforts of multiple specialties will remain crucial to optimizing dialysis access care for certain members of the CKD/ESRD population. Not all dialysis access procedures are suitable for outpatient settings.

Figure 1. Typical arteriovenous fistula creations. Shown are intra-operative photographs depicting the following types of arteriovenous anastomosis: radial artery-cephalic vein side-to-side (A), radial artery-cephalic vein side-to-end (B), brachial artery-cephalic vein side-to-end (C), and proximal radial artery-cephalic vein side-to-end (D).
Figure 2. Basilic vein transposition. Intra-operative photographs showing: exposed mature basilic vein several weeks after initial fistula creation (A), new venovenous anastomosis after tunneling of basilic vein (B), smooth swing of the basilic vein proximal to the tunnel (C), and skin closure at completion of the surgery (D). The transposed basilic vein is located subcutaneously anterior to the skin incision and away from major artery and nerves.

Figure 3. Fistula vein superficialization. Deeply located fistula veins are frequently encountered in obese patients and create problems for cannulation. These ultrasound and photographic images illustrate a superficialization surgery: preoperative ultrasound showing fistula vein 11 mm under the skin surface (A), exposed fistula vein (B), skin marking showing newly located fistula vein after incision healing (C), and ultrasound confirming the fistula vein 3 mm under the skin surface (D).
Figure 4. Fistula aneurysm repair – partial aneurysmectomy approach. Fistula aneurysms are frequently seen and can be associated with various complications such as bleeding. The photographic images shown are: scab over a fistula aneurysm with markings of planned incisions (A), exposed skin and fistula vein defects with mural thrombus inside the aneurysm (B), fistula vein wall defect after debridement (C), and fistula vein after suture repair (D). The skin is subsequently closed.

Conclusion

Nephrologists played historical roles in the conceptualization and creation of dialysis accesses. Qualified Nephrologists can create arteriovenous fistulas safely and achieve excellent clinical outcomes, thereby increasing the fistula prevalence rates in their patient populations. Arteriovenous access creation and maintenance procedures can be safely accomplished in outpatient settings. [47, 49] The integrated outpatient comprehensive dialysis access care model has advantages and may improve the overall dialysis access care. Interventional nephrologists in the United States should play an increasing role in arteriovenous fistula creations as Nephrologist Access Surgeons.

Acknowledgment

The author (SW) would like to thank Drs. Rick Mishler, Jeffrey Packer, and Klaus Konner for their training and guidance. The author also would like to thank the staff at the AKDHC surgery center for their assistance. My work life has been greatly enriched because of their dedication, caring and collaborative spirit, and humor.
References


Secondary Arteriovenous Fistula

David Levine and Surendra Shenoy*
Washington University School of Medicine, Saint Louis, MO, US

Introduction

Although arteriovenous fistulae (AVF) are the preferred vascular access for hemodialysis patients, the growth of chronic kidney disease (CKD) in the United States has paralleled an increase in the prevalence of arteriovenous grafts (AVGs) and central venous catheters (CVCs).

The morbidity and mortality associated with these access modalities has resulted in significant economic burden and patient dissatisfaction. This became clear when the National Kidney Foundation – Dialysis Outcomes Quality Initiative (NKF-DOQI), the first concrete and concerted effort at developing clinical practice guidelines, addressed vascular access as one of the four aspects of the initiative. NKF-DOQI unequivocally advocated the use of AVFs to improve quality of life for dialysis patients [1].

The secondary AVF (SAVF) is a relatively new concept that is based on logical deduction. Access failure always necessitates a CVC as a bridge to dialysis while awaiting new access evaluation, placement, and maturation. The duration from referral to maturation of an AVF is extremely variable.

Moreover, there is a tendency for surgeons to place an AVG in such situations to provide rapidly available access and reduce CVC exposure. Despite early availability for needle sticks, the long term performance of AVGs is significantly inferior to AVFs. The SAVF concept is an attempt to break this vicious cycle and reduce the need for CVCs and the perpetuation of AVG-based dialysis.

This chapter intends to explore the concept of SAVF, whereby an AVF can be constructed from an ailing AVG or an AVF, in an attempt to increase the prevalence of

* Corresponding author: Surendra Shenoy M.D., Ph.D., Professor of Surgery, Washington University School of Medicine, Barnes Jewish Hospital, Saint Louis, MO 63110.
AVFs. We will discuss a standardized approach to patient evaluation and explore innovative techniques to avoid CVCs in patients with ailing dialysis access.

**Definition of SAVF**

- SAVF was a term used to define an AVF that is created utilizing a matured outflow vein from a previous access.

The concept of a SAVF made its first appearance in the revised version of NKF-DOQI in 2001 as an ‘opinion’ to maximize the placement of AVFs. Guideline 29 of this document reads ‘Patients should be re-evaluated for possible construction of a primary AVF after failure of every dialysis AV access’ [2]. This concept was championed by the ‘fistula first breakthrough initiative’ (FFBI) as a ‘change’ concept. The sixth concept in the fistula first change package formally introduced the term ‘secondary fistula’ and promoted placement of fistulae in patients with existing AVGs [3].

The term ‘secondary fistula’ was coined to describe a fistula that was constructed using outflow veins that were already mature (size >6mm, straight segment >10cm, and depth <5mm from the skin surface) due to the presence of a pre-existing access. A SAVF was suggested as an option to a patient who had a failing or failed AVG as the initial (primary) access. The term secondary (used in SAVF) has no connection to and should not be confused with the term ‘primary fistula.’ The term ‘primary fistula’ is used to describe any native vein fistula, even though it may not be the first access in a given ESRD patient (e.g. a brachiocephalic ‘primary fistula’ constructed in the upper arm following failure of a forearm AVG could actually qualify as a SAVF). We therefore avoid using the term primary fistula in this chapter, as it could lead to some confusion for the reader. Rather, we use more descriptive terminology such as ‘primary access’ to describe the first access option and ‘secondary access’ to describe subsequent access attempts. We also use descriptive terminology that includes the names of the vessels used for access construction such as radiocephalic fistula at the wrist (radial artery to cephalic vein at the wrist) or brachiocephalic fistula above the elbow (brachial artery to cephalic vein with the anastomosis above the elbow crease) to describe individual fistulae. Using descriptive terminology is essential to succinctly convey the specifics of the access site and the vessels used in a particular access procedure.

Though a SAVF originally described an AVF that was created with the use of mature outflow veins from a previously existing AVG (as a possible method to increase AVF prevalence), the current change concept six guidelines from FFBI uses this term to describe any AVF created in any patient with an AVG [3]. Thus it includes all patients with a history of previous AVG placement who get a new AVF, regardless of the veins used for the new AVF construction. This all inclusive definition makes the group of SAVF patients quite heterogenous and difficult to analyze. To avoid such confusion, some authors have introduced the term ‘Type I SAVF’ to describe patients who receive a SAVF utilizing outflow veins of a previously placed access. They have used ‘Type II SAVF’ to describe all other patients [4]. Thus a Type II SAVF may include a new AVF constructed in the contralateral extremity after a failed AVG in another extremity. In reality, the Type II SAVF essentially accounts for all other patients with a history of previous AVGs who receive an AVF as their new access. The
principles of access evaluation and planning that are discussed in detail in other chapters refer to all patients, including the group with failed previous accesses (Chapter I, pg 3-18). For this reason, this chapter discusses the rationale, anatomic basis, indications, evaluation, and timing for SAVFs utilizing outflow veins from previously placed access.

### Rationale for SAVFs

The rationale for SAVFs is based on a sound hypothesis. A functioning forearm access often has blood flows of around 800-1200 ml/min. This large volume of blood from a forearm fistula tends to flow through one or more of the upper arm veins to reach the central system. This results in dilation of one or more of the veins in the upper arm that drains the blood flow from the forearm access. Awareness of the presence and availability of such dilated outflow veins in the upper arm plays an important role in planning for future access options and preservation of such veins. Such veins can be used to construct a new AVF that has the potential to be ready for immediate cannulation.

Though the current change concept uses the term SAVF in conjunction with a previous AVG, in reality it is applicable to all patients who have a forearm AVG or AVF as their access for dialysis. Hence, in this chapter we discuss the utilization of the SAVF concept as it applies to all patients with a forearm access.

![Venous anatomy of the upper extremity.](image)

Figure 1. Venous anatomy of the upper extremity.
Anatomic Basis for SAVFs

A basic understanding of the venous anatomy of the upper extremity is essential to plan a SAVF [5]. Figure 1 depicts the most common venous anatomy encountered during vein mapping in dialysis patients. The venous blood drains from the superficial venous system (veins superficial to the deep fascia) to the deep venous system (veins deep to the deep fascia). As the veins progress from the periphery to the center of the body (heart) the deep venous system consolidates from multiple veins ultimately into a single vein (superior vena cava). In the forearm, AVFs are always constructed using superficial veins. The cephalic vein
(or occasionally a tributary) situated in the lateral aspect of the forearm is the most commonly used vein to create a forearm access. The basilic vein situated in the medial aspect of the forearm is used to create a forearm access in a minority of patients. Figure 2 depicts the common sites used for fistula creation in the forearm.

Figure 3 depicts the most common techniques used for forearm AVGs. AVGs often utilize the deep veins near the cubital region to obtain outflow. While AVGs were placed in superficial veins in the past, this practice is becoming less common due to the increasing emphasis on AVF creation (as most patients who have superficial veins that are suitable to support an AVG at the elbow tend to be candidates for forearm or upper arm AVFs). Occasionally an AVG may be placed on a median cubital vein at the elbow in situations where the forearm’s superficial veins are thrombosed.

Thus, regardless of access site (Figure 2) or technique (Figure 3), blood from the forearm access flows into:

(i) The cephalic vein in the upper arm through the lateral cephalic and upper arm cephalic vein (superficial);
(ii) The deep brachial venae comitantes through the perforating vein near the elbow; or
(iii) The median cubital vein to the upper arm basilic or upper arm deep brachial veins. It is not uncommon to see the blood flow preferentially channeled into one of the outflow tracts instead of distributing equally, thus resulting in preferential dilation of one or more of the outflow veins.

If the upper arm cephalic, the upper arm basilic, or the deep brachial veins develop to be large enough in size and long enough in length, they can be used to create an upper arm SAVF when the forearm access fails or becomes dysfunctional (Figure 1). Occasionally, if the forearm basilic vein is used to create a forearm radio-basilic AVF (Figure 2), the outflow blood travels mainly into the upper arm basilic vein. Thus upper arm basilic veins can serve as veins suitable for SAVF creation when the forearm fistula fails or becomes dysfunctional.

End to side anastomosis is the preferred technique to create an AVF. However, it is not uncommon to encounter upper arm AVFs with the inflow below the elbow created with a side to side anastomosis between the forearm cephalic vein and proximal radial artery [6]. Outflow blood in such accesses flows through:

(i) Perforating veins into deep brachial veins (when not ligated);
(ii) Median cubital veins into upper arm basilic veins; or
(iii) Upper arm cephalic veins. A similar situation is also encountered when a perforating vein is used at the level of the elbow (Gracz fistula) without channeling all of the flow into upper arm cephalic veins by ligating flow diverting tributaries [7].

Of the three veins discussed above that have the potential to mature; only the cephalic vein is a superficial vein and is easily seen during clinical examination. It is therefore easily available for conversion to a SAVF. Many of the original SAVF concepts such as the ‘sleeves up’ protocol (discussed below) were developed to target this vein. Whereas brachial veins belong to the deep venous system, the basilic vein becomes a deep vein beyond the lower third of the upper arm (Figure 1). Deep veins generally require ultrasound or radiological imaging (fistulogram) for identification. They also need to be transposed prior to use, as they
are situated deep in the neurovascular bundle along with arteries and nerves supplying the limb. Attempts to cannulate them without transposition can injure these important structures and cause significant discomfort to the patient.

**Indications for A SAVF Evaluation**

- Any patient who is on dialysis with an access obtaining inflow from any artery below the elbow.

Despite an increase in the prevalence of AVFs in the United States, about 28% of patients continue to dialyze with AVGs in either a straight or looped configuration [8]. AVG primary patency is poor and commonly requires one or more interventions within a year of placement [9]. Current data also suggest a need for an increasing frequency of interventions with progressively shorter time between interventions to maintain graft patency [10].

*Thus, any patient who has an AVG in the forearm needs a SAVF evaluation.* While it is mandatory to evaluate a patient who has necessitated an intervention on a forearm AVG, it is also necessary to evaluate a patient with a well-functioning forearm AVG for a SAVF. Well-functioning AVG patients tend to have well-developed graft outflow veins that are suitable for creation of a SAVF. As these patients do not have any issues with dialysis, these mature outflow veins frequently go unnoticed. Over time, these grafts tend to thrombose due to the development of stenosis at the graft-vein anastomosis, stenoses within the graft, or due to pseudoaneurysms at the needle access sites [11]. Failure to have prior knowledge of the presence of well-developed outflow veins and lack of documentation of an access plan in the event of graft thrombosis often results in lost opportunity to create a SAVF. Without a plan, for example, to bar stent placement in the outflow vein, it is common for an interventional thrombectomy to conclude with stent placement, thereby losing the opportunity to create a SAVF that could be available for immediate dialysis.

Due to the FFBI, AVF prevalence has consistently increased [8]. The increase in fistula placements in the US has concordantly paralleled an increase in AVF failure and poor AVF maturation [12]. *All patients with AVF failure and poor AVF maturation or function that receive inflow from an artery below the elbow should similarly be evaluated for SAVF creation.* Those patients with patent but immature veins due to a small diameter or poor interventional or surgical candidacy to make them suitable for needle access are candidates for SAVF evaluation. This is also true for fistula patients with problems such as needle stick difficulties, large aneurysms, repeat thrombectomies, or needing other maintenance interventions. These patients often have outflow veins in the upper arm that might provide an excellent opportunity to create a SAVF.

Finally, *patients with well-functioning AVFs deriving inflow from an artery below the elbow need to be evaluated for a SAVF.* While the need for intervention or creation of secondary fistulae in these patients is extremely rare, there should be a readily available plan addressing the course of action in the event of access thrombosis. Without clear documentation of the plan, opportunity to construct a SAVF is often lost.

*In summary, any patient with a patent access (AVG or AVF) receiving inflow from an artery below the elbow, regardless of its functional status, is a candidate for SAVF*
evaluation. If deemed a potential candidate for a SAVF, this should be recorded and made readily available to dialysis care providers to be used when appropriate.

**Evaluation and Timing of a SAVF**

As a universal principle, every attempt should be made to avoid CVC placement or to minimize CVC duration. Evaluation for a SAVF should start with a thorough history to gather information on the type, site, and duration of function of all accesses (including catheters) the patient has received in the past. The clinical exam should be performed to assess the suitability of the upper arm veins for SAVF creation. A simple clinical test to confirm this would be a digital or tourniquet occlusion of the vein to observe for pulsatility. The appearance of a pulse upon distal occlusion with prompt disappearance usually indicates flow and patency of the system. If there is any suspicion regarding the outflow vein or central vein patency, a Doppler ultrasound examination or a venogram (or both) are reasonable tests to perform.

While ultrasound is an ideal test for evaluation of peripheral veins, venogram is used to evaluate the central veins [13]. The timing of such tests depends on the performance of the existing access. If there is any evidence of pre-existing forearm access problems, these tests should be performed immediately. Management plans should be developed based on this evaluation and conveyed to the patient, dialysis staff, interventionalist, nephrologists, and surgeons involved in the patient’s care.

Clinical examination is one of the critical components of SAVF evaluation. The purpose of a “sleeves up” protocol (Table 1) is to identify and develop a management plan to convert patients undergoing dialysis with a forearm AVG (Figure 4) to an upper arm AVF at an appropriate time [3]. The salient points in this concept include:

1. Nephrologists evaluate every AVG patient for possible SAVF conversion, including mapping as indicated and document the plan in the patient’s record.
2. Dialysis facility staff and/or nephrologists examine the outflow veins of all graft patients (“sleeves up”) during dialysis treatments (minimum frequency, monthly). They identify patients who may be suitable for elective SAVF conversion in the upper arm and inform nephrologists of the suitable outflow vein.
3. Nephrologists refer to a surgeon for placement of a SAVF before AVG failure.

The authors advocate extending this concept to include patients with forearm AVGs and AVFs.

The Fistula First work group recommends that the timing for SAVF evaluation be no later than the first signs of AVG failure by monitoring for thrombosis and that SAVF surgery take place no later than the second intervention for AVG stenosis or thrombosis (opinion).

Any delay in conversion beyond this point is likely to result in loss of the SAVF option secondary to further graft interventions (endovascular or surgical) that may damage or utilize the outflow vein. This often results in AVG abandonment, a CVC, and a new AVG in a different location.
Table 1. Sleeves up Protocol (Recommendations of the fistula first work group)

<table>
<thead>
<tr>
<th></th>
<th>Once a month, clinic rounds include examination of the AVG extremity to the shoulder, by rolling sleeves up or removing shirt if necessary (Figure 4).</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>After the upper arm is exposed to the shoulder, the hand or a tourniquet is used for light compression just below the shoulder, to see if the outflow vein of the forearm graft appears suitable for immediate use as an AVF. If this appears to be the case (often this is the case if the cephalic vein is the outflow vein), the vein is evaluated by:</td>
</tr>
<tr>
<td></td>
<td>• Referring patient for fistulogram or Doppler study to confirm that the outflow vein and draining system back to the heart are normal.</td>
</tr>
<tr>
<td></td>
<td>• If fistulogram is normal, the vein is “tested” by cannulating the outflow vein with the venous needle only for 2 consecutive dialysis sessions.</td>
</tr>
<tr>
<td></td>
<td>• If both cannulation sessions are uneventful, the plan for surgical conversion from forearm AVG to upper arm AVF is discussed with the patient, staff, nephrologists, and surgeon—and documented in chart.</td>
</tr>
<tr>
<td></td>
<td>• Staff follows patient until AVF conversion is performed.</td>
</tr>
</tbody>
</table>

Figure 4. Mature upper arm cephalic vein in a patient with forearm loop graft with pseudoaneurysms.

If the “sleeves up” evaluation does not identify a vein as being clearly suitable for conversion to an AVF, a fistulogram or doppler ultrasound study (provided one has not been recently performed) should be ordered at the first signs of graft failure, both for diagnostic purposes as well as to check for suitability of the outflow vein. All interventionalists should be notified that all contrast or ultrasound studies for AVG failure or thrombosis should include a report on the condition of the outflow veins and central veins with respect to the potential for SAVF construction. If a suitable basilic or cephalic outflow vein is identified but is too deep for safe cannulation, the plan for a transposition AVF should be discussed and
Secondary Arteriovenous Fistula documented, with the timing of the procedure to be based on evidence of AVG failure and patient condition.

SAVF conversion should be performed in a timely fashion to avoid CVCs. In the setting of a well-functioning AVG, it is reasonable to wait for signs of failure. If the graft presents with thrombosis, it is important to make sure the outflow vein that is earmarked for a SAVF is not sacrificed using a stent during the thrombectomy attempt. If the thrombectomy fails or the success of thrombectomy is short lived, proceeding with a SAVF is a reasonable recommendation. With such planning, availability of a mature upper arm cephalic vein (superficial vein) often provides an opportunity to avoid a CVC. However, when the outflow vein belongs to the deep venous system in the upper arm (basilic vein or the brachial vein), conversion to a SAVF necessitates a transposition procedure. In such cases, a bridging catheter may become necessary for 4-5 weeks while awaiting vein incorporation in its new site and wound healing.

When the outflow vein belongs to the deep venous system, the authors advocate an elective planned transposition. In this innovative strategy, once a decision to proceed with a SAVF has been made, the deep outflow vein is electively superficialized, while the ailing forearm access patency is maintained with the help of interventional or surgical means. Once the transposed vein has healed adequately and has been confirmed to be suitable to function as a SAVF conduit, the forearm access is abandoned and a new inflow for the vein is obtained from an arterial source near the elbow. This essentially is the reverse of a two stage basilic/brachial vein transposition procedure. We have successfully performed this procedure in seven patients. This procedure provides an opportunity to troubleshoot complications of transposition while the patient is still being dialyzed through the ailing forearm access, thereby avoiding a CVC.

**Literature Review**

In an attempt to assess the prevalence of a SAVF option, Ash and Beathard reviewed one hundred patients with AVG-related problems referred to their interventional facility [11]. Of the 62 patients who had forearm AVGs, 46 (74%) were deemed suitable candidates for a SAVF. This suggests that, if screened appropriately, the majority of patients with forearm AVGs would be candidates for a SAVF. There are several reports in the literature regarding the construction of upper arm AVFs following a failed forearm AVF [14,15,16]. In a recent publication, Slayden et al reported a cumulative patency of 97% at 2 years for type 1 SAVF [4]. They also proposed a significant cost savings, as an AVF performs significantly better than an AVG.

**Summary**

A SAVF is defined as an AVF created following a failed previous access below the elbow. The concept is an attempt to increase the prevalence of AVFs and to decrease catheter exposure in ESRD patients. Though originally intended for converting patients with an AVG to an AVF as their next access modality, it should also be considered as the subsequent access
modality for all patients with forearm access (AVGs and AVFs). With an increase in the placement and prevalence of AVFs, it is only a matter of time before we encounter more SAVF candidates among patients who are on dialysis with forearm AVFs.

Increased flow from previously placed access provides an opportunity to utilize already mature, pristine veins to create a new AVF. Due to the use of mature veins, many of these AVFs do not have a maturation period and may be available for immediate use. Evaluation and documentation of availability of such veins needs to be performed while the initial access is still functional. All personnel including the patient should be aware of the plan to convert an existing access to a SAVF in a timely manner. Such an approach would not only increase AVF prevalence resulting in significant economic benefit to the health care system, but would also provide the patient with an ideal, well-functioning dialysis access.

References


II. Vascular Access Care
Chapter VII

The Role of the General Nephrologist in Vascular Access Care

Kenneth Abreo\(^1\*\) and Karina Sulaiman
\(^1\)Section of Nephrology, Department of Medicine,
Louisiana State University Health Sciences Center,
Shreveport, LA, US

Introduction

In the United States chronic kidney disease (CKD) affects an estimated 11% of the population and more than 300,000 patients have end-stage kidney disease (ESRD) requiring dialysis [1]. These patients are cared for by the general nephrologist either in the setting of an office practice, a hospital or a dialysis unit. In addition to addressing issues that are unique to CKD and ESRD such as anemia, hyperparathyroidism, and acidosis, the general nephrologist must educate the patient about available dialysis modalities and access [2]. The ultimate life line to the patient’s wellbeing is a well-functioning access either to the blood stream or the peritoneal cavity. If a patient transits from CKD to ESRD with excellent dialysis access, that patient has a survival advantage over those who start dialysis with a central venous dialysis catheter [3]. To achieve the ideal vascular or peritoneal access the general nephrologist must have an intimate knowledge of different dialysis modalities, the foresight to discuss access placement well before dialysis is imminent, the skill set to determine the adequacy of the access, and contact with a collaborative network of health care providers who can work with him/her to ensure that the best access is in place before the patient needs dialytic therapy.

Low arteriovenous fistula (AVF) rates in the United States led to the launching of The Fistula First Breakthrough Initiative known as “Fistula First” in 2003 to maximize the number of AVFs [4]. An eleven step change concept program was developed to increase the placement of AVFs (Table 1).

\(^*\)Corresponding author: Kenneth Abreo, M.D. LSU Health Sciences Center, 1501 Kings Highway, Shreveport, LA 71130, Phone: 318-675-7402, Fax: 318-675-5913, E-mail: kabreo@lsuhsc.edu.
Table 1. Fistula First concepts

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Routine CQI review of VA</td>
</tr>
<tr>
<td>2.</td>
<td>Timely referral to nephrologist</td>
</tr>
<tr>
<td>3.</td>
<td>Early referral to surgeon for “AVF only” evaluation and timely placement</td>
</tr>
<tr>
<td>4.</td>
<td>Surgeon selection based on best outcomes, willingness, and ability to provide access services</td>
</tr>
<tr>
<td>5.</td>
<td>Full range of appropriate surgical approaches to AVF evaluation and placement</td>
</tr>
<tr>
<td>6.</td>
<td>Secondary AVF placement in patients with AVG</td>
</tr>
<tr>
<td>7.</td>
<td>AVF placement in patients with catheters where indicated</td>
</tr>
<tr>
<td>8.</td>
<td>AVF cannulation resources for staff</td>
</tr>
<tr>
<td>9.</td>
<td>Monitoring and maintenance to ensure adequate access function</td>
</tr>
<tr>
<td>10.</td>
<td>Education for caregivers and patients</td>
</tr>
<tr>
<td>11.</td>
<td>Outcomes feedback to guide practice CQI, continuous quality improvement.</td>
</tr>
</tbody>
</table>

Taking these concepts into consideration, the goals of this chapter are to describe a step by step approach that a general nephrologist can follow towards optimum access placement in patients with CKD and those with ESRD on hemodialysis.

This chapter will focus on how and when to prepare a CKD patient for dialysis, when to proceed with a surgical referral, how to select a surgeon, when to refer the patient to an interventionalist, how to examine a vascular access for dysfunction, and how to organize a team approach to vascular access care.

**Progression of Kidney Disease**

Progression of CKD is variable depending on the nature of its cause. For example, diabetic kidney disease progresses fairly rapidly to ESRD once significant proteinuria develops, usually over 3-5 years, whereas hypertensive CKD may take a much longer time to reach ESRD, especially when blood pressure is well controlled. Progression from CKD to ESRD can be variable even in patients having the same disease because of genetic factors, comorbid states, and medical compliance.

In addition, unpredictable illness such as volume depletion or exposure to contrast or nephrotoxic agents can cause acute renal failure in patients with CKD and hasten progression towards ESRD [5, 6]. Taking all these issues into consideration the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF K-DOQI) guidelines suggest that dialysis modalities and access discussions between the physician and patient should occur at CKD Stage 4 when the estimated glomerular filtration rate (eGFR) is between 15 and 30 ml/min [7].

The general nephrologist should keep in mind that the eGFR calculated by the Modification of Diet in Renal Disease (MDRD) formula has not been validated at extremes of age (very young or very old), in certain population groups such as Asians, and those with extremes of muscle mass (morbidly obese or cachetic patients). In such situations obtaining a 24-hour urine creatinine clearance may be preferable to gauge the level of renal function.
Optimum Time for Access Placement

The 2006 K-DOQI guidelines recommend that for the patient with CKD, a vascular access should be placed when the eGFR is < 30 ml/min (CKD 4), when the plasma creatinine > 4 mg/dl, or when there is rapid progression of renal disease [7]. It is also suggested that a fistula be placed at least six months and a graft 3-6 weeks prior to the anticipated start of hemodialysis. Given the high arteriovenous fistula failure rate of 60% in some studies, the best time to place a fistula is a year before hemodialysis is anticipated [8]. The one year interval takes into account the time for referral to a surgeon, the time for access creation and maturation (3 months), and the time spent in performing interventional procedures for the immature or dysfunctional accesses. Patients on hemodialysis with a tunneled central venous catheter require immediate referral for fistula placement because of the extremely high incidence of catheter associated bacteremia and sepsis that are life threatening, and the potential for catheter-associated central vein stenosis precluding access placement on that side [9].

Fistulas can also be placed in stage 5 CKD as long as the patient is clinically and metabolically stable and is preferable to initiating hemodialysis through a tunneled catheter. Recent studies have shown that the mortality of patients undergoing hemodialysis early, at eGFR 10-15 ml/min, was either no different or worse than in patients starting with an eGFR less than 10 ml/min [10, 11]. By delaying the start of hemodialysis the nephrologist can buy time for the stable patient in stage 5 CKD for fistula placement and maturation.

It is good to remember the rule of 30-20-10, at eGFR of 30 ml/min, discuss dialysis options, at eGFR of 20 ml/min, place an arterio-venous fistula, and at eGFR of 10 ml/min initiate hemodialysis if clinically indicated [12]. Studies have shown that early referral of the patient to the surgeon increases the likelihood of AVF placement [13, 14]. Patients who were followed by a nephrologist and developed ESRD predictably had a 46% AVF rate, whereas those followed by a nephrologist but presented with worsening renal failure in an acute setting had a 21% AVF rate and those not followed by a nephrologist had an AVF rate of 2% and a catheter rate of 80% [13].

In another report, patients seen by the nephrologist >3 months before needing HD had a 70% AVF rate whereas when patients saw the nephrologist <3 months before HD, 73% started HD with a catheter [14].

Vein Preservation

The nephrologist has to emphasize to CKD patients and those physicians involved in their care the importance of preservation of the superficial veins of the arm for fistula creation, the so called “vascular real estate”. Needle sticks and intravenous infusions through arm veins can lead to thrombosis and sclerosis resulting in loss of potential veins for fistula creation [15, 16]. When access to arm veins is an absolute necessity, the veins on the dorsum of the hands should be used thus preserving the veins in the forearm and upper arm [17]. If central venous access is needed, PICC (percutaneous intravenous cannulation) lines should never be used as they destroy the superficial veins of the upper arm and can cause central vein stenosis [16]. If central venous access is absolutely needed, the subclavian veins should never
be used because of an inordinate threat to central venous stenosis [18]. The internal jugular veins are preferable because the occurrence of stenosis in these veins is significantly less and even if there is stenosis the subclavian, brachiocephalic, and superior vena cava remain patent for placement of fistulas in the ipsilateral arm [19].

**Physical Examination of the Arm Prior to Access Placement**

Prior to the physical examination a detailed history of placement of central venous catheters, PICC lines, pacemakers and surgery for breast cancer or to the neck and chest should be obtained. This information may guide the selection of the proper arm for access placement. Examination begins with inspection of the arm for swelling, dilated tortuous veins over the shoulder and chest, presence of a pacemaker on the chest, and the scars of the exit sites of previously placed tunneled catheters.

These findings indicate that there could be an underlying central stenosis on a particular side, requiring further testing or the placement of a permanent access on the contralateral side. If a permanent access were to be placed on the side of an occult central stenosis there is usually severe swelling of the arm after surgery and if the central stenosis cannot be treated the access has to be ligated.

**Arterial Evaluation**

Adequacy of the arterial circulation should be evaluated to find out whether it can support an arterio-venous access that provides adequate blood flow for hemodialysis without compromising the circulation to the hand. Arterial stenosis and calcification are common in ESRD particularly in patients with diabetes and hypertension. The axillary, brachial, radial, and ulnar artery pulses should be examined simultaneously in both upper extremities to evaluate the intensity of the pulse (normal, diminished, or absent) and for differences in each limb [20]. Blood pressure should be measured in both arms. A difference in systolic pressure of less than 10 mm Hg is normal, 10-20 mm Hg marginal, and more than 20 mm Hg is highly abnormal and suggestive of subclavian artery stenosis [20].

Finally, the modified Allen test should be performed to evaluate adequacy of circulation in the palmar arch [21, 22, 23]. In brief, with the patient facing the nephrologist with the hand slightly flexed, the nephrologist compresses the ulnar and radial arteries simultaneously, and the patient is asked to squeeze the fist repetitively so that the hand is blanched. On release of the radial artery, the time that it takes for the hand to turn pink reflects on the patency of the radial artery. The steps are repeated with release of pressure on the ulnar artery to assess the patency of the ulnar artery. Usually the blanched palm turns pink in less than 5 sec., a negative Allen test. Prolonged recovery with release of either the radial or ulnar artery, between 5-10 sec (intermediate test), or more than 10 sec (positive test), suggest disease in one of these arteries [24]. A positive test suggests poor collateral circulation in the hand and a greater likelihood of developing steal if the dominant artery to the hand is used for fistula creation.
The Role of the General Nephrologist in Vascular Access Care

Venous Evaluation

A tourniquet placed over the upper arm or a blood pressure cuff inflated to a pressure of 5 mm Hg above the diastolic blood pressure allows the nephrologist to visualize the size and pattern of the superficial veins of the arm. A venous diameter of 2.5 mm at the site of anastomosis to the artery, straight segment of vein, and continuity with the central veins all favor the use of a vein for fistula creation [25]. The nephrologist should also be on the lookout for secondary fistulas in patients who are on hemodialysis with a forearm graft or fistula. The nephrologist simply needs to ask the patient to roll up his/her sleeve to look for dilated veins in the upper arm [26, 27, 28].

Secondary fistulas develop from the out flow tract of a forearm graft or fistula. If the vein in the upper arm has enlarged and arterialized, it can be used for hemodialysis or it can be surgically anastomosed to the brachial or radial arteries. Secondary fistulas can be used immediately and therefore the patient may not have to have a catheter placed when the forearm graft or fistula fails.

Vascular (Venous and Arterial) Mapping with Ultrasound

Vascular mapping with ultrasound and Doppler are complementary tests to the physical examination of the arteries and veins of the patient’s arms. The selection of the appropriate arteries and veins by ultrasound and Doppler for fistula creation has been shown to dramatically improve the success of fistula construction in several reports [29-33]. When ultrasound was added to the physical examination there was a dramatic decrease in fistula failure rate [34]. A preoperative arterial diameter of less than 1.6 mm is associated with a high risk of failure of radio-cephalic arterio-venous fistulas [29-31, 35]. Whereas a diameter of 2 mm or greater is felt to be optimal by others [25].

The quality of the arterial wall may also be important, as a calcified artery is less likely to dilate and thereby result in an immature fistula. The influence of arterial flow on fistula maturation is unclear but it has been suggested that a flow > 34 ml/min in patients meeting the vein criteria leads to a high success rate of 92% [36]. Venous mapping should show a venous diameter of at least 2.5 mm at the anastomotic site, a straight segment of vein of 5-6 cm, and a depth of less than 1 cm with no stenosis and continuity with the proximal central veins [25]. The minimum diameter for the vein draining a graft is 4 mm.

Venous Mapping with Venogram

It is best to avoid venograms for mapping in patients with CKD because of the danger of contrast induced nephrotoxicity. However, if indicated, i.e. high risk patients (see Chapter 1), contrast should be limited or CO₂ angiography should be done. Patients on dialysis who have or had central venous catheters for a fairly long time, should undergo venous mapping with assessment of their central veins to rule out stenosis [37]. The venogram is significantly more sensitive in picking up central venous lesions than the ultrasound.
Surgical Referral

Since the AVF is clearly the ideal access for the patient because of its longevity and low rate of complications, the nephrologist should send an early referral to the surgeon for “AVF only” evaluation and placement. Selecting a surgeon who has extensive experience in placing vascular accesses is vitally important in obtaining a functioning arterio-venous fistula. Between 2002 and 2005 a study in the UK examined the primary success, and the primary and secondary patency rates of AVF placed by 153 senior surgeons (Group A) to 42 junior surgeons (Group B). After 22 months of follow up the success rate for Group A versus B was 94% to 81%, primary patency 80% to 74%, and secondary patency 93% to 81% (38). Adequate training and experience are essential to the success of any vascular access program [39-42]. Surgeons who placed more than 130 fistulas each year had a higher one-year patency when compared to surgeons who placed less than 30 fistulas each year, 80% versus 40% [39-42].

Examination of AVF for Maturity

Four to six weeks after the AVF is in place and the skin incision has healed, the nephrologist must determine whether the AVF has matured for hemodialysis use when needed. Examination is critical in decision-making and poor examination skills may lead the nephrologist to the conclusion that the AVF has matured when in fact it needs to be intervened upon either endovascularly or surgically.

Occasionally the immaturity of the fistula is discovered too late and the patient is initiated on hemodialysis with a tunneled catheter. Sometimes a patient with a pulsatile fistula due to a severe proximal stenosis is referred by the nephrologist for HD with the disastrous consequences of hematoma formation.

Fistula

The physical examination of the AVF should be performed in an organized fashion, starting with inspection [43-45]. On inspection the fistula can be divided into the juxta-anastamotic segment, the body, and the outflow segment. The first 2 cm of the AVF that is anastamosed to the artery is called the juxta-anastamotic segment, proximal to that is the sticking segment that is roughly 4-5 cm long is called the body, and followed by a segment that runs deep called the outflow segment. Inspection can identify large accessory veins that are branches of the fistula. Accessory veins may steal so much blood that the fistula fails to mature. The presence of large aneurysms in body of the fistula is suggestive of stenosis proximal to the aneurysms.

An easily visible fistula is a good sign, suggesting maturity and superficiality. If the fistula cannot be seen it could be either immature or mature but deep. The patient is then asked to raise the arm. If the fistula collapses it indicates an open channel to the central circulation with no stenosis (Figure 1A and 1B). A good sized AVF that collapses is likely to be mature with no stenosis.
The Role of the General Nephrologist in Vascular Access Care

If the distal part of the AVF collapses leaving a prominent proximal segment, a stenosis should be suspected at the junction of the collapsed and prominent segments (Figure 2A and 2B. If the whole AVF does not collapse there may be outflow stenosis. Palpating the fistula has two components, testing for augmentation and testing for accessory veins. Augmentation can be elicited by occluding the juxta-anastamotic segment and palpating distal to it. The thrill of the fistula disappears and is replaced by a pulsatile pulse. Here the examiner is basing his findings on experience.

A mature fistula augments well in that on occlusion of the juxta-anastamotic segment there is a prominent transmitted arterial pulse. Poor augmentation suggests poor arterial inflow, stenosis of the artery-vein junction or juxta-anastamotic stenosis. If the occluding finger is moved an inch at a time proximally along the body of the fistula, if a thrill is felt despite occlusion of the body of the fistula, then one should suspect the presence of an accessory vein. The accessory vein may be important especially in an immature AVF as it could be channeling a fairly large amount of blood thus preventing fistula maturation. On palpation if the fistula seems prominent, the thrill pulsatile, and the walls thickened or graft-like then stenosis should be suspected. It is important not to use this AVF for HD, as puncture will inevitably cause a large hematoma due to the high intrafistula pressures.

Auscultation of the fistula is the last but not the least of the fistula examination. A well matured AVF with no stenosis has a bruit that is continuous and heard in systole and diastole. The bruit is louder at the arterial end of the fistula and decreases in intensity as auscultation moves to the proximal fistula. The presence of a very high pitched systolic bruit with a minimal diastolic component is very suggestive of stenosis. If there are any doubts of a fistulas maturity an ultrasound examination should be ordered.
In many CKD patients AVFs are placed at stage 4 CKD and the AVF will not be used for HD for several months. The general nephrologist has to decide whether the AVF has matured and can be used for HD when needed. On the other hand the nephrologist must be able to diagnose an immature or dysfunctional AVF that could be potentially matured prior to the need for HD. In that case referral to an interventionalist or surgeon would be necessary.

Arterio-Venous Graft

Ultrasound Examination for Maturity

Figure 2.
Mastery of the AVF examination is critical for decision making. When in doubt an ultrasound of the AVF can be ordered to complement the physical examination.

On ultrasound examination a fully mature AVF should fulfill the rule of 5s: It should have a 5 cm straight sticking segment, it should have a blood flow of > 500 ml/min, it should be less than 5 mm below the skin, and it should have a diameter of > 5 mm.

Ultrasound examination also detects stenosis in the AVF. Inflow stenosis compromises maturation where as stenosis in the body or outflow of the AVF results in a pulsatile AVF that is prone to bleed, form aneurysms, and provide inadequate HD due to recirculation. Accessory veins can also be detected and if they are large and steal a substantial amount blood flow they will compromise AVF maturation.

Thus physical examination skills together with ultrasound examination of the AVF detect potential correctable causes for AVF failure. Absence of these skills will make the nephrologist complacent in the belief that the AVF is mature only to realize too late that the AVF indeed cannot be used for HD and the unfortunate patient has to start HD with a tunneled catheter.

Patients who are already on HD need the AVF assessment done promptly to shorten HD with a tunneled catheter. The nephrologist should utilize the expertise of seasoned nurses in HD units who can quickly ascertain whether the AVF can be cannulated. Poor decision making at this juncture often leads to multiple attempts at cannulation or large hematoma formation increasing the patients suffering.

**Vascular Access Dysfunction**

Vascular accesses become dysfunctional with time and use. The majority of AVGs develop venous outflow stenosis resulting in a high thrombosis rate. AVFs also develop stenosis in outflow veins such as the cephalic arch of brachiocephalic AVFs or the “swing site” of transposed brachio-basilic AVFs. An unexplainable persistent drop in Kt/V, gradual decrease in measured blood flow rate, excessive bleeding after HD, formation and enlargement of aneurysms, swelling of the access arm, are all indications for examination of the access using physical exam and ultrasound.

Ischemia to the hand can develop following vascular access placement or occur as a late complication in patients whose distal arterial flow is compromised from the vascular steal that inevitably occurs with all vascular accesses. The symptoms could be as trivial as tingling, numbness, or coldness of the hand to ischemic necrosis of the digits. Vascular compromise occurs more often in accesses originating in the brachial artery. The radial pulse is usually feeble or not felt in the access arm when compared to the contra-lateral arm. Occlusion of the vascular access results in return of the pulse with relief of symptoms.

The patient should be referred to an interventionalist so that the arterial and venous circuit can be thoroughly visualized. Stenotic lesions in the artery can be repaired by angioplasty and a Miller procedure can be accomplished in the Interventional Suite to decrease flow in the vascular access.

The patient can also be referred to the surgeon to perform a vascular access flow reduction procedure such as placation or distal revascularization and interval ligation (DRIL). Sometimes the patient develops ischemia to the nerves of the hand on the side of the access.
resulting in paralysis of the hand, called “monomelic neuropathy”, a condition that is considered an emergency requiring immediate ligation of the vascular access. If gangrene of the finger tips or digits occurs consideration for ligation of the vascular access should be given priority.

It is important that the nephrologist distinguish ischemia of the hand from arthritis or synovitis of the wrist or carpal tunnel syndrome. The latter condition has a distinct neurologic pattern and can be confirmed with an electric conduction study.

In some patients hand pain occurs during hemodialysis and resolves when the patient is off the machine. Usually, this condition is due to ischemia of the hand.

Fistulogram to Detect Maturity and Dysfunction

A fistulogram should be done only on those patients in whom a thorough examination of the AVF followed by ultrasound examination has lead to the detection of a potentially correctable lesion. A fistulogram is not a substitute for a physical examination or ultrasound because this test subjects the patient to contrast reactions and potential renal toxicity from the radiocontrast agent.

Several studies have shown that if the patient is hydrated, and less than 10 cc of isosmolar radiocontrast agent is used, the likelihood of nephrotoxicity is negligible. Patients in CKD 4 and 5 should not be deprived of an angiogram due to concerns about contrast exposure. The interventional suite should be informed of the patient’s level of renal function so that the minimal amount of contrast agent is used.

Challenges in Vascular Access Placement

Patients can often be reluctant to proceed with access placement when there is no immediate indication for dialysis. They should be counseled regarding the complications related to tunneled catheters and the poor outcomes of patients who are initiated emergently on hemodialysis. This process often requires several clinic visits and it is recommended that time be set aside for discussion and additional resources such as patient information pamphlets and educational videos.

Another challenge for the nephrologist is the patient with severe vascular disease with limited options for vascular access. Healthcare providers involved in the care of these patients must work together to explore the available options and resources for such patients and consider less conventional access sites such as thigh grafts and the more recent HeRO Vascular Access Device (Hemodialysis Reliable Outflow) [46].

Nephrologists must also be willing to revisit previously ruled out options such as peritoneal dialysis in such patients, and recognize the necessity of repetitive discussion with the patient to ensure optimal outcomes.

In this regard a vascular access coordinator is a valuable asset to the team of healthcare personnel caring for dialysis patients as well as regularly scheduled meetings organized to specifically address these issues.
### Summary of AVF exam

<table>
<thead>
<tr>
<th>Findings</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fistula easily seen</td>
<td>Normal</td>
</tr>
<tr>
<td>Fistula collapses on raising arm</td>
<td>Normal</td>
</tr>
<tr>
<td>Part of AVF collapses</td>
<td>Stenosis in AVF</td>
</tr>
<tr>
<td>AVF not seen</td>
<td>Immature or deep AVF</td>
</tr>
<tr>
<td>Swelling of arm on the side of AVF</td>
<td>Central stenosis</td>
</tr>
<tr>
<td>Large aneurysms in AVF</td>
<td>Proximal stenosis</td>
</tr>
<tr>
<td>Visible accessory veins</td>
<td>May cause AVF immaturity</td>
</tr>
<tr>
<td>Soft with continuous thrill</td>
<td>Normal</td>
</tr>
<tr>
<td>Augmentation excellent</td>
<td>Normal</td>
</tr>
<tr>
<td>Augmentation poor</td>
<td>Arterial or juxta-anastamotic stenosis</td>
</tr>
<tr>
<td>Pulsatile</td>
<td>Stenosis in proximal AVF</td>
</tr>
<tr>
<td>Persistent thrill on occlusion of AVF</td>
<td>Accessory vein</td>
</tr>
<tr>
<td>Continuous systolic-diastolic bruit</td>
<td>Normal</td>
</tr>
<tr>
<td>High pitched systolic bruit</td>
<td>Stenosis</td>
</tr>
</tbody>
</table>

### Conclusion

General nephrologists are facing the challenge of dealing with multiple complex issues related to vascular access with the increasing prevalence of chronic kidney disease and the rising numbers of dialysis patients. They are often the first physicians to be confronted with these issues and therefore must be educated and prepared to provide optimum care for their patients. Timely referral for access and being capable of addressing access complications is an essential component of their role in the current climate of multilevel care.

### References


Chapter VIII

Monitoring and Surveillance for Vascular Access: Does it Help Our Patients?

*Marius C. Florescu and Troy J. Plumb*
University of Nebraska Medical Center, Omaha, NE, US

**Introduction**

An adequate vascular access is essential for the survival of hemodialysis (HD) patients. HD requires access to blood vessels capable of providing sustained, high blood flow rates. Arteriovenous fistulas (AVF) and arteriovenous grafts (AVG) are preferred to tunneled dialysis catheters, but are not without problems. AVF and AVG are at risk of failure and may require numerous interventions to maintain optimal function. Failure of the vascular access often manifests as thrombosis and has serious consequences on patient morbidity and mortality. Vascular access failure is a slowly developing process which consists of a progressive decline in access blood flow mediated by the progression of stenotic lesions located at different sites of the vascular access [1]. Neointimal hyperplasia is the mechanism responsible for the formation and progression of stenosis. Access monitoring and surveillance is designed to detect abnormalities associated with stenotic lesions before the abnormalities cause severe access dysfunction. Early correction of stenoses may prevent serious access complications such as thrombosis. However, not all the stenoses detected by monitoring and surveillance are clinically significant, lead to access failure, or require treatment. This fact highlights how difficult it can be to interpret the findings of monitoring and surveillance. Ideally, monitoring and surveillance will detect the stenoses that are serious enough to mandate intervention, but before the stenoses are severe enough to cause major access dysfunction (decreased dialysis adequacy, thrombosis).
Definition

Monitoring is the physical examination of the vascular access (AVF or AVG) to detect signs suggestive of vascular access dysfunction. Decreased pulse and thrill or decreased pulse augmentation suggests the presence of peri-anastomotic or arterial stenosis, whereas increased pulsations within the access are suggestive of venous outflow stenosis. Either finding suggests the presence of stenoses that may decrease vascular access blood flow.

Surveillance is the evaluation of the vascular access by means of various tests performed using special instruments. An abnormal test result suggests the presence of pathology.

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) guidelines [2] recommend the use of monitoring and surveillance at least once a month to detect the presence of hemodynamically significant stenoses whose timely correction may improve the patency rates and may decrease the incidence of thrombosis. Monitoring and surveillance data need to be collected by every HD center as part of Quality Assurance (QA)/Continuous Quality Improvement (CQI) program.

Purpose and Rationale of Monitoring and Surveillance

The purpose of monitoring and surveillance is to detect changes within the vascular access which portend impending access failure so preemptive interventions may be performed. The ideal clinical impact of monitoring and surveillance with early intervention would be: increased access function, decreased thrombosis rates, decreased emergent procedures and catheter use, decreased missed dialysis treatments, and decreased hospitalizations and overall healthcare costs. Failure to detect and correct access dysfunction increases morbidity and mortality of HD patients.

Not all identified stenoses require treatment. A functionally significant stenosis that mandates intervention is defined as a stenosis with a decrease of greater than 50% of normal vessel diameter accompanied by hemodynamic or clinical abnormalities. The abnormalities can be: elevated venous pressure, decreased blood flow, reduction in Kt/V, swollen arm, elevated negative arterial pre-pump pressures that prevent increasing the blood flow to acceptable levels.

The care of the HD patient’s access should be a team effort. Multidisciplinary teams should be formed at each HD center. The team should include the nephrologist, mid-level provider, HD nurses and technicians, access coordinators and interventionalists (interventional nephrologist, interventional radiologist, vascular surgeon). The team can have different sizes and compositions but its most important function is to work proactively to maintain access function and patency.
Techniques for Monitoring and Surveillance

Monitoring

Monitoring consists of physical examination of the vascular access in order to recognize clinical signs or symptoms which, when present, suggest the existence of clinically significant stenoses. Recognizing the value of the physical examination, the 2006 updated NKF KDOQI clinical practice guidelines (Guideline 4) for vascular access [2], recommend that "physical examination (monitoring) should be performed to detect dysfunction in fistulae and grafts at least monthly by a "qualified individual"".

Physical examination should evaluate the entire length of the vascular access from the arterial anastomosis to the most central venous drainage that can be examined. Physical examination should combine inspection, palpation and auscultation. Close attention should be paid to the location and nature of the thrills, pulsations and bruits. A decreased pulse or thrill, or decreased pulse augmentation suggests the presence of peri-anastomotic or arterial inflow stenoses. Increased pulsations and failure of the AVF to collapse when the arm is elevated are suggestive of stenoses of the outflow veins. These abnormalities suggest the presence of lesions that may decrease vascular access blood flow and change intra-access pressures. (For more details please see the vascular access physical examination chapter).

In addition to the physical examination of AVF there are other clinical findings whose presence strongly suggests the existence of stenosis. Table 1 presents these clinical findings and their significance. Monitoring of the AVF is inexpensive and noninvasive and in experienced hands accurately detects and localizes stenoses in the majority of AVF and AVG [3-6].

### Table 1. Clinical findings and their significance

<table>
<thead>
<tr>
<th>Clinical findings</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swelling of arm, breast</td>
<td>Central vein stenosis</td>
</tr>
<tr>
<td>Subcutaneous collateral veins on chest and upper arm</td>
<td>Central vein stenosis</td>
</tr>
<tr>
<td>Prolonged bleeding after dialysis</td>
<td>High venous pressure caused by a downstream stenosis</td>
</tr>
<tr>
<td>Pain in the access arm and hand</td>
<td>High venous pressure</td>
</tr>
<tr>
<td>Frequent thrombosis</td>
<td>A predisposing cause that was not addressed (stenosis)</td>
</tr>
<tr>
<td>Difficult to place needles</td>
<td>Access stenosis, too deep access</td>
</tr>
<tr>
<td>Aspirate clots</td>
<td>Access thrombosis</td>
</tr>
<tr>
<td>Inability to achieve target dialysis flow</td>
<td>Decreased access flow, improper needle placement</td>
</tr>
<tr>
<td>Increased venous pressure</td>
<td>Stenosis of the venous outflow</td>
</tr>
</tbody>
</table>
Asif et al. [3] found that the sensitivity and specificity of the physical examination in detecting clinically significant stenoses of the AVF compared with angiography for the outflow stenoses were 92% and 86% and 85% and 71% for inflow stenoses respectively. There was strong agreement between physical examination and angiography in the diagnosis of outflow (agreement 89.4%) and inflow stenosis (agreement 79.6%). More recently Tessitore et al. [7] also found that physical examination accurately predicted the presence and location of stenotic lesions in AVF. It is important to note that in these studies the physical examination was performed by physicians experienced in clinical access assessment. It is unclear whether comparable results may be obtained by less-experienced clinicians or dialysis nurses. Maya et al. [8] reported that the positive predictive value for detecting a greater than 50% stenosis was only 39% for fistulas and 69% for grafts when the physical exam was performed by hemodialysis nurses with less experience examining AVF.

Fortunately, the physical examination of the AVF can be successfully taught. After one month of training, a renal fellow was able to successfully detect AVF inflow and outflow stenosis using only physical examination [9]. Physical examination detected 81% of outflow stenoses and 80% of inflow stenoses when compared with angiograms. The difference between the performance of the nephrology fellow and an experienced interventional nephrologist was not significant. This highlights the importance of teaching and mastering the physical examination by those individuals monitoring the vascular access.

In AVG, Carlos Leon et al. [6] found that the sensitivity and specificity of the physical examination in detecting stenoses compared with angiography for intragraft and inflow stenosis was 100%, 73% and 33%, 73%, respectively. The findings of this study demonstrate that physical examination can assist in the detection and localization of stenoses in AVG.

Despite its potential, monitoring is not effectively used to detect access dysfunction. The basic skills of the vascular access physical examination have been abandoned in favor of technology. Physical exam techniques should be taught to all individuals involved in performing HD treatments. The reasons why the physical examination is underutilized are multiple. HD units are often short staffed with experienced nurses able to perform a proper physical examination of the vascular access. Physical examination of the vascular access is not considered a priority in most HD centers.

Likewise, most physicians do not take the time, do not have the training, or see patients during dialysis when needles and tape impede examination of the access. For the above reasons, we practically (and possibly erroneously) rely on surveillance to provide a reliable test to predict the presence of a clinically significant stenosis in order to refer the patient for vascular intervention.

**Surveillance**

Because AVF and AVG surveillance are different in terms of methods and outcomes, they will be presented separately.

**AVF Surveillance**

The large majority of vascular access stenoses will progress and cause decreases in access blood flow. Depending on the location of the stenosis (venous limb or arterial anastomosis) there will be changes in the intra-access pressure. Intra-access pressure
increases if the stenosis is located in the venous limb or can be unchanged or decreased if the stenosis is located at the arterial anastomosis [10]. Most vascular access surveillance consists of methods that measure the access blood flow (Intra-access blood flow, Duplex ultrasound) or measure intra-access pressure (static dialysis venous pressure). Abnormal values may signal the presence of stenoses that require elective intervention. Table 2 lists the types of vascular access surveillance techniques.

Intra-access blood flow measurement techniques are summarized in Table 3. All the methods of flow measurement produce similar values.

Static venous pressure or intra-access pressure (IAP) is measured within the arterial or venous needle while blood flow through the HD machine is turned off. Many factors may affect IAP.

These include the patient’s blood pressure, intra-access blood flow, needle position, location and degree of stenosis, and the presence of collateral vessels. Changes in blood pressure influence IAP and may vary greatly from one treatment to another, hence it is important to normalize IAP to the mean arterial pressure (MAP), by using the IAP: MAP ratio rather than just IAP to assess the vascular access. Additionally, because so many factors may influence IAP measurements, trend analysis of IAP/MAP is more useful in predicting clinically significant stenoses than any single measurement.

Duplex ultrasound uses the Doppler effect to measure access blood flow. It is reproducible and accurate. Unfortunately, it is not available at the bedside, and the fact that it must be done in the vascular laboratory or hospital severely diminishes its value.

Intra-access blood flow monitoring seems to be the best surveillance method for detecting AVF stenoses because it is easily available in the HD unit, is easy to perform and the results are reasonably accurate HD unit. In AVF, direct flow measurement is superior to IAP. This is most likely a result of the fistula being a low pressure system and hence static pressure monitoring is not very effective.

Polkinghorne et al. reported [11] doubling of the detection of angiographically significant AVF stenoses if access blood flow monitoring was used compared with clinical monitoring alone.

Tessitore et al. [7] compared static venous pressures, blood flow pump/arterial pressure ratio, recirculation and access blood flow in detecting AVF stenoses. They found blood flow monitoring as being the best surveillance method of detecting AVF inflow stenosis. In a different article, the same authors [12] reported that blood flow measurement was the most effective method in predicting wrist AVF stenoses and physical examination in association with blood flow measurement and derived static venous pressure was the best surveillance for more proximally located AVFs.

Table 2. Types of access surveillance techniques

| 1. Intra-access blood flow (direct flow) measurement |
| 2. Static dialysis venous pressure |
| 3. Duplex ultrasound |
Table 3. Direct flow (Intra-access flow) measurement accepted methods

<table>
<thead>
<tr>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duplex Doppler Ultrasound (DDU)</td>
</tr>
<tr>
<td>Magnetic resonance angiography (MRA)</td>
</tr>
<tr>
<td>Variable Flow Doppler Ultrasound (VFDU)</td>
</tr>
<tr>
<td>Ultrasound Dilution (transonics) (UDT)</td>
</tr>
<tr>
<td>Crit-Line III (optodilution by ultrafiltration;Hemametrics): [OABF]</td>
</tr>
<tr>
<td>Crit -Line III direct transcutaneous (HemaMetrics): [TQA]</td>
</tr>
<tr>
<td>Glucose pump infusion technique (GPT)</td>
</tr>
<tr>
<td>Urea Dilution (ureaD)</td>
</tr>
<tr>
<td>Differential Conductivity (Gambro): (HDM)</td>
</tr>
<tr>
<td>In Line Dialysance (Fresenius): (DD)</td>
</tr>
</tbody>
</table>

The threshold of access flow for predicting stenosis is lower in AVF (450-500 mL/min) compared with AVG [13-15]. In line with these findings, KDOQI guidelines recommend intervention when the AVF blood flow is less than 400 to 500 mL/min.

As shown in table 4, KDOQI guidelines recommend that it is acceptable to use recirculation (via a non-urea-based dilutional method) or static pressures (either direct or derived) for surveillance of fistulas.

Recirculation occurs when the HD blood flow is higher than the intra-access blood flow. Given the fact that on average the HD blood flow is 400 ml/min, recirculation signals an intra-access blood flow lower than 400 mL/min and hence an indication for intervention.

Not all the stenoses detected on angiogram need to be treated. An unnecessary angioplasty may cause endothelial damage and accelerate the course of stenosis. Also, we have to keep in mind that vascular access angioplasty, although safe, has risks such as venous rupture and hematoma. Table 5 summarizes the indications to refer the patient for intervention.

Table 4. Surveillance techniques for AVF

<table>
<thead>
<tr>
<th>Technique</th>
</tr>
</thead>
<tbody>
<tr>
<td>Techniques, not mutually exclusive, that may be used in surveillance for stenosis in AVFs include:</td>
</tr>
<tr>
<td>Preferred:</td>
</tr>
<tr>
<td>1. Direct flow measurements.</td>
</tr>
<tr>
<td>2. Physical findings suggestive of stenosis: persistent swelling of the arm, presence of collateral veins, prolonged bleeding after needle withdrawal, or altered characteristics of pulse or thrill in the outflow vein.</td>
</tr>
<tr>
<td>3. Duplex ultrasound.</td>
</tr>
<tr>
<td>Acceptable:</td>
</tr>
<tr>
<td>1. Recirculation using a non–urea-based dilutional method.</td>
</tr>
<tr>
<td>2. Static pressures, direct or derived.</td>
</tr>
</tbody>
</table>
Table 5. Indications for intervention. NKF KDOQI guidelines 2006 updates clinical practice guidelines for vascular access. Guideline 4. [2]

<table>
<thead>
<tr>
<th>When to refer for evaluation (diagnosis) and treatment:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. One should not respond to a single isolated abnormal value. With all techniques, prospective trend analysis of the test parameter has greater power to detect dysfunction than isolated values alone.</td>
</tr>
<tr>
<td>2. Persistent abnormalities in any of the monitoring or surveillance parameters should prompt referral for access imaging.</td>
</tr>
<tr>
<td>3. An access flow rate less than 600 mL/min in grafts and less than 400 to 500 mL/min in fistulae.</td>
</tr>
<tr>
<td>4. A venous segment static pressure (mean pressures) ratio greater than 0.5 in grafts or fistulae.</td>
</tr>
<tr>
<td>5. An arterial segment static pressure ratio greater than 0.75 in grafts.</td>
</tr>
</tbody>
</table>

Effects of AVF Surveillance

There are conflicting results regarding the effectiveness of AVF surveillance. The majority of studies are retrospective, observational and compare AVF outcomes prior to, and after initiation of surveillance [15-18]. There is a general agreement that the introduction of surveillance is associated with an increased number of angioplasties, decreased hospitalizations, decreased missed treatments, and decreased use of HD catheters. There is conflicting data as to whether surveillance and early intervention decrease thrombosis rates or extend the functional life of the AVF. Three studies, [16, 18, 19] one of them prospective, randomized [19] found that surveillance decreases the thrombosis rate and one [17] found no effect of surveillance in decreasing the thrombosis rate.

A prospective randomized study [20] compared clinical monitoring versus clinical monitoring and monthly access blood flow measurement and found that adding surveillance resulted in a non-significant doubling in the detection of angiographically significant AVF stenosis. The study was underpowered to assess the thrombosis rates. The threshold blood flow that prompted intervention was 500 mL/min.

Tessitore et al. [21], presented a 5-year controlled cohort study comparing clinical monitoring to clinical monitoring and blood flow measurement in 159 HD patients with AVFs, 97 followed by clinical monitoring and 62 by adding blood flow surveillance to monitoring. Indications for imaging and stenosis repair were clinically evident access dysfunction in both groups and blood flow < 750 ml/min or a decrease in blood flow of >20%.

This study showed that, in mature AVF, adding blood flow surveillance to monitoring is associated with an increase in access imaging, a better detection and elective treatment of stenoses, reduction in thromboses rates and central venous catheter placements and lower access related costs. The cumulative access patency was only extended in the first 3 years after fistula maturation. In this study, the threshold for intervention was a blood flow < 750mL/min, much higher than other studies, which may explain the more positive effect of surveillance in this study.
In a meta-analysis by Tonelli et al. [22], that included 4 prospective randomized AVF trials (360 patients), access blood flow or ultrasound-based screening decreased the access thrombosis rate, but did not reduce the risk of access loss or costs.

There is insufficient evidence to support the use of surveillance and preemptive repair of stenosis to prolong the functional life of AVFs.

**Summary of AVF Monitoring and Surveillance**

1. Stenosis is the cause of the large majority of fistula thromboses.
2. The published literature suggests that AVF surveillance is associated with decreased thrombosis rates, increase in access imaging, a better detection and elective treatment of stenosis and reduction in central venous catheter placements.
3. There is insufficient evidence to support that surveillance increases AVF survival or decreases costs.
4. The Centers for Medicare and Medicaid Services (CMS) require that the dialysis facilities must have an ongoing program of hemodialysis vascular access surveillance for AVF and AVG.

**Graft Surveillance**

Similar to AVFs, the majority of thromboses in AVGs are caused by the presence of stenosis, and thus, surveillance in AVGs relies upon the detection of decreased access blood flow and/or increased intra-graft pressures as a consequence of progression of graft stenoses.

As shown before, Carlos Leon et al. [6] found that physical examination is instrumental in detecting clinically significant stenoses in AVGs. Similar results were found by Robbin et al. [23]. The physical examination is free, devoid of side effects, does not require additional equipment or personnel. However, physical examination, although easy to learn is not mastered by the HD personnel and clinical monitoring alone was associated with poor ability to detect significant stenoses [24, 25]. In consequence, we have to rely on surveillance to detect AVG abnormalities. AVG surveillance techniques and indications for referral are similar with those for AVF and are outlined in tables 2, 3 and 5. The AVG surveillance methods recommended by KDOQI guidelines are presented in table 6.

**Does Surveillance Decrease the Rate of Graft Thrombosis?**

AVG surveillance methods are effective in predicting clinically significant stenoses [24]. However, detecting and electively treating stenoses is not associated with decreased thrombosis rates or improved graft survival. Fewer than half of grafts with a greater than 50% stenosis will thrombose. Currently we don't have a surveillance test which is able to differentiate stenosed grafts that will thrombose (and might benefit from angioplasty) from stenosed grafts that won't thrombose (and will not benefit from angioplasty). For this reason, AVG surveillance results in numerous unnecessary angioplasties. As shown by Chang et al. [26], vascular injury caused by unnecessary angioplasties may stimulate neointimal hyperplasia and accelerate restenosis.

Retrospective, observational studies report decreased graft thrombosis rates after introducing surveillance techniques [27, 28]. However, all randomized controlled clinical trials comparing the impact of graft surveillance (duplex ultrasound and access flow measurement) to clinical monitoring found that surveillance, although it successfully detects
clinically significant stenoses, does not decrease thrombosis rates and does not increase graft longevity [24, 29-31]. A meta-analysis of prospective, randomized studies evaluating graft surveillance showed no decrease in thrombosis risk or access loss [22].

**Table 6. Surveillance of grafts**

<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Techniques, not mutually exclusive, that may be used in surveillance for stenosis in grafts include:</td>
</tr>
<tr>
<td>Preferred:</td>
</tr>
<tr>
<td>1. Intra-access flow by using one of the accepted methods (outlined in table 3) using sequential measurements with trend analysis.</td>
</tr>
<tr>
<td>2. Directly measured or derived static venous dialysis pressure.</td>
</tr>
<tr>
<td>3. Duplex ultrasound.</td>
</tr>
<tr>
<td>Acceptable:</td>
</tr>
<tr>
<td>Physical findings of persistent swelling of the arm, presence of collateral veins, prolonged bleeding after needle withdrawal, or altered characteristics of pulse or thrill in a graft.</td>
</tr>
<tr>
<td>Unacceptable:</td>
</tr>
<tr>
<td>Unstandardized dynamic venous pressures (DVPs) should not be used.</td>
</tr>
</tbody>
</table>

Why surveillance does not benefit patients with grafts despite effectively detecting stenosis is unclear. Possible reasons for this fact might be: restenosis after angioplasty develops rapidly, the decrease in access blood flow caused by the stenosis is very rapid, benefits of surveillance may be limited only to grafts that are less than 3 months old [32].

**Summary for AVG Monitoring and Surveillance**

1. The large majority of thrombosed grafts have stenotic lesions.
2. Clinically significant stenoses can be effectively diagnosed by physical examination (monitoring) and surveillance techniques.
3. Despite being able to diagnose stenoses, randomized clinical trials have shown that surveillance does not decrease the rate of thrombosis or prolong the survival of AVG.
4. The Centers for Medicare and Medicaid Services (CMS) require that dialysis facilities must now have an ongoing program of hemodialysis vascular access surveillance for AVF and AVG.

**Patient as His Own Vascular Access Monitor**

Patient education regarding monitoring and caring for their own vascular access is recommended by the KDOQI guidelines. There is no randomized trial to demonstrate its benefits but the advantages of patient education seem obvious and there are no foreseeable disadvantages.

Table 7 summarizes the KDOQI recommendations [2] for patient education regarding vascular access care. They apply for AVF as well as for AVG.
Table 7. Vascular access care - Patient education [2]

<table>
<thead>
<tr>
<th>All patients should be taught how to:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Compress a bleeding access.</td>
</tr>
<tr>
<td>2. Wash skin over access with soap and water daily and before HD.</td>
</tr>
<tr>
<td>3. Recognize signs and symptoms of infection.</td>
</tr>
<tr>
<td>4. Select proper methods for exercising fistula arm with some resistance to venous flow.</td>
</tr>
<tr>
<td>5. Palpate for thrill/pulse daily and after any episode of hypotension, dizziness or lightheadedness.</td>
</tr>
<tr>
<td>6. Listen for bruit with the ear opposite access if they cannot palpate for any reason.</td>
</tr>
<tr>
<td>All patients should know to:</td>
</tr>
<tr>
<td>1. Avoid carrying heavy items draped over the access arm or wearing occlusive clothing.</td>
</tr>
<tr>
<td>2. Avoid sleeping on the access arm.</td>
</tr>
<tr>
<td>3. Insist that staff rotate cannulation sites each treatment.</td>
</tr>
<tr>
<td>4. Ensure that staff is using proper techniques in preparing skin prior to cannulation and wearing masks for all access connections.</td>
</tr>
<tr>
<td>5. Report any sign and symptoms of infection or absence of bruit/thrill to dialysis personnel immediately.</td>
</tr>
</tbody>
</table>

**Summary**

Care of hemodialysis vascular access should be a team effort which includes the patient, nurses, technicians, mid-level providers and physicians. Monitoring and/or surveillance can accurately detect access stenoses and is recommended by KDOQI and is a current requirement of CMS. Despite the fact that monitoring and surveillance can detect access stenoses, it is not clear what to do with these results. In AVG, preemptive intervention does not decrease thrombosis rates or prolong graft survival. In AVF, the results of studies using preemptive intervention based on monitoring and surveillance are less clear, however, these studies have not demonstrated increased AVF functional survival or decrease in costs. Because of this, the results of monitoring and surveillance should be interpreted carefully and combined with other clinical factors before making the referral for access intervention.

**References**


The Role of Physical Examination of HD Access for the General Nephrologist

Loay Salman*
Interventional Nephrology Division of Nephrology
University of Miami Miller School of Medicine,
Miami, FL, US

Abstract

Physical examination is emerging as an important tool in the evaluation of an arteriovenous access. Multiple studies have demonstrated that physical examination can accurately detect and localize stenotic lesions in a great majority of patients with an arteriovenous access. Importantly, recent data have emphasized that nephrologists can be easily trained and successfully acquire this skill. Because of its accuracy, non-invasive nature and cost-effectiveness, this tool should be employed by the nephrology community more frequently than it is practiced currently. Emphasis on physical examination by nephrology training programs as well as community medical centers is urgently needed.

Introduction

Because of its success, ease of performance, prompt availability and cost- effectiveness, physical examination is emerging as an important element in the detection of arteriovenous access stenosis. While physical examination can easily diagnose problems such as pseudoaneurysms and access infection, it is vascular access dysfunction where physical examination can be very helpful. Indeed, dialysis access stenosis is the most common cause of access dysfunction. A variety of means, including access flow determination using ultrasound dilution technique and calculation of static and dynamic venous pressures, have

* Loay Salman M. D: Assistant Professor of Medicine, Interventional Nephrology Division of Nephrology, University of Miami Miller School of Medicine, 1120 NW 14th Street, CRB (360), Miami, FL 33136.
been used in the detection of vascular access stenosis. Nevertheless, these interventions are
time-consuming, require frequent calibration of the machines and have an associated cost.
Recent information has emphasized that physical examination can be very accurate in the
evaluation of functional and anatomic location of stenoses within an arteriovenous access [1-12].

In general, the pulse and the thrill found in the arteriovenous access form the backbone of
the physical examination (Table 1). A simple description of various components of an
arteriovenous access is presented in Figure 1.

The common elements used to conduct physical examination of an arteriovenous access
have been described by Beathard [1, 2]. A brief description of the physical examination is
presented below.

**Inspection**

Inspection of the arteriovenous access should not be limited to the site of the access but
expand to include the remaining part of arm, shoulder, breast, neck, and face. Presence of
swelling in any of these areas should be recorded and raise the suspicion of a downstream
stenosis.

The presence of collateral veins should also indicate downstream stenosis. Any scars on
the chest wall should be carefully examined for the previous catheter insertion sites. The
presence of face, neck breast swelling usually represents the presence of a central venous
stenosis.

**Table 1. Various element of physical examination as they relate to different
scenarios are presented**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal</th>
<th>Inflow Stenosis</th>
<th>Outflow Stenosis</th>
<th>Co-existing Inflow and Outflow Stenosis</th>
<th>Central Stenosis</th>
<th>Clotted Access</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pulse</strong></td>
<td>Soft, easily compressible</td>
<td>Feeble pulse (hypopulsation)</td>
<td>Hyperpulsation (water-hammer pulse, angry pulse)</td>
<td>Soft, easily compressible pulse</td>
<td>Variable</td>
<td>Absent pulse</td>
</tr>
<tr>
<td><strong>Thrill</strong></td>
<td>Continuous</td>
<td>Discontinuous (in severe inflow stenosis the thrill can be absent)</td>
<td>Discontinuous (in severe outflow stenosis the thrill can be absent)</td>
<td>Discontinuous (usually absent)</td>
<td>Variable</td>
<td>Absent thrill</td>
</tr>
<tr>
<td><strong>Augmentation Test</strong></td>
<td>Normal</td>
<td>Poor augmentation</td>
<td>Good augmentation</td>
<td>Poor augmentation</td>
<td>Good augmentation</td>
<td></td>
</tr>
<tr>
<td><strong>Arm Elevation Test</strong></td>
<td>Normal collapse</td>
<td>Normal collapse</td>
<td>No collapse</td>
<td>No collapse</td>
<td>No collapse</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical Features</strong></td>
<td>No prolonged bleeding or difficulty in cannulation</td>
<td>Difficulty in cannulation and an increase in negative arterial pressure</td>
<td>Prolonged bleeding and high venous pressure</td>
<td>Edema of the arm and shoulder; breast, supraclavicular, neck and face swelling</td>
<td>Sometimes clots aspiration from the access</td>
<td></td>
</tr>
<tr>
<td><strong>Access Flow</strong></td>
<td>Normal</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Variable</td>
<td>Absent</td>
</tr>
</tbody>
</table>
The Role of Physical Examination of HD Access for the General Nephrologist

Figure 1. Various components of an arteriovenous access circuit (fistula) are shown. Note the inflow that brings flow to the fistula, the body (cannulation zone), the outflow vein and the central venous system that takes blood back to the heart. The direction of the flow is represented by arrows. Double arrow shows the presence of a tight stenosis. In this patient, the arm elevation test would be abnormal as the access would not collapse due to the presence of an outflow stenosis. Incidentally, this access would also be hyperpulsatile as there is no inflow stenosis. Usually such patients report of prolonged bleeding after dialysis. This patient would most likely demonstrate a systolic thrill (bruit) in the cephalic arch region.

**Palpation**

Palpation is the single most important element in the assessing the presence of dysfunction in an arteriovenous access system. One could easily evaluate pulse and thrill on palpation. Palpation allows one to analyze pulse of an arteriovenous access. Normally, an arteriovenous access demonstrates a soft pulse that is easily compressed by the application of gentle pressure. In the presence of a downstream stenosis (outflow stenosis) the pulse becomes augmented (hyperpulsatile, water-hammer pulse). Often, a water-hammer pulse can be seen as strong pulsation on inspection. The clinical history that goes with this scenario is frequently the presence of prolonged bleeding reported by the dialysis staff or the patient. In contrast to the water-hammer pulse, a feeble pulse (flat access, hypopulsation) indicates an upstream stenosis. The clinical history that goes with a feeble pulse often includes inability to aspirate blood from the arterial needle (needle pulling negative pressure). Another element of the physical examination that is determined by palpation is the evaluation of the thrill. It is actually a “buzz” that is present in the arteriovenous access and felt by the examining fingers. In simple terms, the thrill can be continuous or discontinuous. Normally, there is more of a continuous nature to the thrill except for at the arterial anastomosis where it is usually discontinuous (normal to have a discontinuous thrill at the anastomosis). The thrill should be examined from the anastomosis all the way to the chest wall (many a times cephalic arch stenosis gives a discontinuous thrill at the cephalic arch area). In the presence of a stenosis the thrill becomes discontinuous. Depending upon the degree of stenosis, the access is usually
hyperpulsatile upstream from the stenosis and hypopulsatile downstream from the stenosis. Frequently, there is a systolic thrill immediately downstream from the stenosis. The access is usually plump upstream from the stenosis and flat downstream from the stenosis.

**Auscultation**

Auscultation can be performed to assess the bruit in the arteriovenous access. Just as in palpation it allows for the detection of stenosis by presence of continuous or discontinuous bruit.

**Pulse Augmentation and Arm Elevation Tests**

There are two additional tests that can be used to quickly examine the access system. These two tests often form the basis of what has been referred to a “10-seconds fistula examination” by Beathard.

The pulse augmentation test evaluates the inflow segment while the arm elevation test assesses the outflow tract. Pulse augmentation is performed by a complete occlusion of the access several centimeters beyond the arterial anastomosis and evaluation of the strength of the pulse. The test was considered normal when the portion of fistula upstream from the occluding finger demonstrated augmentation of pulse [1, 2, 5].

It is important to mention that the presence of the side branches can also be detected on physical examination during the augmentation test. Upon occlusion of the outflow of an arteriovenous access by the examining finger two things should normally occur. 1) The thrill should disappear. 2) The part of the access upstream from the occluding finger should become hyperpulsatile (augment). If the thrill persists after the occlusion of the access the presence of an accessory outflow pathway is detected. In this case, the access would not augment as the anticipated increase in pressure is dissipated by the presence of the accessory pathway.

One could also pinpoint the location of the side branch by moving the occluding finger toward the anastomosis of the fistula. When the thrill disappears and the access augments the examiners has just passed the site of the side branch. Moving the finger away from the anastomosis would bring the thrill back. This maneuver confirms the location of the side branch.

Arm elevation test is performed by elevation of the extremity with the fistula and examination of the normal collapse of the access [1, 2, 5]. The test is considered abnormal when the fistula remains plump after arm elevation and fails to collapse. It is important to mention that a near totally collapse of the access upon arm elevation may also indicate a normal access.
Does Physical Examination Accurately Assess Access Dysfunction?

While the elements of physical examination mentioned above are logical, concerns regarding their validity in the anatomical assessment and functional evaluation of an arteriovenous access are raised.

Comparison of Physical Examination to Angiography

Multiple reports have evaluated the role of physical examination in the detection of stenosis when compared with the gold standard (angiography) [3-6]. In a recent study, Asif et al. [5] applied Kappa Statistics to ascertain the agreement between the physical examination and angiography. Briefly, kappa value is calculated by dividing the observed agreement beyond chance by the maximum agreement beyond chance. Kappa values range from 0.0 to 1.0. Zero indicates no agreement beyond chance, whereas 1.0 denotes a perfect agreement. Values between 0.0 to 0.2 and 0.2 to 0.4 confer a slight and fair agreement, respectively. Kappa values between 0.4 and 0.6 denote a moderate agreement. Finally, kappa values >0.6 denote a substantial agreement beyond chance [5].

Physical examination in the diagnosis of outflow stenosis demonstrated excellent sensitivity and specificity (92 and 86%, respectively) with an outstanding agreement provided by the kappa value of 0.78 [5]. Such high sensitivity makes the physical examination a valuable tool to screen for the presence or absence of outflow stenosis.

The diagnostic elements of the physical examination used in the assessment of inflow stenosis included the presence of a weak pulse (hypopulsation, flat access), lack of a continuous thrill, and abnormal augmentation test. The physical examination in the assessment of inflow stenosis had good sensitivity (85%) and moderate specificity (71%) [5]. The agreement demonstrated by the kappa value of 0.55 between the physical examination and the angiographic images for the inflow stenosis was somewhat less than that for the outflow stenosis. The cause of this discrepancy was unclear. Perhaps grading of how well an access augments upon occlusion into various categories will detect more stenoses on physical examination. For example, an access with a 50% inflow stenosis will still augment but not as robustly as an access with no inflow stenosis. It is conceivable that some of such cases were missed on our physical examination because we categorized the test into those who augmented (even if it was a slight augmentation) and those who did not. Despite this, the kappa value of 0.55 showed strong agreement beyond chance between the physical examination and angiography.

The frequency of coexisting lesions in this study was consistent with previously published information [13]. Physical examination to detect a coexisting lesion presented an interesting scenario. Here, both an abnormal augmentation and arm elevation tests assisted in establishing the diagnosis of coexisting lesions. A previous study found strong agreement beyond chance (kappa value=0.54) regarding the diagnosis of coexisting inflow-outflow lesions between the physical examination and angiography [5].

Clinical features that contribute to the diagnosis of central stenosis include edema of the arm and shoulder; breast, supraclavicular, neck, and face swelling; and abnormal arm
elevation test [1, 2, 5]. In a recent study, the physical examination presented excellent specificity of 99%, making it a good test to rule out the disease; however, its sensitivity was poor, rendering physical examination not useful as a screening tool. Intuitively, one would imagine that by virtue of its clinical features, the diagnosis of central stenosis would be easy to establish by physical examination. Why, then, did the study demonstrate poor agreement (kappa value = 0.17) between the physical examination and angiography in the diagnosis of central venous stenosis? This might be explained by the fact that a great majority (59%) of patients in that study with central stenosis had a coexisting outflow lesion [5]. In this context, the presence of an outflow lesion could prevent downstream flow to the degree that the symptoms of central venous stenosis might be masked. The examination of the lesions in the body of the AVF has good specificity (84%) in the context of low prevalence (10%) [5].

Functional Assessment of the Access System by Physical Examination

Data have not only documented physical examination’s utility in detecting stenoses but also assessed functional status of the vascular access [7-10]. A recent study, Trerotola et al. [7] found physical examination to be an excellent predictor of the outcomes of hemodialysis access interventions. One hundred and seventeen access interventions were reviewed. Physical examination was performed to establish thrill, thrill with slight pulsatility, pulse with slight thrill, and pulse at three locations along the graft (proximal, mid-portion, and distal). Thrill at distal physical examination was predictive of outcome (p=0.04) and even more so when thrill and thrill with slight pulse combined were compared with pulse with slight thrill and pulse combined (p=0.03). Similar but less-pronounced effects were seen at mid-portion and proximal physical examinations. Of interest, normalized pressure ratios (intra-graft venous limb pressure/intra-graft systemic pressure without outflow occlusion and intra-graft venous limb pressure/cuff systemic pressure) were found to be weak predictors of access interventions (p=0.07 and p=0.08, respectively). The study demonstrated that the presence of a thrill or slightly pulsatile thrill at the distal (venous) end of a dialysis graft is the best predictor of outcome after percutaneous intervention. The authors concluded that physical examination should supersede normalized pressure ratios as an endpoint of interventions. In this context, physical examination serves as an essential component of quality assurance of access interventions. In another study [8], physical examination was compared to ultrasound with volume flow measurements. The results of the study demonstrated that physical examination could reliably rule out the low flows. Agarwal and McDougal also evaluated the value of physical signs in predicting flow rates and graft survival [9]. These investigators found that thrill along the venous limb was the single best test. Average flow rates for no thrill, presence of thrill (but distal to the mid- arm) and axillary buzz were approximately 500, 750, and 1,000 mL/min, respectively. The authors concluded that physical examination was a useful test to predict graft flow and its failure. Recently, in an elegant study, Campos et al. [10] revealed the superiority of physical examination over intra-access pressure determination in the diagnosis of access stenosis. The above-cited studies demonstrate the importance of physical examination and help establish its validity in the diagnosis of vascular access dysfunction.

In conclusion, physical examination is an important tool that can be employed to detect vascular access dysfunction. Recent information has provided evidence that this skill can be
easily taught [14, 15]. It is suggested that this test should be used as common practice by all nephrologists.

References


Chapter X

Options for Patients with Hand Pain and Nerve Injuries Related to Dialysis Access

Arif Asif
University of Miami Miller School of Medicine,
Miami, FL, US

Abstract

Dialysis access-associated hand pain and nerve injury are serious conditions in hemodialysis patients. Both have the potential of causing significant pain and discomfort as well as loss of optimal hand function. Although stealing of blood away from the high-resistance forearm arteries into the low-resistance arteriovenous access is generally assumed to be the cause, recent information has emphasized that arterial stenoses and vascular calcification also make a significant contribution. Nerve injury can follow soon after the creation of an arteriovenous fistula. The so called “ischemic monomelic neuropathy” can have devastating consequences for the patient. Treatment of hand ischemia should start with a detailed history and physical examination to help rule out other (non-ischemic) causes of hand pain. While a complete arteriogram to evaluate the circulation of the extremity from the aortic arch to the palmar arch is essential for the evaluation of patients with hand ischemia, history and clinical settings are the most important elements in establishing a timely diagnosis of ischemic monomelic neuropathy. The choice of treatment modality and procedure to apply should be based upon this evaluation. This chapter presents the strategies to combat hand ischemia and ischemic monomelic neuropathy.

* Arif Asif M.D: Director, Interventional Nephrology Professor of Medicine, University of Miami Miller School of Medicine, 1120 NW 14th Street (CRB Suite 360), Miami, FL 33136, E-mail: Aasif@med.miami.edu, Phone 305-243-3583.
Introduction

Whereas shunting of blood to a low resistance area (arteriovenous access) can result in hand ischemia, increased resistance to blood flow offered by the presence of arterial stenosis and vascular calcification can also play a critical role in the pathogenesis of peripheral hypoperfusion [1]. In contrast, the exact mechanism of nerve injury (ischemic monomelic neuropathy) sustained after the creation of an arteriovenous access is not entirely known [1]. The following sections would address hand ischemia and nerve injury as two separate entities and discuss the current strategies to combat the two situations.

Hand Ischemia

There are at least three mechanisms that can cause hand ischemia. A) High blood flow volume through an arteriovenous anastomosis may cause stealing of blood from forearm arteries. This steal can produce peripheral ischemia (“true steal”). It is important to note, however, that in a great majority of forearm as well as proximal arteriovenous accesses clinically silent retrograde flow can be seen [1]. In this context, demonstration of retrograde flow alone does not predict nor indicate the existence of hand ischemia. B) Distal arteriopathy due to vascular calcification and diabetes is an important factor that may also contribute to the development of symptoms of hand ischemia [1]. Vascular calcification affects both intimal and media layers. Disturbance in mineral metabolism in the uremic milieu, calcium-containing phosphate binders and vitamin D treatment of secondary hyperparathyroidism, increased oxidized low-density lipoprotein cholesterol, increased oxidative stress and hyperhomocysteinemia may contribute to the pathogenesis. C) Arterial occlusive disease is a major mechanism that can cause hand ischemia.

Out of the three mechanisms it seems that arterial stenoses play a major role in the pathogenesis of hand ischemia in hemodialysis (HD) patients with an arteriovenous access. Recent data have emphasized that significant (≥50%) arterial stenoses are commonly seen in dialysis patients presenting with symptoms of hand ischemia or vascular access dysfunction [2-8]. These lesions can occur anywhere within the arteries of the upper extremities including the proximal arteries and have been demonstrated to cause peripheral ischemia in hemodialysis patients [2-4]. Using arteriography, the incidence of arterial stenosis in patients with peripheral ischemia has been reported to occur in a significant number of patients. In one study [2], complete arteriography from the aortic to the palmar arch was performed to assess the presence of arterial stenosis in HD patients presenting with symptoms of peripheral ischemia (n=13). It was found that 62% of the 13 patients referred for the evaluation of symptoms of hand ischemia syndrome demonstrated a significant (≥50%) arterial stenosis. In another report of patients with hand ischemia [4], stenosis in the inflow circulation was found in over 80% of the patients who underwent complete arteriography (n=12).

At a conceptual level the goal for managing hand ischemia must focus on augmenting blood flow distal to the access to relieve ischemia while preserving the lifeline of the patient. A variety of percutaneous interventions including percutaneous balloon angioplasty, intravascular coil insertion and endovascular stent placement are available to achieve this goal. Use of one or a combination of these interventions has made access ligation the
The presence of an arterial stenosis can have a significant effect on the surgical procedure performed to correct distal ischemia. Recognition of these stenoses before planning a surgical procedure is very important. For example, in the presence of a significant arterial stenosis proximal to the anastomosis, a banding procedure applied to correct arterial steal can result in a critical decline in access blood flow culminating in access thrombosis.

Many reports have focused on the use of surgical interventions including banding/plication, tapered graft insertion, distal revascularization-interval ligation (DRIL) and revision using distal inflow procedure to correct steal resulting in distal ischemia [9-15]. However, a minimally invasive percutaneous technique designed to limit excessive flow (true steal) through the anastomosis causing distal ischemia has been reported recently [16]. This technique is based upon the application of a ligature around an inflated angioplasty balloon to create a stenosis of a defined size. According to this technique, the body of the access is punctured and entered in a retrograde direction. A complete arteriography (with and without occlusion) to ascertain the presence of stenosis or aberrant anatomy is performed. Under local anesthesia, a small (1-2 cm) incision is made over the access some 2-3 cm from the arterial anastomosis. At this point, blunt dissection is performed so that that a ligature (nylon, prolene) can be passed around the access. An angioplasty balloon is then positioned at the inflow. The size of the balloon is based on the size of the artery just distal to the arterial anastomosis (4-5 mm balloon for elbow fistulae), the goal is to create a significant stenosis once the ligature has been applied. The balloon is then inflated in the juxta-anastomotic region and a ligature is snugly applied on the external surface of the access to create a stenotic lesion. The balloon is deflated and the symptoms are assessed. In the absence of resolution of symptoms another ligature juxtaposed to the first one to create a segment of high resistance can be applied. All 16 patients treated in this manner demonstrated immediate symptomatic and angiographic improvement of flow to the forearm post procedure. The study did not provide information regarding quantification of the reduction of access flow or augmentation of perfusion to the hand.
The advantages of the percutaneous approach include demonstration of arterial anatomy as well as clarification of the etiology of hand ischemia. Both angioplasty of an occlusive lesion and reduction of flow into the access can be performed using minimally invasive techniques. Other benefits include performance of the procedures on an outpatient basis, utilization of local anesthesia and reduced incidence of procedure related complications. It is important to note, however, that the outcome of these interventions depends strongly on the experience and persistence of the interventionalist. The advantage of the surgical approach is that surgical interventions can still be successful where endovascular approaches have failed. In summary, a team approach would only result in benefits for the patient.

Ischemic Monomelic Neuropathy (Nerve Injury)

Ischemic monomelic neuropathy (IMN) is a nerve injury sustained after the creation of an arteriovenous access. It is a complication of vascular access that is observed almost exclusively in diabetics particularly those with pre-existing neuropathy [16, 17]. This entity is characterized by the development of acute pain, weakness and paralysis of forearm and hand muscles often associated with sensory changes.

IMN occurs very early (minutes to hours) after the creation of an arteriovenous access. It is caused by ischemic infarction of the vasa nervosa. It is most commonly seen in cases of upper arm accesses [16, 17]. IMN can be diagnosed clinically based on an acute onset of pain following access creation with a history of diabetes and dominant neurologic symptoms and signs.

Table 1. Various features of arteriovenous access-associated hand ischemia and nerve injury are presented

<table>
<thead>
<tr>
<th>Predominant feature</th>
<th>Hand Ischemia</th>
<th>Nerve Injury</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cold hand with pain on or off dialysis</td>
<td>Weakness and paralysis of muscles with prominent sensory loss</td>
</tr>
<tr>
<td>Presentation</td>
<td>Acute and chronic</td>
<td>Acute</td>
</tr>
<tr>
<td>Access type</td>
<td>Common with upper arm but also seen with forearm accesses</td>
<td>Only with upper arm accesses</td>
</tr>
<tr>
<td>Tissue involved</td>
<td>Skin&gt;Muscle&gt;Nerve</td>
<td>Nerves</td>
</tr>
<tr>
<td>Etiology</td>
<td>Vascular insufficiency leading to distal hypoperfusion</td>
<td>Vascular insufficiency causing nerve damage</td>
</tr>
<tr>
<td>Radial Pulse</td>
<td>Usually diminished</td>
<td>Usually present</td>
</tr>
<tr>
<td>Diagnostic evaluation</td>
<td>Thorough history, physical examination and arteriography</td>
<td>History and the clinical features</td>
</tr>
<tr>
<td>More prevalent in</td>
<td>Diabetics, peripheral vascular disease, smokers</td>
<td>Diabetics, peripheral vascular disease</td>
</tr>
<tr>
<td>Management strategies</td>
<td>Percutaneous and surgical interventions</td>
<td>Access ligation</td>
</tr>
</tbody>
</table>
Typically, the hand is warm and the radial pulse variably present. Prompt ligation of the access and rehabilitation of the decrease in hand and upper extremity function have been the traditional approaches to combat this situation.

Diabetes mellitus can be associated with limb pain due to isolated nerve involvement [18]. However, this neuropathy is generally symmetrical. Carpal tunnel syndrome is due to entrapment of the median nerve. Diagnostic clues include pain in both hands as median nerve entrapment is bilateral in a large proportion of cases. Wasting of the lateral thenar muscles is often present at diagnosis, denoting advanced nerve compression [19-21]. An EMG showing reduction of motor conduction can help establish the diagnosis [20].

**Conclusion**

Hand ischemia and nerve injury can result in devastating consequences for the patient including loss of the access and hand function. Prompt diagnosis is needed to optimally manage both conditions. While multiple strategies are available today to combat hand ischemia, limited interventions exist for patients with nerve injury secondary to the creation of an arteriovenous access. At present, ligation of the arteriovenous access is often undertaken to manage ischemic monomelic neuropathy.

**References**


Chapter XI

Renal and Vascular Ultrasonography for General Nephrologists

Lauren F. Alexander,1* Heidi R. Umphrey,1 Carl A. Abts,1 Mark E. Lockhart1 and Michelle L. Robbin1#
1Department of Radiology, University of Alabama at Birmingham, Birmingham, AL, US

Introduction

Ultrasound is often the first screening test in the evaluation of acute and chronic renal disease because of its wide availability, lack of ionizing radiation, portability and relative lower cost. The use of color and spectral Doppler to evaluate renal vasculature and suspicious renal lesions adds helpful information without potential nephrogenic or systemic toxicity. This review is a brief summary of the utility of ultrasound for assessment of the normal and abnormal urinary system. Preoperative vessel evaluation prior to hemodialysis access creation, as well as evaluation of the normal and abnormal postoperative fistula and graft will also be addressed.

Normal Renal Sonography

The kidneys are located in the retroperitoneal space, surrounded by perinephric fat in Gerota’s fascia, and bounded by the anterior and posterior pararenal space. The right kidney
is slightly lower and smaller than the left due to the adjacent liver. Median normal renal size is 10.9 cm on the right and 11.2 cm on the left [1] with an accepted range of 9-12 cm. Usually a single renal artery and vein supply and drain each kidney, although there can be a variable number of renal arteries, either small accessory arteries supplying only a portion of the kidney, or two or more arteries contributing equally. The right renal vein drains directly into the IVC. The left renal vein passes anterior to the aorta to reach the IVC, but may be retroaortic or branch both anteriorly and posteriorly around the aorta, a circumaortic renal vein.

The renal parenchyma is composed of the outer cortex and inner medulla with smooth convex outer border of the cortex, although persistent fetal lobulations may be present. After six months of age, the outer cortex has echogenicity equal to or slightly hypoechoic to the liver. In patients with hepatic steatosis, the liver echogenicity is increased (figure 1), limiting evaluation of the renal echogenicity by comparison with the liver alone.

The echogenicity of the spleen can also be used for comparison, as the kidney should always be hypoechoic relative to spleen. The medullary pyramids are hypoechoic or isoechoic relative to the cortex.

The central kidney or hilum is composed of the collecting system, renal artery and renal vein branches, and a variable amount of adipose tissue. The nondilated collecting system is usually difficult to visualize at ultrasound, but is generally anechoic due to the presence of urine. Hilar vessels are also anechoic tubular structures on grayscale images. Vessels can be distinguished from the collecting system by demonstrating flow on color Doppler evaluation.

## Renal Pathology

Broad categories of renal abnormalities typically evaluated by sonography include medical renal disease, cystic and solid masses, calcifications, and hydronephrosis.

![Figure 1. Normal right kidney, delineated by calipers. The adjacent liver (black arrow) has markedly increased echogenicity compared with the right kidney, consistent with steatosis.](image-url)
Medical Renal Disease

Most pre-renal and renal causes of acute renal failure have no unique sonographic correlate; however, ultrasound is useful to assess for obstructive causes (see below). In early stages of chronic renal disease, the kidneys may appear normal or even mildly enlarged, as in early diabetic nephropathy. Renal enlargement is also seen with infiltrating processes that may result in eventual renal failure, such as amyloidosis and HIV nephropathy. In end stage renal disease, the kidneys are often small (less than 8-9 cm) with increased echogenicity and cortical thinning (figure 2) [2]

Renal echogenicity is a subjective descriptor. In general, 9 cm is often used as a lower limit of size, as kidneys smaller than 9 cm are often associated with irreversible disease [3]. However, kidney length correlates with body height [1], and a 9 cm kidney may be normal in a smaller individual, yet “too small” for a taller individual. Cortical thinning is nonspecific, with overall decreased renal volume as renal atrophy progresses; however, cortical thinning is more often seen in vascular disease than glomerular disease [4]. A size discrepancy greater than 2 cm between the kidneys is suggestive of unilateral disease, such as renal artery stenosis on the side of the smaller kidney or infiltrative process in the larger.

Cystic Renal Lesions

Cystic renal lesions range from incidental, benign cysts to malignant cystic neoplasms. Single or multiple simple cysts occur in approximately 50% of individuals over 50 years of age [5]. Simple cysts that need no further follow-up should be anechoic with an imperceptible or thin, smooth wall, with increased through transmission, or increased “brightness” posterior to the cyst (figure 3).

Figure 2. Small echogenic kidney (between calipers) as seen with end stage renal disease. The borders of the kidney are difficult to differentiate from the adjacent fat.
Figure 3. A simple cyst (between calipers) in the left kidney is anechoic with increased through transmission (arrows) posterior to the cyst.

No flow is present within the cyst or cyst wall at color Doppler evaluation. Cysts with thick walls, complex internal echoes, or significant wall calcification need follow-up (figure 4). If the complex cyst diameter is greater than approximately 1 – 1.5 cm, pre and post contrast evaluation with CT or MRI would be useful. Contrast enhanced ultrasound is an emerging tool for evaluation of complex cyst enhancement [6]. Any solid nodule within a cyst, particularly if there is flow within the nodule, is worrisome for malignancy. Clinical history is important; signs and symptoms of infection should suggest renal abscess in a complex renal lesion.

Autosomal dominant polycystic kidney disease (ADPKD) results from cyst formation and enlargement over time, resulting in progressive renal failure and hypertension in middle age. Ultrasound is useful for screening those at risk due to family history. In these patients, the development of multiple, bilateral cysts, particularly in people younger than 30 years old, with renal enlargement is usually diagnostic (table 1). In at-risk patients below age 30, the absence of cysts does not exclude the diagnosis [7].

Acquired renal cystic disease (ARCD) develops in patients with end stage renal disease on dialysis. The diagnosis should be considered when patients have more than three cysts per kidney or when cysts replace greater than 25% of the renal parenchyma [8]. The incidence of ARCD increases with time on dialysis, occurring in up to 90% of patients on dialysis for 5-10 years [9]. The residual renal parenchyma is often small and echogenic, blending with the perinephric fat (figure 5).

The large number, size variability, and complexity of the cysts often make it difficult to completely exclude a solid neoplasm, which is also a limitation in ADPKD. Risk of developing renal cell carcinoma is increased in ARCD, especially as the duration of dialysis increases [10]. If a cystic lesion with any of the suspicious features described above is identified, renal cell carcinoma should be considered. Other complications of ARCD include cyst hemorrhage, infection, and perinephric hematomas [11]. The sonographic features of hemorrhagic or infected cysts can overlap with those of cystic RCC. Often, additional assessment with CT or MRI is necessary.
Figure 4. Exophytic complex cyst with thickened septations (arrow) arising from the right kidney (a). No color Doppler flow is seen within the septation (b).

Figure 5. Acquired renal cystic disease. The renal parenchyma is echogenic, and there are numerous small cysts. The kidney borders are delineated by cursors.

Table 1. Criteria for sonographic diagnosis of autosomal dominant polycystic kidney disease (ADPKD) in at-risk patients [7]

<table>
<thead>
<tr>
<th>Age</th>
<th>Number of cysts for ADPKD diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 – 39</td>
<td>At least 3 cysts total (unilateral or bilateral)</td>
</tr>
<tr>
<td>40 – 59</td>
<td>At least 2 cysts in each kidney</td>
</tr>
<tr>
<td>≥ 60</td>
<td>At least 4 cysts in each kidney</td>
</tr>
</tbody>
</table>
Solid Renal Neoplasms

The most common primary renal neoplasm is renal cell carcinoma, with four histologic subtypes: clear cell, papillary, chromophobe, and collecting duct. Most RCCs are clear cell (70%) or papillary (10 – 15%) and occur sporadically; however, hereditary RCC can occur, such as in patients with Von Hippel-Lindau [12].

Solid RCC presents as an isoechoic or hypoechoic mass, often with some internal color Doppler flow (figure 6, 7). The absence of flow at ultrasound does not exclude neoplasm. A small RCC (less than 3 cm) may have increased echogenicity mimicking an angiomyolipoma, be too small to accurately assess for flow, or be poorly detected with ultrasound. Small exophytic masses are easier to detect with ultrasound than those that are not contour deforming. Approximately 15% of RCC are cystic [12]. When RCC is identified, careful evaluation of the contralateral kidney should be performed to assess for synchronous lesions, which can occur in approximately 5% of cases [13]. The renal vein should be inspected for thrombus, the liver assessed for metastases, and the retroperitoneum evaluated for lymphadenopathy. All solid lesions need further evaluation with CT or MR for more complete characterization. Complex cysts can occasionally mimic a solid mass if not well seen, and benign solid lesions are difficult to differentiate from RCC by ultrasound alone.

Angiomyolipoma (AML) is a benign renal hamartoma composed of mature adipose tissue, smooth muscle and blood vessels, often discovered incidentally. Most are sporadic: twenty percent of all AML are associated with tuberous sclerosis (TS), but 80% of patients with TS have at least one AML. Masses that measure at least 4 cm have an increased risk of spontaneous hemorrhage. At ultrasound, AMLs have increased echogenicity due to the intralesional adipose tissue, a diagnostic feature of large lesions [12]. Hyperechoic lesions with a hypoechoic rim or intralesional cysts are more worrisome for RCC [14]. Hyperechoic lesions should have an additional study with CT or MRI to confirm the presence of intralesional fat and to differentiate from RCC. Other benign renal lesions include oncocytoma, reninoma, and hemangiopericytoma. These lesions cannot be differentiated from RCC by ultrasound or other routine imaging methods and require biopsy or resection for definitive diagnosis [12].

Figure 6. Solid, hypoechoic mass in the lower left kidney with color Doppler flow (arrow), worrisome for renal cell carcinoma.
Renal and Vascular Ultrasonography for General Nephrologists

Renal Calcifications

Onset of renal stone disease is most common in men ages 20-40 years. Nonobstructing stones are often asymptomatic, but can be associated with flank pain and microscopic or gross hematuria [15]. At ultrasound, stones are usually seen as echogenic foci with posterior shadowing in the calices or renal pelvis (figure 8).

Obstructing stones generally cause flank pain. Stones most commonly obstruct at one of three areas of ureteral narrowing: 1) just past the ureteropelvic junction; 2) where the ureter crosses the iliac vessels; or 3) at the ureterovesicular junction [16].

Ultrasound can usually detect stones greater than 5 mm; however, smaller stones may be missed. Compared with noncontrast CT, ultrasound sensitivity for stones is as low as 24%. Up to 73% stones ≤ 3 mm and 57% stones > 3 mm seen on CT may be missed at ultrasound [17].

The use of “twinkle artifact” can be used to help confirm small stones. When color Doppler is applied to renal stones, a rapidly changing color complex appears below the stone in 80% of cases (figure 9) [18]. The twinkle artifact has a 78% positive predictive value for nephrolithiasis but a true positive rate of only 49% compared with noncontrast CT [19].

Nephrocalcinosis refers to calcification of the renal parenchyma, and may be cortical or medullary (table 2). Cortical calcification results in increased cortical echogenicity, producing acoustic shadowing. In medullary nephrocalcinosis, the renal pyramids are hyperechoic relative to the adjacent cortex (with or without shadowing), with eventual calcification and stone formation resulting in acoustic shadowing [20-21].
Lauren F. Alexander, Heidi R. Umphrey, Carl A. Abts et al.

128

Figure 8. A large shadowing stone (curved arrow) at the left renal pelvis with moderate dilatation of the renal pelvis (arrowhead).

![Figure 8](image)

Figure 9. (A) A small echogenic focus (white arrow) is present in the lower right kidney without shadowing. (B) Addition of color Doppler shows twinkle artifact (arrowhead), confirming a small calculus.

![Figure 9](image)

Table 2. Causes of neprocalcinosis [21]

<table>
<thead>
<tr>
<th>Cortical</th>
<th>Medullary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute cortical necrosis</td>
<td>Hyperparathyroidism</td>
</tr>
<tr>
<td>Chronic glomerulonephritis</td>
<td>Renal tubular acidosis (type 1)</td>
</tr>
<tr>
<td>Chronic hypercalcemic states</td>
<td>Medullary sponge kidney</td>
</tr>
<tr>
<td>Ethylene glycol poisoning</td>
<td>Papillary necrosis</td>
</tr>
<tr>
<td>Rejected renal transplant</td>
<td>Milk alkali syndrome</td>
</tr>
<tr>
<td>Oxalosis</td>
<td>Oxalosis</td>
</tr>
</tbody>
</table>
Hydronephrosis

Urinary obstruction results in dilation of the collecting system (hydronephrosis) and/or ureter (hydroureter), depending on the level of obstruction (figure 10). Hydronephrosis may not develop in the first few hours of obstruction. Collecting system dilatation is not specific for obstruction, as it can also be seen in vesicoureteral reflux or brisk diuresis [4]. Chronicity of obstruction can be inferred from cortical thickness, as the cortex can become markedly thinned in long-standing obstruction. The entire urinary tract should be evaluated to determine the point of obstruction, whether it is at the UPJ, along the ureter, or at the bladder. A large post-void residual with hydroureteronephrosis in male patients is usually due to bladder outlet obstruction from prostatic hypertrophy. In many cases, the ureters cannot be seen along their entire course and CT or MRI is necessary for further evaluation for cause of hydronephrosis.

Renal Vascular Imaging

Renal Doppler imaging is not routinely performed in the evaluation of acute or chronic renal failure; however, evaluation of the renal vessels is indicated in certain settings. Doppler evaluation of the renal arteries can be performed as an initial screening test in patients with uncontrolled hypertension. Evaluation of the renal veins can be performed if renal vein thrombosis is suspected. Ultrasound allows for the evaluation of the renal vessels without radiation, or potential systemic or nephrotoxicity from intravenous iodine or gadolinium contrast administration; sonography is particularly useful in patients with decreased renal function [22-23].

Figure 10. Moderate hydronephrosis (white arrow) and hydroureter (black arrow) due to an obstructing distal ureteral stone several centimeters cranial to the bladder with twinkle artifact (arrowhead).
Evaluation of the renal vessels can be challenging, due to their deep location and overlying bowel gas. Meticulous technique and intensive sonographer training is necessary to perform a quality examination. Patient fasting 6-8 hours prior to examination decreases bowel gas, critical to improve sonographic windows.

Normal renal arteries arise directly from the aorta approximately 1-2 cm caudal to the superior mesenteric artery and course laterally to the kidneys. One or more accessory renal arteries may be present in 20-30% of individuals [24-25]. The high incidence of accessory renal arteries and the difficulty seeing them at ultrasound should not stop sonographic evaluation for renal artery stenosis (RAS), as the incidence of clinically significant renal artery stenosis isolated in an accessory renal artery is less than 1% [26]. A normal renal artery spectral Doppler waveform should have rapid systolic upstroke with an early systolic peak. Flow gradually decreases over late systole and diastole, with persistent antegrade flow throughout the cardiac cycle (figure 11). Normal peak systolic velocity (PSV) varies but should be less than 200 cm/sec. The resistive index (RI) can be used to characterize the amount of diastolic flow and is calculated as (PSV – end diastolic velocity) / PSV. The range for RI in normal adult kidneys is usually 0.50 – 0.70 [27].

Although renal artery stenosis (RAS) accounts for only a small proportion of hypertensive patients, it is potentially curable. Screening for RAS is most common in young adults with hypertension or older patients with poorly controlled hypertension despite medication compliance. The most common cause of RAS is atherosclerosis, usually involving the renal artery ostium or proximal main renal artery [28]. Fibromuscular dysplasia is the second most common cause of renal vascular hypertension, occurring more commonly in young or middle age female patients, involving the mid to distal artery [29], and is more difficult to detect with ultrasound.

The two main methods for detecting RAS at Doppler ultrasound are direct visualization of the stenosis and indirect evaluation of the downstream effect of the stenosis on the intrarenal arterial branches.
Direct criteria for stenosis include a peak systolic velocity greater than 200 cm/sec, usually with turbulent flow and aliasing on color Doppler imaging (figure 12). An elevated ratio of renal artery PSV to abdominal aortic PSV of 3.5 : 1 or greater also suggests significant RAS [30-31]. When the renal artery cannot be seen in its entirety or at all, assessment of the intrarenal segmental artery waveforms allows for indirect detection of RAS. A normal intrarenal arterial waveform should have a brisk systolic upstroke with a small early systolic peak (figure 13). With RAS, this systolic acceleration time becomes prolonged (greater than 0.7 sec), and the early systolic peak is absent.

In some cases of RAS, the waveform becomes small with delayed systolic upstroke, known as the “tardus parvus” waveform (figure 14) [32]. Routine evaluation of both the main renal arteries and intrarenal waveforms likely yields the most sensitive screen for RAS.

Figure 12. Turbulent color Doppler flow in the main renal artery (MRA) with marked elevated peak systolic velocity of 3 m/sec.

Figure 13. Normal intrarenal artery waveform with brisk upstroke and early systolic peak (arrows).
Renal vein thrombosis is uncommon in adults but can be seen with dehydration, nephrotic syndrome, hypercoagulable states, trauma, or tumor thrombus from RCC. Acute thrombus presents as low level echoes within a dilated vein and may be occlusive or nonocclusive. Careful analysis of the waveform must be performed to avoid misdiagnosing arterial flow in tumor thrombus as a patent vein. While complete lack of venous flow confirms thrombus, identification of venous flow does not exclude nonocclusive thrombus if the entire vein cannot be visualized [33], as collateral flow develops quickly in the native kidney.

Renal Biopsy with Ultrasound

Image-guided renal biopsy can be performed to sample the renal cortex to assess for potentially reversible causes of disease, as results may alter management in up to 40% of cases of impaired renal function [34]. The use of image guidance with ultrasound or CT yields better tissue samples and results in fewer complications [35].

Prior to the procedure, the patient must be assessed for hypertension and bleeding risks. Pre-procedural laboratory values should include a platelet count > 50,000 and INR 1.5 or less. Anticoagulation should be held 1-5 days prior to procedure depending on mechanism of action [36]. Mild conscious sedation with midazolam hydrochloride and fentanyl is preferred at our institution with continuous vital sign monitoring by an interventional nurse. Some institutions perform biopsies with only local anesthesia with lidocaine.

Prone positioning is most useful for native kidney biopsy. After appropriate sterile preparation and lidocaine administration, a needle path is chosen, targeting a relatively less vascular portion of the kidney, often the lower pole. The hilum should be avoided to prevent
injury to large artery and venous branches or to the collecting system. Core biopsy is necessary to obtain adequate glomeruli for diagnosis, typically 8 – 12 glomeruli at a minimum. The type of biopsy device depends on user preference. Biopsy with larger gauge needles can limit the number of passes, although large gauge or multiple passes both have increased risks of hemorrhage. [37].

Complications of percutaneous renal biopsy include hemorrhage, pneumothorax, adjacent organ injury, and infection. Minimal perinephric hemorrhage can be expected. Larger hemorrhage requires close monitoring and overnight hospitalization in case blood transfusion or embolization is required. Pseudoaneurysms and arteriovenous fistulas (figure 15) are infrequently seen on post procedural ultrasound, but may be present at follow-up. Microscopic and gross hematuria may occur in a small percentage of cases. Persistent gross hematuria should raise concern for collecting system injury [37-38].

**Hemodialysis Access Evaluation**

Two types of permanent hemodialysis access can be placed, either an arteriovenous fistula (AVF) or a synthetic arteriovenous graft (graft). Mature AVFs are the preferred hemodialysis access when possible, because they are less often associated with thrombosis and infection [39-41].

Several studies have shown that preoperative sonographic evaluation of the upper extremity arteries and veins can increase the number of successful AVF creation by altering surgical planning [42-45]. Post-operative ultrasound may be beneficial in determining AVF maturation [46-47]; however, there is disagreement in the current literature on the role of close access monitoring in early detection and intervention to increase the longevity of an access [48-59].

Creation of an AVF is preferred when clinically feasible and anatomically possible. Access should be placed in the non-dominant arm allowing activities of daily living to be performed while the non-dominant arm heals; however, a dominant arm fistula is preferential to a non-dominant arm graft in most patients. Potential access sites in decreasing order of preference are listed in table 3.

The cephalic vein is preferred over a basilic vein transposition for fistula formation because the procedure involves less dissection and venous handling. Additional less common access configurations may also be utilized based on surgical experience [60-61].

**Table 3. Potential hemodialysis access sites in decreasing order of preference**

<table>
<thead>
<tr>
<th>Potential Access Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forearm AVF (radiocephalic AVF, or transposed forearm basilic vein to radial artery fistula)</td>
</tr>
<tr>
<td>Upper arm brachiocephalic AVF or transposed brachiobasilic AVF</td>
</tr>
<tr>
<td>Forearm loop graft</td>
</tr>
<tr>
<td>Upper arm straight graft (brachial artery to upper basilic vein)</td>
</tr>
<tr>
<td>Upper arm axillary artery to axillary vein loop graft</td>
</tr>
<tr>
<td>Thigh graft</td>
</tr>
</tbody>
</table>
Pre-Operative Evaluation for Hemodialysis Access

Sonographic evaluation of hemodialysis access planning and assessment has been previously reported with attention to technical details to optimize evaluation [47, 62-64]. The upper extremity arteries and veins are evaluated with the patient sitting upright, and veins are evaluated with a tourniquet in place [65]. The patient should be in the supine position for evaluation of the internal jugular and subclavian veins to optimally fill these vessels.

A high frequency transducer should be used; a linear array transducer 12-15 MHz or higher is preferred. Suggested preoperative criteria include a minimum intraluminal arterial diameter of 2.0 mm and a minimal intraluminal venous diameter of 2.5 mm for AVF [42, 47]. The criteria for graft creation include a minimum intraluminal venous diameter of 4.0 mm and a minimum arterial diameter threshold of 2.0 mm [42]. The lower third of the brachial and radial arteries are evaluated for intimal thickening, calcification, stenosis or occlusion, with measurement of the intraluminal diameter. Arterial calcification may be categorized, depending on surgeon preference. Arterial waveforms are inspected for normal triphasic or biphasic flow, and peak systolic velocity (PSV) is measured.

A high radial artery take-off from the brachial artery should be suspected when two arteries with paired veins are seen in the upper arm. The arteries should be followed into the forearm to distinguish this common anatomic variant from a prominent arterial branch supplying the elbow.

Vein assessment is performed with visual inspection and compression along the entire venous length. Cephalic vein internal diameters are measured in the forearm. Cephalic and basilic vein internal venous diameters are measured in the upper arm. The axillary vein, subclavian vein and internal jugular veins should be assessed for compression and/or normal waveforms.

Post-Operative Hemodialysis Access Evaluation

Review of pertinent patient history and operative notes as well as an initial ultrasound scan allow for adequate overview of the hemodialysis access. The caudal third of the feeding artery is assessed for stenosis and intraluminal diameter measurement in the transverse plane. Color and spectral Doppler are performed in the longitudinal plane with measurement of PSV and end diastolic velocity (EDV). The waveform is inspected for normal low resistance monophasic flow. For an AVF or a graft, the draining vein is inspected for wall thickening, stenosis, and thrombosis along its entire length. In a fistula, the intraluminal draining vein diameter and the distance from skin surface are measured at several points cranial to the AVF anastomosis. The draining vein is evaluated for accessory vein branches with size and distance from anastomosis recorded for each branch in the first 10 – 15 cm cranial to the anastomosis. Flow volume measurements are obtained within the graft or mid draining vein of an AVF in an area with parallel vessel walls, minimal vessel tortuosity and no stenosis (figure 16).

If the access is thrombosed, a longitudinal grayscale image is obtained to show intraluminal thrombus. Color and spectral Doppler images are obtained to verify the lack of flow. Power Doppler may be more sensitive for detection of residual slow flow. Any fluid
collections should be measured and inspected for echogenic foci or gas. Although air bubbles can be the result of a recent access stick, suspicion should be raised about the potential for infection. If there is clinical suspicion for arterial steal, the arterial flow to the hand should be evaluated downstream from the anastomosis. The artery downstream from the anastomosis will show flow reversal, which may be asymptomatic. The subclavian and internal jugular veins should be included in the sonographic evaluation in clinical scenarios such as arm swelling.

The brachiocephalic veins are indirectly assessed by Doppler imaging of the internal jugular and subclavian veins. Normal central veins show respiratory phasicity and/or transmitted cardiac pulsatility at spectral Doppler evaluation. Monophasic subclavian and internal jugular venous waveforms are suggestive of central venous stenosis or occlusion.

A normal AVF has antegrade flow throughout the arterial and venous limbs without visible narrowing or flow disturbance. Any areas of aliasing, visible narrowing or focal increased velocity are suggestive of stenosis, and are further described in the following section.

Figure 15. Post biopsy images show a small arteriovenous fistula (arrow) with high velocity, low resistance flow on color Doppler.

Figure 16. Spectral Doppler shows antegrade flow and satisfactory flow volume of 891 cc/min in the AVF draining vein.
Average volume flow in a functioning AVF is at least 300 to 800 ml/min [46, 54, 66-67]. When sonographic fistula measurements were correlated with clinically determined maturation, approximately 70% of AVFs were able to be used for hemodialysis with a minimum draining vein of ≥ 4 mm or a blood flow rate of ≥ 500 ml/min. [46]. If both criteria were present, the likelihood of fistula maturation was 95%, but only 33% of fistulas were adequate for hemodialysis if neither criterion were met. In contradistinction, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative published sonographic criteria suggestive of maturation: draining vein greater than 6 mm diameter, blood flow rate greater than 600 cc/min, and less than 6 mm skin depth [39].

A normal graft is seen as two echogenic lines which represent strong specular reflection from the polytetrafluoroethylene (PTFE) graft material. Flow within the graft should be antegrade with low resistance, arterialized flow. Any focal turbulence, visible narrowing, or focally elevated velocity suggests stenosis. Antegrade flow without focal turbulence or aliasing is seen in the draining vein of a normal graft. Since there is a larger volume of blood flow in grafts, the lack of phasicity in the central veins is less specific for central occlusion in patients with grafts than in patients with fistulas.

**Abnormalities of Hemodialysis Access**

Abnormalities of AVFs include stenosis, thrombosis/occlusion, pseudoaneurysm, peri-fistula fluid collections, and arterial steal. An AVF stenosis is characterized by visual narrowing as assessed on gray scale imaging and an increased ratio of the PSV at the stenosis as compared to the PSV measured 2 cm upstream from the stenosis. The criteria vary depending on the location of the stenosis. A stenosis in the juxta-anastomotic region is characterized by the following criteria: 1) location within 2 cm of the anastomosis, encompassing both the feeding artery and the draining vein [68-69]; 2) visible narrowing; and 3) a PSV ratio of greater than or equal to 3:1. A draining vein stenosis is characterized by visible narrowing and a PSV ratio of 2:1 (figure 17).

![Figure 17](image-url)

Figure 17. Stenosis of the draining vein with visual narrowing (a) and elevated peak systolic velocity of 529 cm/sec (b).
Arterial inflow stenoses are rare but can occur and are characterized by visible narrowing and a PSV ratio of 2:1. The most common locations for stenoses in an AVF are at the juxta-anastomotic region, followed by the draining vein, and then central veins [50]. Stenoses are clinically relevant since they can be associated with subsequent thrombosis. AVF thrombosis is diagnosed when no flow is identified within the AVF. Thrombus is usually visualized within the vessel lumen on gray scale imaging (figure 18). Slow flow can be identified with power Doppler.

Figure 18. a. Transverse (T) and longitudinal (L) images through a partially thrombosed draining vein. b. Flow volume measurement obtained cranial to the partial thrombosis in the draining vein shows very low flow.
When suboptimal compression is applied after cannulation, pseudoaneurysms may form. Color Doppler of a pseudoaneurysm shows a typical “yin/yang” flow pattern (figure 19). Fluid collections are commonly seen as avascular, hypoechoic lesions, and usually represent post access or post procedure hematomas (figure 20). Echogenic foci with shadowing within a fluid collection may represent gas, and infection should be considered in the appropriate clinical setting.

Graft abnormalities are similar to those listed above for AVF, and also include graft degeneration. Studies have shown that grafts with decreased blood flow are at increased risk for thrombosis [54, 70-72]. Three sonographic criteria characterize graft stenosis as follows: 1) visual luminal narrowing on gray scale imaging, 2) a high velocity jet on color Doppler, and 3) a PSV ratio greater than 2:1 for the venous anastomosis or draining vein or 3:1 for the arterial anastomosis. The most common site of graft stenosis is the venous anastomosis followed by draining vein, intragraft, arterial anastomosis, and central veins [46]. The graft is thrombosed when echogenic material is noted within the graft and no flow is identified within the graft; power Doppler can be utilized to exclude slow flow. The formation of pseudoaneurysms in grafts is relatively common and the “yin/yang” flow pattern is also seen with color Doppler.

Unique to grafts is degeneration of the synthetic material, which is seen at ultrasound as an irregular graft wall which may be associated with numerous pseudoaneurysms along the graft. Arterial steal is defined as flow reversal in the native artery caudal to the anastomosis and may or may not be symptomatic. Symptoms include hand pain and burning worsening during dialysis. Ischemia or tissue necrosis of the fingers can occur. Sonographic evaluation demonstrates reversal of flow in the distal artery and rarely shows an occluded artery. Brief manual compression of the graft will usually demonstrate a change in the reversed arterial flow, yielding an antegrade high resistance flow pattern toward the hand [73].

Figure 19. Pseudoaneurysm arising from the draining vein of an arteriovenous fistula with “yin-yang” color Doppler flow.
Summary

Ultrasound is an invaluable non-invasive method to assess the kidneys, ureters and bladder for morphology, stones, and obstruction, and medical renal disease. Renal artery stenosis and renal vein thrombosis can be detected using spectral and color Doppler techniques. Both gray scale and Duplex Doppler are useful in assessing extremity arteries and veins prior to hemodialysis access, as well as evaluation of graft and fistula function following creation.

References


Lauren F. Alexander, Heidi R. Umphrey, Carl A. Abts et al.


Role of Nurses and Technicians in Vascular Access Care

Donna Merrill
Interventional Nephrology
University of Miami Miller School of Medicine
Miami, FL, US

Abstract

Over 90% of the end stage renal disease patients receive long-term hemodialysis therapy. Consequently, vascular access that is used to provide dialysis therapy becomes an important element of the management of an end stage renal disease patient. Increasingly, nephrologists are managing vascular access care of renal patients. As a result, new opportunities have been created for nephrology nurses and technicians. It is a well-known fact that patients with end stage renal disease require interventions from the time they are diagnosed with chronic kidney disease and throughout their lives on renal replacement therapy. While physicians play a major role in the diagnosis and treatment of these patients, nurses and technicians are also playing an important role in this aspect of patient care. This chapter describes the role of nurses and technicians in the procedural aspect of renal patients.

Introduction

Since the existence of renal replacement therapy, nurses and renal technicians have played an important role and quickly developed nephrology nursing as a subspecialty to care for this challenging group of patients. Today there are many possibilities for exploration of new areas of practice for nephrology nurses and renal technicians. Nephrology nurses and

*Donna Merrill: Interventional Nephrology, University of Miami Miller School of Medicine, Miami, FL 33136.
technicians have become an integral part of both hemodialysis units and endovascular procedures.

As patients with chronic kidney disease (CKD) are identified, a variety of nephrology-related procedures may be needed. If a CKD patient progresses to end stage renal disease (ESRD), choices for renal replacement therapy (RRT) such as transplant, peritoneal dialysis (PD) or hemodialysis (HD) are offered. If the patient chooses hemodialysis detailed information regarding vascular access types must be provided to a patient initiating hemodialysis therapy.

A vascular access nurse/technician can be a great help in providing information regarding vascular access types. This individual can impart vascular access education to the hospitalized patients, those seen in the CKD clinic and those receiving long-term dialysis therapy in a hemodialysis unit. Two basic elements of this education include the advantages and disadvantages of different vascular access types (arteriovenous fistula [AVF], arteriovenous graft [AVG] and tunneled hemodialysis catheter [TDC]). A nurse/technician can help the patient choose the best vascular access type. The advantages and disadvantages of each vascular access type are shown in the Table. Based on the complications, mortality and morbidity an arteriovenous fistula is the best available access. It is critical to mention that a TDC has the highest risk of developing infection and sepsis. Furthermore, TDC possess the highest risk of death compared to an arteriovenous fistula or an arteriovenous graft. It is for these reasons that National Kidney Foundation-Kidney Dialysis Outcomes and Quality Initiative (NKF-KDOQI) vascular access guidelines prefer an arteriovenous fistula to provide long-term hemodialysis therapy [1]. Similarly, the “Fistula First” also takes a position that whenever possible an arteriovenous fistula should be created to provide long-term hemodialysis therapy [2].

While an AVF is the best available access, there have been situations where an arteriovenous fistula is not created. To increases the likelihood of an arteriovenous fistula, the “Fistula First” project has emphasized the use of a set of “change concepts”. A nurse/technician can help the patient understand the “change concepts” and request some of the vital steps to be completed prior to the fistula creation. Vessel mapping is one such “change concept” and it is one of the most critically important steps to be completed prior to the fistula creation. Undoubtedly, vessel mapping increases fistula prevalence [2]. A nurse/technician can provide information regarding vessel mapping in general and types of vessel mapping techniques. Patients can be taught regarding the role of physical examination in the detection of veins and arteries required to create an AVF. A nurse/technician can also provide information regarding the use of ultrasound and contrast angiogram as vessel mapping techniques for situations where vessels are not readily apparent on physical examination. It is also important to mention that the functional and anatomical information obtained by ultrasound and angiography surpasses that obtained by simple physical examination [3, 4].

Because TDCs are associated with the highest risk of mortality, a nurse or a technician can also target HD patients receiving long-term dialysis using a dialysis catheter. This could begin with presentation of advantages and disadvantages of various vascular access types to catheter consigned patients [5]. Such patients could also be offered vessel mapping. Once mapping is accomplished, a VAC can make arrangements for the creation of an arteriovenous fistula. In a prospective study, 121 catheter consigned patients were educated about vascular access types by a nephrology nurse and mapping was offered [5]. Eighty-seven agreed to
Role of Nurses and Technicians in Vascular Access Care

undergo mapping. Seventy-two of the 86 received an arteriovenous access and got rid of their catheter thereby reducing the mortality risk. This study provides evidence in support of a major impact that a nurse can have on patient care and death rate.

Another important area where a nurse can assist is the creation of a secondary fistula [6-8]. A dialysis nurse or a technician can easily identify patients with problematic arteriovenous grafts (large pseudoaneurysms, the need for frequent angioplasty, recurrent thrombosis episodes) and present information regarding the advantages of the fistula and highlight the use of the outflow vein of the graft to create a secondary fistula. In many instances, the outflow vein can easily be identified by performing a simple physical examination (the “sleeves up” approach) [6]. In other situations, an ultrasound or an angiogram might be needed. Multiple studies have documented the success of this approach and provided long-term patency success.

Nurses and technicians can easily follow the progress of a newly created fistula. Early arteriovenous fistula failure is an important problem that can lead to failure of a great majority of fistulae. Fortunately, many of these fistulae can be salvaged successfully by performing simple percutaneous interventions [9]. A dialysis nurse or a technician can perform simple physical examination to diagnose or bring a newly created fistula that has not been able to support dialysis therapy to the attention of the nephrologist. Indeed, it has been documented that nurses can predict fistula maturation with over 80% accuracy using simple physical examination [10].

A nurse can also facilitate and coordinate salvage procedures thereby improving fistula availability for dialysis and minimizing reliance on catheters. Cannulation injuries can result in the loss of a fistula. Nurses and technicians can set up educational programs to minimize such occurrences.

Recently, nurses and technicians are participating in the procedural aspect of HD access. Many centers across the United States are using nurses and technicians in outpatient vascular access centers. These roles have ranged from patient monitoring to assisting with the procedures as well as pre and post procedural care. The nurse or a technician is a central figure in the day-to-day administration of the hospital-based procedure room and is also an important member of the interventional team performing the outpatient interventions.

As part of this team, the nurse may assist in the percutaneous procedure, monitor the patient during surgery, and/or administer conscious sedation under the supervision of the nephrologist. The nurse also plays a major role in the pre and postoperative care of these patients. A critical care background is helpful in this position, though not a must. Advanced cardiac life support training and conscious sedation certification are required. The nurse/technician can also serve as a liaison with the dialysis staff, answering questions, providing information regarding the substance of the patient's procedure, and involving the interventionalist where needed.

Vascular access surveillance is another important area where a vascular access nurse/technician can have a major impact in identifying patients with a dysfunctional arteriovenous access. Here early identification can help minimize thrombotic episodes and number of missed dialysis days due to lack of vascular access. Assessment of dynamic venous pressure, static venous pressure and clinical features of prolonged bleeding, arm, shoulder or face edema can all help to identify a dysfunctional access. A program for vascular access surveillance using ultrasound dilution determination of access flow can also be
employed to accurately identify vascular accesses at risk. A nurse or a technician can easily manage such a program and have a positive impact on the health of vascular access.

**Table 1. Advantages and disadvantages of vascular access types**

<table>
<thead>
<tr>
<th>Concern</th>
<th>Arteriovenous Fistula</th>
<th>Arteriovenous Graft</th>
<th>Tunneled Dialysis Catheter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costs of Care</td>
<td>Lowest</td>
<td>Higher than fistula</td>
<td>Highest</td>
</tr>
<tr>
<td>Mortality</td>
<td>Lowest</td>
<td>Higher than AVF (a)</td>
<td>Highest</td>
</tr>
<tr>
<td>Infection Risk</td>
<td>Lowest</td>
<td>Higher than AVF</td>
<td>Highest</td>
</tr>
<tr>
<td>Risk of Metastatic Infection</td>
<td>Lowest</td>
<td>Lowest</td>
<td>Highest</td>
</tr>
<tr>
<td>Patency Rates</td>
<td>Significantly better than TDC</td>
<td>Significantly better than TDC</td>
<td>Lowest</td>
</tr>
<tr>
<td>Thrombosis Risk</td>
<td>Lowest</td>
<td>Higher than AVF</td>
<td>Highest</td>
</tr>
<tr>
<td>Early failure</td>
<td>Highest</td>
<td>Lower than AVF</td>
<td>Lowest</td>
</tr>
<tr>
<td>Patient Factor</td>
<td>Painful cannulation</td>
<td>Painful cannulation</td>
<td>Painless connection</td>
</tr>
<tr>
<td>Timing of Availability for Dialysis</td>
<td>Usually a maturation period of at least 4-6 weeks is required</td>
<td>Usually a maturation period of at least 2 weeks is required (b)</td>
<td>Immediately available for dialysis therapy</td>
</tr>
</tbody>
</table>

Note: Arteriovenous fistula (AVF), arteriovenous graft (AVG) and tunneled dialysis catheter (TDC). At least in prevalent hemodialysis patients with diabetes (a) [11]. A specific form of dialysis graft can be made available for dialysis within a few days of placement.

Vascular access stenosis is major culprit leading to vascular access dysfunction, thrombosis and loss of vascular access. There is limited research on the development of neointimal hyperplasia. Nurses have played a major role in the clinical nephrology research. A nephrology nurse or a technician interested in the basic research element of vascular access could have a role in this aspect of vascular access research.

In summary, vascular access provides an important and fertile avenue for nurses and technicians both for clinical care and research activities. These individuals can serve under multiple roles in this area providing patient education, improving communication, facilitating appointment, participating in research and improving patient care.

**References**


Introduction

Despite impressive advances in the management of end stage renal disease (ESRD), complications of vascular access, specifically thrombosis, have remained a persistent problem since the nascent stages of dialysis. The annual cost of maintaining dialysis access is estimated to be approximately 15-30% of the total cost of dialysis, excluding professional fees [1]. Clearly, maintaining patency of vascular access is an important health care problem.

Attempts at pharmacologic prevention of access thrombosis have permeated the literature since the inception of chronic hemodialysis [2]. Agents that inhibit platelet function or the clotting system have received the most attention.

Although, warfarin analogues were often utilized to prevent access thrombosis in the Scribner shunt era, these agents were largely abandoned because of an unacceptable increase in bleeding complications. In recent years, agents specifically targeted to interfere with vascular smooth muscle cell growth (e.g., paclitaxel-eluting stents) have emerged as an exciting alternative to traditional methods of anticoagulation [3].

Theoretically, these agents target the precursor lesion ultimately responsible for vascular access occlusion, i.e., intimal hyperplasia (Figure 1). This chapter will review conventional and novel pharmacologic approaches to the prevention of vascular access thrombosis.
Pathophysiology of Access Thrombosis

Although, the precise pathophysiology of thrombus formation in vascular access is incompletely understood, there is a significant correlation between thrombosis and the severity of intimal hyperplasia at or near the venous anastomosis. Romero, et al. noted a 91% incidence of arterial and/or venous stenosis in all late synthetic graft thrombosis [4]. The majority of occlusions were associated with thrombosis in the venous system, usually in close proximity to the venous anastomosis. The pathological hallmark at these sites revealed intimal proliferation consisting almost entirely of vascular smooth muscle cells [5]. The specific mechanisms responsible for intimal hyperplasia are poorly understood, however, turbulent flow at the confluence of the graft and low-pressure venous system is thought to result in shear-stress induced endothelial injury, followed by platelet micro-thrombus formation and the release of growth promoting factors such as platelet-derived-growth factor (PDGF) [6]. This formulation is similar to the response-to-injury model proposed by Ross and Glomset [7].

Importantly, turbulence in the graft coupled with vascular encroachment can generate a shear force in excess of 2000 dynes/cm [8]. This force far exceeds the force necessary to cause experimental injury in dog endothelial cells. Importantly, the injured endothelium (or activated platelets) also directly liberates cytokines and growth factors that enhance smooth muscle cell growth and migration into the media. Repeated exposure of the draining vein to endogenous growth factors results in progressive narrowing.

An additional factor contributing to turbulent flow is the presence of central venous stenosis in the draining axillary or subclavian veins (usually incident to central venous cannulation). Occasionally intragraft stenosis occurs as a consequence of repeated needle puncture.

![Image of vascular access thrombosis](image_url)

Figure 1. Vascular access thrombosis is envisioned as a 2 stage process: 1) intimal hyperplasia resulting in progressive narrowing of the draining vein with concomitant turbulent flow resulting in endothelial injury, and 2) thrombosis as platelets adhere to the underlying collagen of the injured vessel. In this construct, intimal hyperplasia is viewed as the necessary precursor lesion for the development of access thrombosis. Therefore, therapies designed to inhibit venous intimal hyperplasia should theoretically offer an advantage over standard anticoagulation.
Rarely access thrombosis is not associated with an anatomical abnormality. In these instances exposure to activated platelets within the dialysis circuit may precipitate access thrombosis. Other possible factors contributing to access thrombosis in the absence of an anatomical lesion include, hemoconcentration during the dialysis procedure, the procoagulant effects of erythropoietin, patient comorbidities, and genetic polymorphisms in procoagulant and anticoagulant proteins (Figure 2) [9]. Simply put, the development of access thrombosis is the result of a perturbation in the normal procoagulant/anticoagulant equilibrium.

Interestingly, since platelet aggregation is often impaired in the patient with ESRD the role of platelet activation per se in the pathogenesis of access thrombosis should be viewed with skepticism. More likely, disruption of the thromboresistant nature of the endothelium yields access thrombosis. However, the thromboresistant properties of the dialysis graft and draining veins have not been subjected to rigorous study.

A comprehensive understanding of the cellular mechanisms involved in mediating vascular access occlusion is essential to design targeted therapeutic strategies that reduce or prevent access thrombosis.

Figure 2. Plausible model depicting various hemodynamic, metabolic, and genetic factors involved in the development of access thrombosis. Ideally, pharmacologic approaches would target these variables or be individualized to maximize efficacy. Since endothelial injury is viewed as an essential step in this model, therapies that stabilize the endothelium should ideally be employed. Note that recent studies suggest that polymorphisms in the procoagulant versus anticoagulant system may play a more important role in the pathogenesis of vascular access thrombosis than previously recognized. HTN, hypertension; TGF-b, transforming growth factor-beta; NO, nitric oxide; PAI-1, plasminogen activator inhibitor-1; EPO, erythropoietin.
<table>
<thead>
<tr>
<th>Drug(s) class</th>
<th>Placebo</th>
<th>No (n)</th>
<th>AVF</th>
<th>AVG</th>
<th>Results</th>
<th>P</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andrassy et al., 1973</td>
<td>ASA</td>
<td>yes</td>
<td>92</td>
<td>yes</td>
<td>Thrombosis: 4% in ASA vs 23% in placebo</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Kaegi et al., 1975</td>
<td>SPZ</td>
<td>yes</td>
<td>45</td>
<td>yes</td>
<td>Thrombosis: 0.64 per patient month in placebo vs 0.21 thrombi per pt month in SPZ</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Harter et al., 1979</td>
<td>ASA</td>
<td>yes</td>
<td>44</td>
<td></td>
<td>Thrombosis: 32% ASA vs 72% in placebo</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Fiskerstrand et al., 1985</td>
<td>TIC</td>
<td>yes</td>
<td>18</td>
<td>yes</td>
<td>Thrombosis: 2/6 in TIC vs 5/9 in placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grontoft et al., 1985</td>
<td>TIC</td>
<td>yes</td>
<td>42</td>
<td>yes</td>
<td>Thrombosis: 2/19 in TIC vs 8/17 in placebo</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Domoto et al., 1991</td>
<td>ASA+SPZ</td>
<td>yes</td>
<td>15</td>
<td></td>
<td>Thrombosis frequency reduction from 0.114 per month to 0.04 per month with Rx.</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Sreedhara et al., 1994</td>
<td>DP</td>
<td>Yes</td>
<td>84</td>
<td>yes</td>
<td>Thrombosis 17% vs 32%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sreedhara et al., 1994</td>
<td>DP, ASA+DP, ASA</td>
<td>yes</td>
<td>84</td>
<td>yes</td>
<td>New PTFE grafts: Thrombosis rates 21±9% on DP, 25±11% on DP+ASA, 42±13% on placebo and 80±12% on ASA. RR of thrombosis with DP was 0.35(p=0.02) and for ASA 1.99 (p=0.18)</td>
<td>DP beneficial in pts with new PTFE grafts. In old PTFE (with thrombectomy and/or revision; thrombosis was high in all groups(overall 78%)</td>
<td></td>
</tr>
<tr>
<td>Grontoft et al., 1998</td>
<td>TIC</td>
<td>yes</td>
<td>258</td>
<td>yes</td>
<td>Thrombosis: 12% in TIC vs 19% in placebo</td>
<td>=0.10</td>
<td></td>
</tr>
<tr>
<td>Kaufman et al., 2003</td>
<td>ASA+CLO</td>
<td>yes</td>
<td>200</td>
<td></td>
<td>Incidence of first graft thrombosis, HR=0.81</td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td>Janicki et al., 2003</td>
<td>TIC</td>
<td>yes</td>
<td>60</td>
<td></td>
<td>Thrombosis: 2/30 in ticlopidine vs 5/30 in control</td>
<td>No benefit</td>
<td></td>
</tr>
<tr>
<td>Drug(s) class</td>
<td>Placebo</td>
<td>No (n)</td>
<td>AVF</td>
<td>AVG</td>
<td>Results</td>
<td>P</td>
<td>Comments</td>
</tr>
<tr>
<td>--------------</td>
<td>---------</td>
<td>--------</td>
<td>-----</td>
<td>-----</td>
<td>---------</td>
<td>------</td>
<td>----------</td>
</tr>
<tr>
<td>Trimarchi et al., 2006</td>
<td>CLO</td>
<td>24</td>
<td>yes</td>
<td>yes</td>
<td>Thrombosis: 1/12 in CLO vs 11/12 in untreated; Graft patency longer in CLO</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Dember et al., 2008 (DAC)</td>
<td>CLO</td>
<td>877</td>
<td>yes</td>
<td>Yes</td>
<td>Thrombosis: 12.2% in CLO vs 19.5% in placebo, RR = 0.63</td>
<td>0.018</td>
<td></td>
</tr>
<tr>
<td>Hasegawa et al., 2008</td>
<td>ASA</td>
<td>1411</td>
<td>yes</td>
<td>yes</td>
<td>37% lower risk in ASA, AHR 0.63, P &lt; 0.03</td>
<td>&lt;0.03</td>
<td></td>
</tr>
<tr>
<td>Dixon et al., 2009</td>
<td>DP+ASA</td>
<td>649</td>
<td>yes</td>
<td>yes</td>
<td>Primary patency at one year: 28% vs 23%</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Dixon et al., 2011</td>
<td>ASA+DP</td>
<td>649</td>
<td>yes</td>
<td>yes</td>
<td>ASA use associated with dose dependent prolongation of primary unassisted graft patency, AHR = 0.83</td>
<td>0.06</td>
<td></td>
</tr>
</tbody>
</table>

ASA, aspirin; DP, dipyridamole; SPZ, sulfinpyrazone; CLO, clopidogrel; TIC, ticlodipine; HR, hazard ratio; RR, relative risk; OR, odds ratio; AHR, adjusted hazard ratio; AVF, arteriovenous fistula; AVG, arteriovenous graft.
Table 2. Anticoagulation Agents

<table>
<thead>
<tr>
<th>Drug(s) class</th>
<th>Placebo</th>
<th>AVF</th>
<th>AVG</th>
<th>Results</th>
<th>p-value</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mokrzycki et al., 2001</td>
<td>Warfarin in TCC</td>
<td>yes</td>
<td>105</td>
<td>no</td>
<td>No</td>
<td>TCC failure: 8/41 in warfarin vs 8/44 in placebo. No significant effect of warfarin on thrombosis free survival</td>
</tr>
<tr>
<td>Crowther et al., 2002</td>
<td>Warfarin</td>
<td>yes</td>
<td>107</td>
<td>yes</td>
<td>Graft survival, OR=1.76 in favor of placebo</td>
<td>0.74</td>
</tr>
<tr>
<td>Haire et al., 2004</td>
<td>r-UK, 500IU/ml</td>
<td>yes</td>
<td>180</td>
<td>No</td>
<td>No</td>
<td>r-UK was superior to placebo in restoring catheter function (54% vs 30%)</td>
</tr>
<tr>
<td>Weijmer et al., 2005</td>
<td>Trisodium citrate 30% vs heparin 5000U/ml</td>
<td>no</td>
<td>291</td>
<td>no</td>
<td>No difference in thrombosis</td>
<td>0.75</td>
</tr>
<tr>
<td>Coli et al., 2006</td>
<td>Warfarin + TIC before TCC malfunction vs warfarin + TIC after malfunction</td>
<td>no</td>
<td>144</td>
<td>no</td>
<td>No</td>
<td>Thrombosis/malfunction: 12% in 1st group vs 52% in 2nd group. Early warfarin therapy significantly reduces thrombosis in TCC</td>
</tr>
<tr>
<td>Lok et al., 2006</td>
<td>Trisodium citrate 4% vs heparin</td>
<td>no</td>
<td>353</td>
<td>no</td>
<td>No</td>
<td>CVC exchange rate and TPA usage improved in citrate group</td>
</tr>
<tr>
<td>Grudzinski et al., 2007</td>
<td>Sodium citrate 4% vs heparin 10,000U/ml</td>
<td>no</td>
<td>27</td>
<td>yes</td>
<td>no</td>
<td>No</td>
</tr>
<tr>
<td>Sharatkumar et al., 2007</td>
<td>Unfractionated heparin infusion post-op, then subcutaneous LMWH until access maturity</td>
<td>no</td>
<td>39</td>
<td>yes</td>
<td>yes</td>
<td>Thrombosis was less in heparin group 12.5% vs 83% in untreated group</td>
</tr>
<tr>
<td>Stuard et al., 2010</td>
<td>ASA+CLO vs ASA+CLO+topical heparin gel</td>
<td>no</td>
<td>303</td>
<td>no</td>
<td>no</td>
<td>No</td>
</tr>
<tr>
<td>Moran et al. 2011</td>
<td>Gentamicin in 4% sodium citrate vs Heparin 1000U/ml as CVC lock</td>
<td>no</td>
<td>225</td>
<td>no</td>
<td>no</td>
<td>No</td>
</tr>
</tbody>
</table>

TCC, tunneled cuffed catheter; r-UK, recombinant urokinase; TIC, ticlopidine; LMWH, low molecule weight heparin; ASA, aspirin; CLO, clopidogrel; CVC, central venous catheter; tPA, tissue plasminogen activator; AVF, arteriovenous fistula; AVG, arteriovenous graft; AVF, arteriovenous fistula; AVG, arteriovenous graft.
<table>
<thead>
<tr>
<th>Drug (s) class</th>
<th>Placebo</th>
<th>AVF</th>
<th>AVG</th>
<th>Results</th>
<th>p-value</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gradzki et al., 2001</td>
<td>ACEI</td>
<td>121</td>
<td>no</td>
<td>yes</td>
<td>RR for AVG failure 53% less in ACEI group</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>Schmitz et al., 2002</td>
<td>Fish oil</td>
<td>yes</td>
<td>24</td>
<td>no</td>
<td>Primary patency: 75.6% fish oil vs 14.9% control</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>Saran et al., 2002</td>
<td>ACEI, ARB, CCB, ASA and other anti-platelet drugs, warfarin, statins</td>
<td>yes</td>
<td>yes</td>
<td></td>
<td>CCB improved primary AVG patency (p=0.034) -ASA associated with better secondary AVG patency (p=0.01) -ACEI associated with improved secondary AVF patency (p=0.01) -warfarin worsened primary AVG patency (RR=1.33)</td>
<td></td>
</tr>
<tr>
<td>Lee et al., 2006</td>
<td>Paclitaxel coated PTFE graft</td>
<td>yes</td>
<td>19</td>
<td>no</td>
<td>% Luminal stenosis 10.4% in paclitaxel group vs 60.5% in untreated</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Yevzlin et al., 2006</td>
<td>ASA, ACEI, CCB, statin, heparin, warfarin, antiplatelet agents excluding ASA</td>
<td>1712</td>
<td>yes</td>
<td>yes</td>
<td>Increased risk of AVF failure was associated with ASA (HR 2.49), otherwise no associations</td>
<td>0.005</td>
</tr>
<tr>
<td>Saigure et al., 2007</td>
<td>Sirolimus eluting stents(SES) vs untreated metal stents</td>
<td>no</td>
<td>266</td>
<td>yes</td>
<td>yes</td>
<td>Thrombosis 55% in ACEI vs 71% in untreated (p=0.04), AVG patency duration 671 days in ACEI vs 460 days in the untreated group (p=0.012).</td>
</tr>
<tr>
<td>Ichimoto et al., 2009</td>
<td>Statin, folic acid, or combined therapy</td>
<td>no</td>
<td>128</td>
<td>no</td>
<td>yes</td>
<td>Thrombosis rate 3.8% in SES vs 2.4% in untreated. Restenosis rate was 30% in SES vs 40% in untreated</td>
</tr>
<tr>
<td>Pisoni et al., 2010</td>
<td>Statin</td>
<td>601</td>
<td>yes</td>
<td>yes</td>
<td>Primary AVF failure 37% on statin vs 38%. Primary AVG failure 20% on statin vs 14%</td>
<td>NS</td>
</tr>
<tr>
<td>Jackson et al., 2011</td>
<td>ARB ± antiplatelet drugs</td>
<td>332</td>
<td>yes</td>
<td>yes</td>
<td>Reduced hazard of AVF failure with ARB</td>
<td>0.008</td>
</tr>
<tr>
<td>Lok et al., 2012</td>
<td>Fish oil</td>
<td>yes</td>
<td>202</td>
<td>no</td>
<td>yes</td>
<td>Graft thrombosis 48% in fish oil vs 61% in placebo, (p=0.06). Rate of graft failure in fish oil group (5.43 vs 5.94 per 1,000 access days, p=0.001). Thrombosis events in fish oil (1.71 versus 3.40, p=0.001).</td>
</tr>
</tbody>
</table>

ACEI, converting-enzyme inhibitor; ARB, angiotensin receptor blocking agent; CCB, calcium channel blocker; ASA, aspirin; RR, relative risk; PTFE, polytetrafluorethylene; NS, not significant; AVF, arteriovenous fistula; AVG, arteriovenous graft.
Pharmacologic Agents

Three general classes of agents have been employed to prevent vascular access thrombosis: 1) Antiplatelet drugs (Table 1), 2) Anticoagulants (Table 2), and 3) Miscellaneous therapies (e.g., anti-proliferative agents, such as sirolimus or alternative therapies such as fish oil, Table 3). In addition, many trials have employed combination approaches.

Anti-Platelet Agents (Table 1)

Aspirin (ASA) irreversibly inhibits cyclooxygenase-1 and 2 (COX-1 and 2), via acetylation, which decreases the formation of prostaglandin derivatives, such as thromboxane A2, thus inhibiting platelet aggregation.

Early studies in patients with arteriovenous fistulas (AVF) revealed a 4-fold reduction in thrombosis rate (6 vs 23%) with ASA treatment compared to the control group [10]. A similar trial by Harter showed a 32% incidence of thrombosis in the ASA treated group compared to 72% in untreated dialysis patients (p<0.01) [11]. A larger randomized trial (n=1411) in patients with an AVF revealed that ASA was associated with a 37% lower risk of fistula thrombosis (p<0.03) [12].

Aspirin has also been studied in combination with other drugs for maintenance of vascular access patency. In particular, sulfinpyrazone, a metabolite of phenylbutazone exhibits anti-platelet effects that were first observed in patients with gout. Sulfinpyrazone is metabolized to a sulfide metabolite, which is a potent competitive cyclooxygenase inhibitor.

Sulfinpyrazone was initially studied in patients with AVF. Kaegi observed 0.64 thrombi per patient month in placebo treated patients compared to 0.21 in patients treated with sulfinpyrazone (p<0.001) [13]. Domoto employed ASA plus sulfinpyrazone in 15 patients with an AVF and revealed a thrombosis frequency of 0.114 per month in the untreated patients compared to 0.04 per month in the treatment group (p<0.001) [14]. However there was a higher rate of gastrointestinal bleeding in the treatment group.

Dipyridamole(DP) has also been studied in combination with ASA. DP inhibits the activity of adenosine deaminase and phosphodiesterase, which causes an accumulation of adenosine, adenine nucleotides, and cyclic AMP; these mediators inhibit platelet aggregation and produce vasodilatation. Importantly, DP inhibits growth of vascular smooth muscle cells in vitro [15].

Sreedhara examined the effects of DP vs ASA plus DP in 84 patients with new polytetrafluorethylene (PTFE) arteriovenous grafts (AVG) for 18 months [16]. Thrombosis rates were 17% in the DP group vs 32% in the placebo group. The combination group (ASA plus DP) exhibited a thrombosis rate of 23%. Surprisingly, a fourth arm that received ASA alone showed the highest thrombosis rate of 50%. The investigators concluded that DP, but not ASA, was beneficial in patients with new PTFE grafts.

A large randomized placebo controlled double blind trial of extended release DP(200mg daily) and ASA(25mg twice daily) was performed in 649 patients with new PTFE grafts [17]. The patients were randomly assigned to receive either DP combined with ASA (n=321) vs placebo (n=328) and followed until loss of primary unassisted patency (i.e., patency without
thrombosis or requirement for intervention). The incidence of primary unassisted patency at 1 year was 23% in the placebo group and 28% in the combination group. However the treatment group exhibited a significantly longer duration of primary unassisted patency (p=0.03). In addition, the stenosis rates were less in the treatment group over the study period. Importantly, the incidences of cumulative graft failure, death, the composite of graft failure or death, and serious adverse events (including bleeding) did not differ significantly between study groups.

In a follow-up analysis, the effects of ASA administration at baseline on primary unassisted graft patency, was compared to combination (extended release DP and ASA) treatment and placebo [18]. 43% of the study participants reported using ASA at baseline. The incidence of primary unassisted patency among participants at 1 year was 30% vs 23% among those not using ASA at baseline (p=0.06).

Ticlopidine is a derivative of pyridine that is well absorbed orally and inhibits both the primary and secondary phase of ADP induced aggregation in platelets. Fiskerstrand conducted a double blind randomized trial in 18 patients comparing ticlopidine vs placebo [19]. Patients undergoing placement of new AVF were enrolled and the medication was started 2 days prior to surgery (250 mg twice daily). In this small clinical trial, the incidence of thrombosis was lower in the ticlopidine group (2 events in 6 patients) compared to placebo (5 events in 9 patients).

Grontoft performed a larger (n=42) randomized controlled clinical trial comparing the effects of placebo vs ticlopidine (250 mg bid) in patients after creation of a new AVF [20]. Thirty-six patients completed the trial. Fistula thrombosis occurred in 8 out of 17 patients receiving placebo versus 2 out of 19 in the treated group (p<0.05). A similar, but larger randomized trial was conducted in 258 patients with an AVF [21]. Treated patients received ticlopidine 250mg twice daily and were compared to placebo. The drug was started 3 days before and continued for 28 days after surgery. Thrombosis rates were 19% in the placebo group vs 12% in the ticlopidine group (p=0.10). The risk of early occlusion was 35% lower in the ticlopidine group, but this did not achieve statistical significance. Janicki compared the effects of ticlopidine (125 mg twice dialy) in 60 patients (30 received the drug) with a new AVF [22]. 2 patients in the treatment group and 5 in the control group developed a thrombosis. No drug related complications were observed during the study period.

Clopidogrel (CLO) irreversibly binds to adenosine diphosphate receptors, thus, inhibiting platelet activation and aggregation.

Kaufman conducted a randomized,double-blind trial in 30 hemodialysis centers that compared placebo to ASA (325mg daily) plus CLO (75mg daily) [23]. All patients were undergoing hemodialysis with an existing PTFE graft in the arm. The study was stopped after randomization of 200 participants, as recommended by the Data Safety and Monitoring Board because of a significantly increased risk of bleeding among the participants receiving ASA and CLO therapy (44 bleeding episodes in the treatment group versus 23 in the controls). Although the study was discontinued early, the authors concluded that it was unlikely that the treatment group would have experienced a reduction in graft thrombosis.

Trimarchi conducted a prospective study of 24 hemodialysis patients with new PTFE grafts; 12 were randomized to CLO 75 mg daily, starting 2 days after surgery and compared to 12 untreated patients [24]. 11 thrombotic episodes were noted in the untreated patients versus only one in the CLO group (p<0.001).
In addition, graft patency was significantly prolonged in the CLO group (380.8 +/- 170 vs. 90.1 +/- 57.2 days, p < 0.001). No major bleeding episodes were reported.

The Dialysis Access Consortium (DAC) group recently examined the effects of CLO on thrombosis rates in patients with a new AVF [25]. This double-blind study randomized 441 patients to CLO (300mg loading dose followed by 75mg daily) and 436 patients to placebo for 6 weeks starting within 1 day of fistula creation. The patients were followed for 150-180 days after fistula creation. Fistula thrombosis occurred in 12.2% on CLO compared to 19.5% receiving placebo (p=0.018). The authors concluded that CLO reduces the frequency of early thrombosis of new AVFs but does not increase the proportion of fistulas that eventually become suitable for dialysis.

Anticoagulants (Table 2)

Drugs that inhibit the clotting cascade have also been used to prevent access thrombosis. In general, these drugs have received less attention (particularly in recent years) because of an unacceptable increase in bleeding complications. Most recent trials have examined the effects of locally delivered anticoagulation in patients with dialysis access catheters rather than systemic administration.

Heparin binds to antithrombin III, thus stabilizing the protein and interfering with several steps in the normal coagulation cascade.

Hemmelgarn studied the effects of 2 catheter-locking regimens (5000 units/ml of heparin three times per week vs 1 mg of recombinant tissue plasminogen activator in each port) in 225 patients undergoing long-term hemodialysis in which a new central venous catheter had been inserted [26]. Catheter malfunction occurred in 40 of the 115 patients assigned to heparin only, compared to 22 of the 110 patients assigned to rt-PA (p=0.02).

Weijmer conducted a prospective study of 291 patients with dialysis catheters [27]. The catheter lumen was instilled with 30% citrate and compared to 5000 units/ml of heparin. There was no difference in the frequency of thrombosis between the two groups (p=0.75). Interestingly, catheter related bacteremia was less in the citrate group (p<0.001).

A recent retrospective study revealed no difference between heparin and citrate locking protocols in terms of the frequency of thrombosis (p=0.07) or catheter exchange (as a result of malfunction) [28]. Catheter related bacteremia was similar in both groups (p=0.36).

Lok performed a prospective study that assessed catheter thrombosis in two consecutive time periods, one in which heparin was used versus a second in which citrate was employed [29]. The frequency of tissue plasminogen activator used for catheter malfunction (p=0.002) or catheter exchange (p=0.01) as a result of malfunction were lower with the citrate lock, as compared with the heparin lock.

Stuard evaluated the efficacy of topically applied heparin (combined with antiplatelet therapy) in patients with newly created AVF [30]. 39 patients received either ASA or CLO (started immediately after surgery) with or without a topical heparin spray (heparin sodium spraygel, Viatromb) as an adjuvant treatment. The topical spray was started 2 weeks after surgery at a dose of 2750-3700 units twice a day during the first month and continued at the same dose once daily for the duration of follow up (7.9 months). All fistulae remained patent at 3 months and only one occluded at 6 months. Addition of the spraygel reduced the risk of
patency loss by 16.7% at three months and by 22.2% at six months. This small study suggests that topically applied heparin may sustain AVF patency.

Sharatkumar examined the effects of an infusion of unfractionated heparin in 27 patients with a newly placed AVF [31]. The infusion was followed by subcutaneous low molecular weight heparin (LMWH) daily until maturity. Thrombosis rates were 12.5% in the heparin group vs 83% in the group that did not receive heparin (P < 0.05). Moran studied the role of gentamicin in a 4% sodium citrate lock vs heparin [32]. The rates of rt-PA use, as a measure of catheter clotting, was similar in both groups; 2.36 vs 3.42 events/1000 catheter days (p=0.2).

Warfarin inhibits vitamin K dependent coagulation factor synthesis (Factors II, VII, IX, X, protein C and protein S) and has been used in the prevention of access thrombosis since the Scribner shunt era. It is infrequently used in the modern era because of the risk of bleeding complications and its long half-life.

Crowther examined the effects of low intensity warfarin treatment (target INR of 1.4-1.9) vs placebo in 107 patients with synthetic grafts (56 allocated to warfarin) [33]. The patients were followed for 37 months before the trial was terminated early due to a significant increase in bleeding. Time to event analysis revealed no significant differences in the likelihood of graft survival between the two groups (p=0.74). 6 major bleeds occurred in the warfarin group compared to none in the patients receiving placebo.

Mokrzycki in a randomized study of 105 tunneled cuffed catheters, compared fixed low-dosage warfarin (1 mg/d) with placebo for prophylaxis of catheter-related thrombosis [34]. There was no difference in the risk for thrombosis among the two treatment groups.

A recent randomized trial performed by Coli revealed a dramatic reduction of catheter thrombosis in patients who were treated with therapeutic warfarin (target INR of 1.8 to 2.5), in conjunction with ticlopidine [35]. 144 patients were randomized to warfarin plus ticlopidine as primary prophylaxis (before an event) compared to secondary prophylaxis (i.e., after the first episode of thrombosis/malfunction). 12% of the patients randomized to warfarin-based anticoagulation as primary prophylaxis developed an event (thrombosis/malfunction) compared to 52% in patients whom received the regimen as secondary prophylaxis. The authors concluded that early initiation of anticoagulation is associated with a significant reduction in catheter thrombosis.

Prior to 1998, the treatment of choice for catheter occlusion/malfunction was instillation of low-molecular-weight human-sourced urokinase. In 1998, production of human-sourced urokinase was halted because of irregularities in the manufacturing process. Concurrently, a recombinant high-molecular-weight urokinase (r-UK) derived from a non-human mammalian cell line was under development. This new formulation possessed similar fibrinolytic activity as compared to the human-sourced compound.

Haire examined the efficacy and safety of recombinant urokinase in nondialysis catheters [36]. A total of 180 patients were enrolled at 43 sites in the United States and Canada. Most patients were adults, although 20% were ≤18 years of age. Central venous access (CVAD) subtypes included implanted subcutaneous ports (45%), PICC lines (26%), non-tunneled percutaneous catheters (18%), and tunneled percutaneous catheters (10%). All CVADs were occluded by virtue of their inability to withdraw blood (withdrawal occlusion). Additionally, 32% of catheters were completely dysfunctional as blood could not be withdrawn and fluids could not be infused (total occlusion). Analysis of the results revealed that r-UK was superior at restoring catheter function compared to placebo (54% versus 30%, p=0.002). There were
no major hemorrhagic events within 72 hours after instillation and the incidence of non-hemorrhagic events was similar among the r-UK and placebo groups.

Miscellaneous Agents (Table 3)

Fish oil, or more specifically omega-3 fatty acids, offers several theoretical advantages over existing agents since omega-3 fatty acids modulate multiple pathways involved in the pathogenesis of vascular access thrombosis. For example, omega-3 fatty acids increase membrane fluidity (membranes are less susceptible to injury), decrease TXA₂ synthesis, improve blood rheology (reduce turbulence and favor streaming), and inhibit vascular smooth muscle cell proliferation [37]. Omega-3 fatty acids (presumably via their effects on TXA₂ synthesis) reduce platelet aggregation and prolong bleeding time. Recently, omega-3 fatty acids have been shown to inhibit smooth muscle cell proliferation and to facilitate endothelial cell migration in vitro [38-41]. In addition, omega-3 fatty acids directly inhibit endothelial secretion of growth factors (such as platelet-derived growth factor, PDGF) as well as inhibit the secretion of tumor necrosis factor-α and interleukins 1 and 6 [42,43]. Collectively, these actions engender an antiproliferative state, which could favorably influence the development of intimal hyperplasia and subsequent graft stenosis.

Studies from our laboratory in rodents revealed a striking effect of fish oil on the development of myointimal hyperplasia [38]. 15 Sprague-Dawley rats were randomly assigned to receive standard chow, chow enriched with 17% fish oil or chow enriched with 17% sunflower oil (an omega-6 fatty acid) and then subjected to left common carotid artery injury with a 2F catheter. Both carotid arteries were removed after 21 days and analyzed for the severity of intimal hyperplasia. Marked expansion of the intima was observed in rats subjected to balloon injury on (intimal area = 140+/−30 µm²) compared to sham rats (<10 µm²). In contrast fish oil markedly attenuated the increase in neointima formation (intimal area = 30+/−15mm² p<0.001, Figure 3).

In a double-blind randomized study, Schmitz evaluated the effects of fish oil compared to placebo on PTFE graft thrombosis [44]. Patients began therapy within two weeks of graft placement and were monitored for 12 months or until thrombosis developed.

The results of this study revealed that the primary patency rate at one year was dramatically improved in the fish oil group (14.9% patency in controls versus 75.6% in fish oil treated).

Recently, Lok reported the results of fish oil administration in 202 patients with synthetic AVG [45]. Graft thrombosis was 48% in the fish oil group vs 61% in placebo (p=0.06). The rate of graft failure in the fish oil group was 3.43 vs 5.94 per 1000 access days (P<0.001). Thrombosis events in fish oil group was 1.71 vs 3.4 in the control group per 1000 access days (P<0.001). Importantly, in the both the Lok trial and Schmitz study, there was a significant reduction in systemic blood pressure. Moreover, the Lok trial also revealed an important reduction in cardiovascular events. Thus, the effects of fish oil extend beyond improving primary patency and appear to ameliorate cardiovascular disease in the dialysis patient.

Other unique approaches have been employed to reduce access thrombosis, including the administration of calcium channel blockers and/or ACE inhibitors. For example, a post-hoc analysis of the DOPPS database in AVG revealed a significant improvement (p<0.001) in
primary patency rates in patients receiving calcium channel blockers. In tandem, ACE inhibitors appeared to have a small but significant effect on improving fistula outcome, but this effect was not observed in AVG [46].

The effects of ACEI are intriguing since angiotensin II has been shown to modulate vascular smooth muscle cell growth and is produced locally at the site of vessel injury, where it may serve as an autocrine growth factor. Furthermore, the angiotensin receptor blockers (ARBs) may also play a role in promoting access patency by exerting an analogous pathobiological effect.

A handful of small clinical trials have been conducted to evaluate the effect of ACE inhibitors or angiotensin receptor blockers on graft function. Gradzki retrospectively analyzed the survival of 121 grafts, 25 of which were placed in 19 patients treated with an ACEI compared to 96 that were placed in 68 patients not receiving an ACEI [47]. The follow-up ranged from 1 month to 5 years. The relative risk for access failure was 53% less in the ACEI group compared to the untreated patients (p<0.03).

Sajgure et al retrospectively analyzed 266 accesses from 4 dialysis centers [48]. Primary patency, time to first access failure, and medication use were included in the analysis. Groups were analyzed according to the sustained administration of an ACEI. Importantly, ACEI use was associated with greater access patency duration in PTFE grafts (671.1 days vs 460.0 days, p=0.012). In addition, the ACEI group had fewer clotting events (55% vs 71%,

Figure 3. Representative morphology in studies using fish oil in a rodent model of arterial injury. Upper panel, sham; middle panel, angioplasty; lower panel, angioplasty plus 17% fish oil. Note the significant decrease in intimal area in the fish oil treated animals compared to the untreated group (middle panel).
p=0.042). However, the use of ACEI was not associated with a beneficial effect in the primary patency of AVFs.

Jackson performed a retrospective analysis of all upper extremity hemodialysis accesses placed from 2005 to 2009 at the Veteran’s administration in Washington, DC [49]. Demographics, exposure to medication, and time to failure were analyzed. Of the 212 autogenous and 120 prosthetic accesses, concurrent administration of ARBs was associated with reduced autogenous (p=0.008) and prosthetic (p=0.039) access failure. A subgroup analysis revealed that the effect of ARBs could be partially explained by the concomitant administration of antiplatelet agents (ASA, CLO).

Other novel approaches include the use of statins, which may reduce neointimal hyperplasia, independent of their lipid lowering effects. Statins also increase fibrinolysis, promote mobilization of endothelial progenitor cells, and decrease the level of C-reactive protein [50]. However, most clinical studies have not shown a beneficial effect of statin use on primary or secondary survival of dialysis grafts. Righetti, in a retrospective analysis from an Italian cohort, showed a small benefit that was attributed to the use of statins [51]. In an experimental model, Herucci demonstrated a favorable effect on thrombosis rates with statins, however Pisoni was unable to confirm a beneficial effect in a large number of dialysis patients [52].

Recently, a post-hoc analysis of the DOPPS trial in adult hemodialysis patients revealed that concomitant statin treatment was not associated with improved primary patency (P=0.805) or secondary patency (P=0.920) of fistulas or grafts [53]. Pisoni performed a retrospective analysis to determine access outcomes of 601 patients receiving an upper-arm fistula or graft at a single dialysis center [52]. Primary fistula failure was observed in 37% receiving statin therapy vs 38% not receiving statins. Primary graft failure occurred in 20% of patients on statins vs 14% in the untreated group. Cumulative fistula and graft survival was similar in both groups and, therefore, the investigators concluded that statin therapy is not associated with improved fistula or graft outcomes. At this point the use of statins to prevent access thrombosis is, at best, controversial.

Additional approaches include the use of perivascular polymers to achieve direct application of a drug to exposed vessels. Systemic therapies might not be effective, because of the need to achieve high tissue concentration at the site of vascular injury. Perivascular drug delivery using agents such as nitric oxide, paclitaxel, and tyrphostins have shown promise in experimental models. Experimental coronary angioplasty models, have examined various modes of endovascular drug delivery systems, including double balloon systems, hydrogel-coated balloon catheters, porous and micro-porous balloons, and coated stents, with reasonably consistent success. In particular, sirolimus and paclitaxel eluting stents have proven useful at inhibiting neointimal hyperplasia and intrastent restenosis of the coronary arteries [54]. Despite these promising early studies and obvious theoretical advantages of such an approach, few clinical studies have examined the role of these agents in the development of dialysis access thrombosis. Lee examined the effects of a paclitaxel coated PTFE graft on neointimal hyperplasia and graft stenosis in a porcine model [3]. The extent of graft stenosis was analyzed 6 weeks after engraftment. The percentage luminal stenosis was 10.4% in paclitaxel group vs 60.5% in the untreated grafts (P<0.05).

Emerging gene therapies, which modify the response to vascular injury have not been studied in the setting of vascular access [55]. Nonetheless, experimental gene transfer of endothelial and inducible nitric oxide synthase, cyclin-dependent kinase inhibitors,
retinoblastoma tumor suppressor protein, hepatocyte growth factor, and transcription factors such as E2F have been explored in many settings. For example, the PREVENT III study was a prospective, randomized, double-blinded, multicenter phase III trial of edifoligide (an E2F decoy) for the prevention of vein graft failure in patients undergoing infrainguinal revascularization for critical limb ischemia (CLI) [56]. 1404 patients with CLI were randomized to a single intraoperative ex vivo vein graft treatment with edifoligide versus placebo. In this clinical trial, ex vivo treatment of lower extremity vein grafts with edifoligide did not confer protection from reintervention for graft failure. External radiation or endovascular radiation has also been evaluated in the experimental setting [57]. Although promising, no studies have been performed in the setting of dialysis vascular access. Perivascular delivery of a nitric oxide donor is another strategy on the horizon [58]. Nitric oxide inhibits neointimal hyperplasia and platelet aggregation, which would theoretically reduce the incidence of graft thrombosis.

Summary

Thrombosis of vascular access remains the malediction of patients receiving maintenance hemodialysis. Although, various pharmacologic agents have been advocated to prevent access thrombosis no approach has gained widespread acceptance. The lack of enthusiasm for routinely utilizing pharmacological approaches to prevent access thrombosis (e.g., anti-platelet agents) is largely attributable to a limited understanding of the biology of graft failure and the lack of large randomized-controlled clinical trials demonstrating unequivocal efficacy. Nevertheless, it is well established that venous intimal hyperplasia at or near the graft confluence precedes thrombosis in virtually all instances of access failure. Until a clear understanding of the cell and molecular biology of access thrombosis emerges, the use of drugs with differing mechanisms of action and dose-response relationships will surely hamper rationale study design and interpretation. We currently advocate the daily administration of fish oil because of its wide therapeutic index, relatively low cost, and added cardiovascular benefits (lower blood pressure, improved lipid profile, and reduced incidence of fatal events).

References


III. ARTERIOVENOUS FISTULAE
Chapter XIV

Basics of AVF Maturation

Aris Urbanes
Lifeline Vascular Access Grosse Pointe Park, MI, US

Definitions

There is no universally accepted or utilized definition of a mature arteriovenous fistula (AVF). Maturation fundamentally involves an increase in blood flow and pressure with concomitant thickening of the vessel wall and dilation of the lumen, allowing complication-free cannulation during dialysis at prescribed blood flow rates. While some investigators deem a fistula mature if it can be used successfully for one dialysis treatment, others define a mature fistula by a more stringent criteria of successful two-needle cannulation with dialysis blood flow rates of ≥ 300 ml/min for three hours, for one month. [1] A related, although not identical, concept is that of suitability. This concept has been defined by the Dialysis Access Consortium as the ability to use the fistula for dialysis with two needles and maintain a dialysis machine blood flow rate adequate for optimal dialysis (≥ 300 mL/min) during eight of 12 dialysis sessions occurring during a 30-day period. [2] K/DOQI provides the “rule of 6” as a guideline for defining non-maturation. [3] This “rule” stipulates that a fistula be a minimum of 6mm in diameter with discernable margins when a tourniquet is in place, less than 6 mm deep, and have a blood flow of greater than 600 ml/min at the six week post-creation period. There are other aspects of fistula development, such as architecture and anatomy, that are not related to the maturation process per se but which have a direct and crucial effect on the functionality of the fistula. These include the length of the useable segment, the rectilinearity of the fistula, and the depth of the fistula from the surface of the skin. Clearly, a sizeable fistula with large blood flow and thick walls will be non-functional if rendered inaccessible because it is too deep for easy access of a dialysis needle or if there is no straight segment for cannulation. This is sometimes encountered in the obese arm or in those patients with mega-fistulae that are tortuous and serpentine throughout their course. That not all investigators define maturity of an AV fistula by the same criteria and that there is often not a distinction made between maturity and functionality complicate the reading of current access literature. A standardization of these terms is urgently needed.
Early Changes

The hemodynamic and biochemical changes that occur upon creation of an arteriovenous fistula are seen very quickly after the surgical anastomosis is created. Blood flow and internal diameter measurements of the brachial artery are noted to increase after the first day of surgery and continue to up to 36 weeks thereafter although the steepest rise is seen in the first four weeks. [4]

Using a mouse AVF model, Abeles [5] observed up-regulation of three classes of genes within the first week of surgery. These included genes relating to extracellular matrix formation, chemokine and PDGF signaling. Specifically, expression of genes for tenascin-C (an extra-cellular glycoprotein), thrombospondin (an adhesion-modulating protein) and lysyl oxidase (initiates the cross-linking of collagen and elastin) were not seen in control artery or vein specimens, but were significantly up-regulated in the fistula segment.

Although minimally expressed in the control samples, the gene for osteopontin involved in adhesion, is also up-regulated in the fistula samples. These biochemical changes were accompanied by parallel morphologic changes in vessel wall thickness. The peak seen at three days was felt to be a combination of increase in ground matrix and inflammatory reaction which subsequently receded.

In a rat femoral arteriovenous fistula model, Langer [6] observed dilatation of both downstream iliac vein and inferior vena cava by about 180% at three weeks post-creation. The subsequent increase in venous return to the heart caused an increased end-diastolic volume, heart rate and stroke volume resulting in increased cardiac output.

Morphologically, eccentric hypertrophy and increase in cardiac weight was observed at the 12 week point.

Matrix metalloproteinases have also been shown to be expressed in greater amounts in fistulas that mature versus those that do not. [7] MMPs are important in promoting migration of vascular smooth muscle cells (VSMC) and in matrix digestion and reorganization which leads to wall remodeling. IGF-related proteins, long known to play an important role in atherogenesis, have recently been shown to be present at significantly higher levels in stenotic areas of a fistula compared to non-stenotic segments and serum levels. [8]

The physical stimulus for all these changes is the frictional force of blood exerted on the vessel wall, also known as shear stress.

**Table 1. Changes in blood flow and inner diameter of the brachial artery following AVF creation [4]**

<table>
<thead>
<tr>
<th></th>
<th>Blood flow (mL/min)</th>
<th>Inner diameter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>baseline</td>
<td>56.2 ± 20</td>
<td>4.3 ± 7.0</td>
</tr>
<tr>
<td>day 1</td>
<td>365.0 ± 129.3</td>
<td>5.4 ± 1.0</td>
</tr>
<tr>
<td>day 7</td>
<td>438.4 ± 86.0</td>
<td>5.7 ± 0.9</td>
</tr>
<tr>
<td>day 28</td>
<td>720.4 ± 132.8</td>
<td>6.1 ± 0.8</td>
</tr>
<tr>
<td>cannulation</td>
<td>997.6 ± 259.7</td>
<td>6.4 ± 0.6</td>
</tr>
<tr>
<td>(ave day 56)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Wall thickness of AVF [5]

<table>
<thead>
<tr>
<th></th>
<th>thickness (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>baseline</td>
<td>72.06 ± 1.68</td>
</tr>
<tr>
<td>day 1</td>
<td>151.09 ± 0.84</td>
</tr>
<tr>
<td>day 3</td>
<td>220.24 ± 11.87</td>
</tr>
<tr>
<td>day 5</td>
<td>191.78 ± 2.20</td>
</tr>
<tr>
<td>day 7</td>
<td>157.16 ± 12.83</td>
</tr>
</tbody>
</table>

Directly related to blood viscosity and flow and inversely related to vessel radius, [9] shear stress provides the necessary signal for production of important anti-inflammatory and anti-coagulant proteins essential for autocrine and paracrine function that return the system to homeostasis. Vascular remodeling and vessel wall proliferation result in luminal dilation and wall thickening which promptly reduce shear stress towards baseline levels. [10]

Alongside shear stress, the transmural pressure generated within the fistula and exerted against the vessel wall activates smooth muscle resulting in proliferation and increases extracellular matrix formation and cytokine production. [11] Ironically, these forces at play that cause maturation of an AVF are the same ones, albeit in an altered imbalance, that results in neointimal hyperplasia and vessel stenosis.

**Evaluation of the Maturing Access**

It is imperative that a newly created arteriovenous fistula be evaluated at appropriate time points so that intervention or surgical revision can be expeditiously performed. Failure to promptly recognize the symptoms and signs of a non-maturing fistula will invariably result in needlessly protracted catheter use and possible loss of what would otherwise have been a functional fistula. Results with salvage are encouraging, with typical success rates in excess of 75% [12-15] and up to 95%. [16]

When confronted with a newly created arteriovenous fistula, the clinical nephrologist must systematically and deliberately evaluate whether or not maturation is occurring as expected and then make the appropriate referrals for either endovascular or surgical salvage if not. If maturation is proceeding satisfactorily, then the next question will be one of suitability for cannulation and timing of use for dialysis.

An adequate evaluation involves an understanding of the physical changes a maturing AVF undergoes over time and an appreciation of the tools available to diagnose suspected pathology.

**Timing of Evaluation**

As mentioned earlier, the changes that are observed following the surgical creation of arteriovenous fistula occur relatively quickly and are sustained for a period of time, although the steepest and most noticeable incremental change in blood flow are seen within the first two weeks [17,18] and in luminal diameter in the first month [19] post-creation.
Brachial arterial flow as measured by Doppler ultrasound shows a 549% increase from baseline to first day post-creation. [4] The incremental changes are less pronounced from that point onwards, up until the time of cannulation. These changes are mirrored by the thickness of the fistula wall. Robbin noted that the incremental change in fistula diameter and blood flow are flat between 2nd, 3rd and 4th months post-creation. [19]

It appears, therefore, that the crucial and significant majority of changes that portend of and lead to maturation of the fistula should be evident by the first month post-creation. The fistula should be evaluated at this point or the patient may be consigned to longer waiting periods and dialysis via catheter and its attendant complications including inadequate treatment, infection, micro-inflammation, malnutrition and increased all-cause mortality.

**Examination of the Maturing AVF**

Evaluation of the fistula begins with a focused, deliberate, and organized physical examination. Following the principles of bedside clinical examination, a suggested approach might be one as outlined in table 3.

Knowing how old the fistula is gives the clinician a reference point as to how much progress is expected at a given time. While a faint thrill would not be unexpected in a fistula that is one week old, it certainly would be indicative of inadequate arterial inflow in a fistula that is one month old. With the luxury of serial examinations, one can assess the impact of an intervention or revision and whether new pathology may have been uncovered by the procedure.

**Table 3. Bedside evaluation of a maturing arteriovenous fistula**

<table>
<thead>
<tr>
<th>Step</th>
<th>Information/data gathering</th>
<th>Clinical correlate</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>date of creation</td>
<td>expected changes</td>
</tr>
<tr>
<td></td>
<td>intervention or revision since creation</td>
<td>suitability for intervention or revision if needed</td>
</tr>
<tr>
<td>Look</td>
<td>visibility and location of the fistula</td>
<td>anatomy</td>
</tr>
<tr>
<td></td>
<td>collapses or softens when raised above level of the heart</td>
<td>accessibility for cannulation</td>
</tr>
<tr>
<td></td>
<td>visible dilated veins that are not part of the fistula</td>
<td>venous drainage obstruction</td>
</tr>
<tr>
<td>Feel</td>
<td>strength and quality of thrill</td>
<td>adequate arterial inflow</td>
</tr>
<tr>
<td></td>
<td>extent of thrill through fistula conduit</td>
<td>useable length of fistula</td>
</tr>
<tr>
<td></td>
<td>thrill versus pulse</td>
<td>strength of arterial inflow</td>
</tr>
<tr>
<td></td>
<td>augmentation in response to occlusion</td>
<td>unimpeded egress of blood</td>
</tr>
<tr>
<td>Listen</td>
<td>low-pitch systolic-diastolic bruit</td>
<td>adequate arterial inflow and outflow</td>
</tr>
<tr>
<td></td>
<td>faint bruit at artery-vein anastomosis</td>
<td>poor arterial inflow</td>
</tr>
<tr>
<td></td>
<td>high-pitched, especially systolic-only, bruit</td>
<td>outflow stenosis</td>
</tr>
</tbody>
</table>
A scenario in which this may be encountered is when a venous outflow obstruction is non-critical, and therefore not suspected on the basis of examination, but becomes hemodynamically and physiologically important following successful improvement in inflow either through angioplasty or a creation of a neo-anastomosis. In fact, up to one third of non-maturing fistulas have more than a single culprit lesion. [12,13,15,20-22]

Without impediment to antegrade drainage, the fistula collapses or softens significantly when the arm is raised to a level above the heart. This simple maneuver is highly reproducible and predictive except in a few instances: (1) central venous occlusion; (2) presence of collateral veins or side-branches that allow egress of blood through other channels; and (3) concomitant upstream high-grade stenosis, usually in the artery-vein anastomosis or juxta-anastomotic region.

The most striking example is that of a cephalic arch stenosis resulting in a pulsatile, tumescent, and non-collapsible brachiocephalic fistula. It is unlikely that a brachiocephalic fistula will present in this fashion in the first month post-creation, although it is a common manifestation of this vexing problem in mature fistulas. The physiologic response to any occlusion is a distension of the vessel and a pulsatile, sometimes hyperpulsatile, character as blood flowing in encounters resistance to egress. This is true whether the occlusion is an anatomic stenosis or an externally applied artificial one, such as a tourniquet or an occluding finger. This is the basis for the normal augmentation response that one looks for when evaluating an inflow lesion (see figures 1 and 2).

The most common single lesion responsible for failure to mature of an AVF is inflow restriction. This can be the artery itself or the artery-vein anastomosis, but more commonly, it is the juxta-anastomotic region of the fistula.

In any case, the physical manifestation of these lesions is identical. The fistula is poorly developed, may or may not be readily evident on cursory examination, with a feeble thrill that is very limited in physical expanse combined with varying characteristics of bruit, and an abnormal augmentation response (see figure 3).

In the presence of an efferent channel stenosis, the findings are likewise predictable. In the segment of the fistula downstream from the stenosis, findings will be similar to that of an inflow lesion. That is, the fistula may only be faintly visible but will collapse when raised above the level of the heart and the thrill will be weak. Augmentation in this segment will be abnormal.

Figure 1. Normal physical findings.
Upstream from the stenosis, however, the findings will be different. If inflow is robust, the fistula will appear engorged and may be hyperpulsatile. The thrill may be replaced by pulsations and the fistula will not flatten nor collapse when the arm is elevated. There will be high-pitched, possibly systolic-only, bruit in the area of the stenosis (see figure 4).

The presence of side-branches, another cause of failure to mature, may render the examination confusing. Maneuvers to evaluate either inflow or outflow may give false negative results depending on where the side branches are or where the occluding finger is positioned when checking for augmentation response. Even if there were a stenosis in the main channel, the presence of the side-branch would still allow the fistula to collapse upon elevation because the side-branch provides an alternative egress for blood.

Likewise, when performing the test for augmentation, if the side-branch were between the occluding and the palpating fingers, augmentation would be abnormal because the side-branch provides an alternative conduit through which pressure and flow are relieved.

The correct maneuver, therefore, would be occlude both the main channel of the fistula and the side-branch in order to assess for an augmentation response indicative of adequate inflow. This also provides a physiologic evaluation of the importance of the side-branch and it’s contribution to the fistula’s failure to mature (see figure 5).
A careful and focused clinical examination performed by a trained individual is a reliable and reproducible tool that can predict culprit lesions fairly accurately. Clinical examination had the highest positive predictive value for outflow venous lesions and lowest for lesions within the body of the fistula.

Not surprisingly, the highest negative predictive values were for lesions of the body of the fistula. [23] When compared to intra-access pressures, the clinical examination fared just as well in its diagnostic accuracy, sensitivity, and specificity (Table 4). [24]

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>inflow</td>
<td>0.85</td>
<td>0.71</td>
<td>0.84</td>
<td>0.72</td>
</tr>
<tr>
<td>body of fistula</td>
<td>0.40</td>
<td>0.84</td>
<td>0.23</td>
<td>0.92</td>
</tr>
<tr>
<td>outflow</td>
<td>0.92</td>
<td>0.86</td>
<td>0.91</td>
<td>0.87</td>
</tr>
<tr>
<td>inflow + outflow</td>
<td>0.68</td>
<td>0.84</td>
<td>0.65</td>
<td>0.85</td>
</tr>
<tr>
<td>central veins</td>
<td>0.13</td>
<td>0.99</td>
<td>0.80</td>
<td>0.80</td>
</tr>
</tbody>
</table>
Table 5. Diagnostic accuracy of physical examination and intra-access pressures in AVF [24]

<table>
<thead>
<tr>
<th>Variable</th>
<th>Physical examination</th>
<th>Intra-access pressures</th>
</tr>
</thead>
<tbody>
<tr>
<td>sensitivity</td>
<td>0.96</td>
<td>0.60</td>
</tr>
<tr>
<td>specificity</td>
<td>0.76</td>
<td>0.88</td>
</tr>
<tr>
<td>accuracy</td>
<td>0.88</td>
<td>0.71</td>
</tr>
<tr>
<td>positive predictive value</td>
<td>0.86</td>
<td>0.88</td>
</tr>
<tr>
<td>negative predictive value</td>
<td>0.93</td>
<td>0.60</td>
</tr>
</tbody>
</table>

Other Diagnostic Studies and Post-Operative Risk Stratification

Invariably, following a sedulous examination of the fistula, the clinician will have sufficient indication to move forward with additional diagnostic tests that will subsequently direct therapy. Therapy may be isolated arterial angioplasty, [25] fistula or venous angioplasty with or without an arterial component, [13,15,20,26,27] other endovascular salvage procedures aimed at assisting maturation, [28-30] or surgical revision. [31,32]

Ultrasound and color Doppler ultrasound have great utility in non-invasively identifying characteristics that place the fistula at high-risk of non-maturation.

Using intra-operative blood flow rates, a rate of < 120 mL/min had a 91% positive predictive value of the fistula not reaching maturation without intervention. [33] Berman suggests using an intra-operative blood flow of 140 mL/min for radiocephalic and 308 mL/min for brachicephalic fistulas as a threshold below which that fistula is at high-risk of non-maturation. [34] Arriving at a similar intraoperative blood flow of 160 mL/min as the threshold below which the risk for failure is significant, Won [35] further reported that fistulas with intra-operative flows of < 70mL/min all uniformly failed.

Findings on ultrasonography corroborate suspicions of lagging maturity and culprit lesions. Together with the clinical examination, these diagnostic tests are particularly helpful. Robbin concluded that a combination of 4 cm luminal diameter and a blood flow of ≥ 500 mL/min measured at one month post-creation, had 95% positive predictive value of a fistula maturing to adequacy for use. [19] Evaluating the arterial side, resistive indices were noted to be lower in radiocephalic fistulas that matured versus those that failed. This was the case when measured one and five weeks post-creation. [36]

Summary

The maturation of a surgical arteriovenous fistula is an elegant and complex process that results from physical, humoral, neural and biochemical signals and feedback. On-going investigation as to the signaling mechanisms and our ability to modulate and regulate these will be essential to our understanding of and affecting the maturation process. In the meanwhile, salvage procedures to promote maturation have been proven successful and offer a promising alternative to abandoning the fistula or consigning the patient to dialysis with a
catheter. The trained clinical nephrologist should be able to perform an assiduous and rigorous bed-side evaluation of the fistula in order to assess it’s progress and to make appropriate referrals for endovascular or surgical intervention. Post-operative risk stratification and other ancillary diagnostic tests are supportive of the clinical evaluation and should be employed to enlighten the decision-making, especially in cases where the physical examination may be ambiguous or non-revelatory.

References


Peripheral Arterial Disease in CKD

Cardiovascular disease (CVD) is the cause of death in 40-50% of End Stage Renal Disease (ESRD) patients. An individual with ESRD has a CVD mortality rate 15 times higher than the general population. In fact CVD is the leading cause of death in patients with Chronic Kidney Disease (CKD), regardless of stage. Thus, even a patient with early stage CKD is 5 to 10 times more likely to die from a cardiovascular event than progress to ESRD. [1]

Cardiovascular disease is a generic term, which includes diverse pathologies. CVD encompasses coronary heart disease, cerebrovascular disease, heart failure and peripheral vascular disease (PAD). Patients with CKD, irrespective of the type of CVD are at increased risk. Although PAD is a CVD risk equivalent, many times the presence of PAD is under emphasized as a major risk factor. Individuals with PAD are at increased risk, in part due to the high prevalence of coronary artery disease. Some studies report > 60% incidence of significant CAD (>70% stenosis of at least one artery) in all individuals with PAD. In a study at the Cleveland Clinic; 1000 cardiac catherizations were performed as pre-operative assessment for elective PV surgery. Of these one thousand catherizations 92% of patients had some degree of CAD. [2] This exemplifies the extent of CAD in individuals with known PAD.

PAD can occur in any arterial distribution and is not limited to atherosclerotic pathologies. Upper extremity occlusive disease (e.g. subclavian artery stenosis), Carotid/Cerebrovascular disease, Renovascular disease, Aortic aneurysms/dissections and Collagen vascular diseases; all fall under the umbrella of PAD. However, generally PAD is used to describe extremity atherosclerotic occlusive disease.
PAD can be defined both from an anatomical as well as a functional perspective. Anatomically, PAD is primarily extracardiac atherosclerotic disease. In the functional definition; arterial narrowing may cause a mismatch between oxygen supply and demand resulting in symptoms of intermittent claudication (I.C.) or tissue loss. Intermittent claudication (derived from the Latin word for limp) is defined as a reproducible discomfort of a defined group of muscles that is induced by exercise and relieved with rest.

Individuals with CKD are at an inherent increased risk for PAD. O’Hare and colleagues showed that in patients with CKD, there was a prevalence of 24% for PAD. [3] Again, the morbidity of lower extremity PAD is compounded by the fact that it often coexists with other conditions that are associated with adverse outcomes, such as CAD and diabetes.

Additionally, there is growing evidence that CKD itself confers increased risk for PAD; and therefore, the Inter-Society Consensus for the Management of PAD (TASC II) guidelines recognized CKD as a risk factor for PAD. [4]

PAD is also of concern because of the progressive nature of the disease and risk for amputation. For the nondialysis patient with PAD, 1 to 3% with claudication will undergo an amputation in 5 yr. [5] Among patients with ESRD, amputation for PAD is more prevalent compared with the general population. [6] In addition, revascularization procedures among dialysis patients are often associated with subsequent amputation and high mortality at 1 yr. [7] Given the increased risk and pervasiveness of PAD in CKD, it behooves practitioners to be aware of these interlinked disease processes.

**Epidemiology/Risk Factors**

PAD is a chronic, progressive, debilitating, systemic disease. Approximately 12 million Americans have PAD, as defined by an ABI < 0.9. Prevalence also corresponds with age. Thus by age 85 years, more than half have PAD. [8, 9] The incidence of PAD is around 1 million/year. This leads to an astounding 150,000 amputations done per year. Patients with impaired renal function have a greater than two-fold risk for developing lower extremity PAD. The NHANES 1999–2000 found that 24% of individuals older than 40 years who had a creatinine clearance <60 ml/min per 1.73 m², had an ABI of <0.9. [10] Furthermore, according to United States Renal Data System report, dialysis patients have an incidence of clinical symptomatic PAD of 15%. [11] Therefore, treating PAD can increase quality of life, functional status and possibly reduce CV risk and amputation. [12]

**Risk Factors**

Risk factors for PAD include: smoking, diabetes, hypertension, dyslipidemia, Sedentary life style, Age >50, Obesity and other PVD (ie AAA, carotid stenosis).

No study has examined risk factors for PAD specifically in patients with CKD. However, as mentioned earlier, CKD itself is increasingly recognized as a risk factor for PAD. Erlinger and colleagues, showed CKD confers significant risk for PAD compared with traditional factors, such as tobacco use, diabetes, hypertension, dyslipidemia and age. [13] Smoking and
Diabetes confer the greatest relative risk for PAD in non-CKD patients. However in ESRD, diabetes appears to be the most important factor for PAD risk and outcomes.

It is known that, diabetes is the leading cause of kidney disease for individuals who initiate dialysis in the United States. Dialysis patients with concurrent diabetes; have the lowest survival of 25% at 5 yr. [14] The coexistent renal disease, diabetes, and PAD belies a poor prognosis.

Table 1. Risk Factors for PAD

<table>
<thead>
<tr>
<th>Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Dyslipidemia</td>
</tr>
<tr>
<td>Sedentary life style</td>
</tr>
<tr>
<td>Age &gt;50</td>
</tr>
<tr>
<td>Obesity</td>
</tr>
<tr>
<td>Other PVD (ie AAA, carotid stenosis)</td>
</tr>
</tbody>
</table>

In addition to the high prevalence of traditional PAD risk factors in the CKD population there are unique conditions that confer increase risk of PAD. Individuals with CKD are predisposed to hyperphosphatemia, hyperparathyroidism, and chronic inflammation. All these factors have been implicated in the development of PAD. Evidence suggests that elevated serum phosphorus is an independent risk factor for PAD in dialysis patients. [15] An inflammatory state exists in dialysis patient due to a number of factors including; “uremic” factors, the dialysis techniques, and oxidative stress. This chronic inflammatory state is associated with hypoalbuminemia, Increased Homocysteine levels, elevated C-reactive protein and increased lipoprotein (a). [16, 17] All these factors have been linked to the development of PAD. [18]

In summery, CVD is the leading cause of mortality and morbidity in CKD. CVD encompasses many pathologies including PAD. PAD should be considered as CAD risk equivalent. Since, PAD is a marker for systemic arterial disease involving heart, brain, and kidneys. The patient population with CKD is particularly at risk for PAD; therefore, nephrologists must be knowledgeable about screening, diagnosis, and treatment strategies for this condition.

Vascular Access

When thinking of vascular access the venous system usually comes to mind; as this is the point for insertion of HD catheters or AV fistula repair. However as the realm of interventional nephrology grows with renal artery interventions and denervation, the importance of arterial access becomes more relevant. Therefore, this chapter focuses on techniques and complications of arterial access.
They say that the three most important things in real estate are Location, Location, and Location; this holds true for vascular access as well. One must be familiar with the anatomy in order to obtain access at the preferential site.

Although, there are other means of arterial access such as the radial or brachial artery; the common femoral artery (CFA) is the most frequently used vascular access site for performance of arterial procedures. The ideal location for access in the CFA is below the Inguinal ligament and above its bifurcation. The Inguinal ligament runs from the anterior superior iliac spine to the pubic tubercle.

It is essential that access be below the Inguinal ligament as obtaining access above the ligament will dramatically increase chances of retroperitoneal bleeding. The Inguinal ligament represents the border where the femoral artery enters the abdominal cavity. Thus access obtained above the Inguinal ligament will result in difficulty in obtaining hemostasis through manual compression because the vessel does not lay over any bony prominence, ie femoral head. Angiographic confirmation that the access is inappropriately high is obtained by noticing the entry point above the inferior epigastric artery (Figure 1).

Figure 1. Shows appropriate access; below Inferior Epigastric artery and above the bifurcation of Profunda artery and SFA.
Access is obtained too low ie in the profunda artery or superficial femoral artery, leads to increased chances of pseudoaneurysms.

Many operators try to use the inguinal crease as a landmark for locating the best access point for the CFA, but this is not reliable. The inguinal skin crease is highly variable in relation to the CFA. In elderly and obese patients the crease tends to be much lower.[19] Lechner et al evaluated 100 patients for the variability of the extraperitoneal puncture space between the inguinal ligament and the inguinal crease. The distance between the inguinal crease and the inguinal ligament varied from 0 to 11 cm (average 6.7 cm +/- 1.9 SD), the average value for women (7.5 cm +/- 1.9 SD) being significantly greater than that for men (6.3 cm +/- 1.9 SD, p = 0.0128). The bifurcation of the common femoral artery was found below the inguinal crease in 20%, at the same level in 3.5%, and above it in 76.5% of cases.

The most reliable method to denote the ideal CFA access site is to use fluoroscopy to locate the femoral head. In 97% of people the femoral artery lies on the medial third of the femoral head. [20] Additionally, access obtained at the level of the femoral head will aid in hemostasis, allowing manual compression of the CFA over the femoral head. After locating the femoral head under fluoroscopy, the location can be marked using a hemostat placed on the patient. Once the CFA is localized, local anesthetic is administered. After adequate anesthetic, the operator delineates the course of the vessel using his third and fourth fingers located over the site of maximum impulse. The needle is directed in the long axis following the course of the artery as delineated by the operator's fingers. The needle should be inserted approximately at angle of 45° and directed towards the inferomedial aspect of the femoral head. Entry into vessel is confirmed by observing brisk, pulsating flow of bright red “arterial blood” out of the hub.

If vessel can not be accessed easily; movement of the needle can be used to direct the tip to enter the artery. Once the operator is in close proximity to the artery bobbing of the needle will be noted. If the needle is bobbing vertically, advancement of the needle deeper will produce entry into the vessel. If the needle’s movement is seen to be inclining to the right; the needle should be withdrawn 1-2 cm and redirected rightward. The same principle holds true if the needle’s bobbing is seen to be towards the left. The needle should be pulled back 1-2 cm and then redirected leftward before being advanced.

Once the vessel is entered, confirmed with brisk blood flow; a wire exchange is performed using the modified Seldinger technique. [21] The originally described Seldinger technique involves puncturing both the anterior and posterior walls then withdrawing the needle back into the vessel lumen before advancing the wire. While the modified Seldinger technique involves puncture of only the anterior wall of the vessel. Use of the modified Seldinger technique decreases the risk of complications such as hematoma or retroperitoneal bleeding.

Once access is obtained the J-wire is advanced through the needle. Confirmation that the access is in the artery rather than the vein can be performed by observing the wire crossing across the spine before advancing up the aorta (in right CFA approach).

At times the wire cannot be advanced. The first step in trouble shooting is to remove the wire and confirm that the tip of the needle is still in the artery by noting brisk flow of blood from the hub. If pulsatile, brisk flow is not present the needle tip will need to be repositioned back into the vessel.

If there is brisk flow but the wire still cannot be advanced, it may be because the wire is hitting the contralateral wall. In this case the angle of entry should be reduced and/or bevel
rotated before attempting to reintroduce the wire. The wire should advance easily. Never forcefully try to advance the wire as this may mean the wire is subinitimal and aggressive deployment of the wire will lead to vessel dissection. After insertion of a J-wire, the needle is removed while securely holding the guidewire in place with the left hand. An optional step, a skin nick using the scalpel, may be made at the puncture site to ensure ease of sheath insertion.

The previously prepped and flushed sheath and dilator are then advanced over the wire, until the hub of the sheath is resting on the skin entry. The wire and the dilator are removed from the sheath. The sheath is aspirated through the side-arm. Back blood flow should be brisk. The sheath is then flushed with heparinized saline. If the sheath cannot be aspirated readily, the sheath may be against the vessel wall. The sheath should be pulled back 1 cm and aspiration should be attempted again. Once the sheath has been aspirated and refushed, the operator is ready to proceed with the endovascular procedure.

Hemostasis

After percutaneous intervention hemostasis must be achieved. This can be performed either by using manual pressure or using an approved vascular closure device. Hemostasis via manual pressure should not be undertaken until the ACT (Activated Clotting Time) is <170. Thus the sheath should be left in place until the ACT is <170 or with bivalirudin having been off for at least two hours. As a rule of thumb, manual pressure should be maintained for at least 3 minutes for every French size of the sheath. For example a 5 French sheath requires a 15 min hold. If bleeding continues, prolonged manual pressure or a FemStop Femoral Compression System (Radi Medical Systems, Inc., Wilmington, MA) can be employed. Other options include the use of closure devices, if the groin anatomy is amenable (i.e., no evidence of ipsilateral peripheral vascular disease and sheath placement is in the common femoral artery above its bifurcation).

Examples of closure devices include, appropriately sized Angioseal (St. Jude Medical, Inc., St. Paul, MN), Perclose (Abbott Laboratories, Abbott Park, IL) or Mynx Closure device (AccessClosure Mountain View, CA) in the radiographic suite, followed by 2 hours of bedrest.

Regardless of how careful and meticulous to detail an operator is, complication can occur. Recognition of possible complication can greatly reduce deleterious events. The most common complications that can occur with access:

Hematoma. This is a collection of blood within the soft tissues surrounding the entry site. Hematoma may first be recognized by noting an expanding lump at the access site. Immediate and prolonged manual pressure followed by mechanical compression ie femstop device should be employed. If bleeding from the hematoma is controlled, the hematoma will usually resolve within several weeks as the blood is reabsorbed from the soft tissues.

Retroperitoneal Hematoma (RPH). This is bleeding inside the peritoneal cavity. Symptoms that may be observed are abdominal pain, groin pain, back pain, diaphoresis, bradycardia and hypotension. If any of these signs occur immediate diagnostic testing should be undertaken ie CT of the Abdomen. Risk factors include female gender, low body surface area, double wall stick and high femoral artery puncture. [22]
Pseudoaneurysm. Or “false aneurysm”, is a collection of blood within the arterial wall. The risk of rupture increases with increased size of the pseudoaneurysm. Symptoms can include groin pain or pulsatile mass. Pseudoaneurysm is usually diagnosed with groin ultrasound. Mode of treatment is based upon size of pseudoaneurysm. Treatment includes ultrasound guided compression or thrombin injection for small pseudoaneurysm and surgical repair for large pseudoaneurysm.

Arterio-venous (AV) Fistula. Bleeding from the arterial puncture may track into the adjacent venous puncture, forming an arteriovenous fistula. Usually, an audible continuous bruit can be heard at the groin site if an AV fistula manifests. Small AVF resolve spontaneously. Surgical repair is required to repair enlarging fistulae to prevent hemodynamic compromise. AV fistula is often associated with a low groin puncture. They are confirmed with a Doppler ultrasound.

Arterial Thrombosis. Where reduced distal pulses occur following catheterization. Predisposing factors for arterial thrombosis include a small vessel lumen, peripheral vascular disease, diabetes mellitus, and female gender. [21] This usually requires surgical correction or additional percutaneous intervention. PCI therapy requires obtaining access on the contralateral common femoral artery; thereby the catherater can be delivered by going over iliac bifurcation to affected side vessel.

With the growing utilization of arterial access for percutaneous interventions; it behooves the operator to be aware of the proper techniques thereby mitigating possible complications. Additionally, there should be a keen awareness of what can go awry and how to rectify these complications. The use of good techniques and early recognition/treatment of complication will enhance patient safety and procedural success.

References


Chapter XVI

AVF Outcomes in the “Fistula First” Era

Tushar J. Vachharajani
W.G. (Bill) Hefner VA Medical Center, Salisbury, NC, US

Key Points

- History of vascular access care
  Between 1966-1980’s – AVF/AVG/CVC introduced as a viable vascular access
  1997 – KDOQI guidelines for vascular access
  2003 – NVAII established
- Trends in AVF use since 2003
  Increase in AVF in the prevalent HD patients
  Marginal improvement in AVF in the incident HD patients
- Lessons from FFBI
  Individualized approach
  Fistula first – Catheter last concept
  Pre-dialysis care
  New role for the nephrologist as a leader

Background for Fistula First Breakthrough Initiative

A well functioning vascular access is essential to provide efficient hemodialysis (HD) therapy. The three main types of vascular access used to provide maintenance HD are arteriovenous fistula (AVF), arteriovenous graft (AVG) and central venous catheter (CVC). The arteriovenous fistula was first created and described by Brescia et al. in 1966 to treat renal failure patients with hemodialysis without using any synthetic material [1]. Over the years increasing longevity of life, improvement in dialysis technology and ever expanding
eligibility for dialysis therapy has resulted in a rapid growth of end stage renal disease patients. The use of materials such as bovine and Dacron grafts to create a vascular access helped provide dialysis when a native AVF was not feasible [2,3]. The innovations in the double lumen catheter design and ease of placing a CVC to provide dialysis became prevalent in mid 1980. [4,5] The technical success with these alternate vascular accesses (AVG and CVC) led to reduction in AVF over the next decade. The change in vascular access preference in the late 1980’s and early 1990’s led to increased morbidity and mortality in the dialysis population with higher health care expenses. [6] The complications resulting from a vascular access remain the leading cause of morbidity and mortality in the HD patients. Catheter use is associated with higher rates of infection and compromised dialysis treatment [6-8]. A functioning AVF is recognized to be the most desirable access for longevity and with lowest associated morbidity and mortality rates [6,9,10]. The National Kidney Foundation first published the Kidney Disease Outcomes Quality Initiative- Clinical Practice Guidelines for Vascular Access in 1997, in an attempt to improve the outcomes related to vascular access in the United States [11]. The Centers for Medicare and Medicaid Services (CMS; the government reimbursement agency in the US) recognized the need for improving vascular access care to curtail the costs associated in the treatment of patients with end stage renal disease (ESRD). Under the direction of CMS, the End-Stage Renal Disease (ESRD) Network Program consisting of a national network of 18 ESRD Networks, responsible for each US state, territory, and the District of Columbia was established. The ESRD Network Program’s responsibilities include assuring effective and efficient administration of health care benefits and improving quality of care provided to ESRD patients [12]. The total Medicare costs for the ESRD program in 2002 was US $17 billion with vascular access related cost amounting to US $200 million. [13,14] In 2003, the CMS and the ESRD Networks adopted a project called National Vascular Access Improvement Initiative (NVAII) to increase the appropriate use of AVF for HD access. The primary goal of this continuous quality improvement project was to achieve the AVF target of 50% in the incident and 40% in the prevalent HD patients [15]. The initial goal was achieved by 2005 and the initiative became known as Fistula First Breakthrough Initiative (FFBI) with a revised national prevalent AVF goal of 66%. [15]

“Change Concepts” of FFBI

An interdisciplinary working group identified and developed 13 “Change Concepts” (Table 1). The “Change Concepts” focused on providing support for educational materials, tools for tracking outcomes and address clinical and organizational improvements that would lead to achieving the new goal of 66% AVF in the prevalent HD population. The ESRD Networks played a major role in catalyzing change, creating efficient ways to share knowledge and resources and building strong alliances with the facilities and medical professionals in their regions. The success of creating an AVF has been linked to patient characteristics, with poor outcomes reported in patients who are elderly, female, obese and those with other co-morbidities such as peripheral arterial disease, diabetes mellitus, cardiac disease and poor functional capacity [10,17-19]. The likelihood of creating a successful AVF despite these factors was 3-fold higher in Europe as compared to the United States [10]. The
main focus of “change concepts” of FFBI is to improve the AVF rate in the HD patients in the United States.

Table 1. Fistula First 13 change concepts for increasing arteriovenous fistulas [16]

<table>
<thead>
<tr>
<th>Change Concept</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Routine CQI review of vascular access</td>
</tr>
<tr>
<td>2. Timely referral to nephrologist</td>
</tr>
<tr>
<td>3. Early referral to surgeon for ‘AVF only’ evaluation and timely placement</td>
</tr>
<tr>
<td>4. Surgeon selection based on best outcomes, willingness and ability to provide access services</td>
</tr>
<tr>
<td>5. Full range of surgical approaches to arteriovenous fistula evaluation and placement</td>
</tr>
<tr>
<td>6. Secondary arteriovenous fistula placement in patients with arteriovenous grafts</td>
</tr>
<tr>
<td>7. Arteriovenous fistula placement in patients with catheters where indicated</td>
</tr>
<tr>
<td>8. Arteriovenous fistula cannulation training</td>
</tr>
<tr>
<td>9. Monitoring and maintenance to ensure adequate access function</td>
</tr>
<tr>
<td>10. Education for caregivers and patients</td>
</tr>
<tr>
<td>11. Outcomes feedback to guide practice</td>
</tr>
<tr>
<td>12. Modify hospital systems to detect CKD and promote arteriovenous fistula planning and placement</td>
</tr>
<tr>
<td>13. Support patient efforts to live the best possible quality of life through self-management</td>
</tr>
</tbody>
</table>

AVF: arteriovenous fistula; CKD: chronic kidney disease; CQI: continuous quality improvement.

**Trends in Prevalent and Incident Vascular Access in FFBI Era**

The “change concepts” provides the road map for the strategic plan to improve the AVF rate in both the incident and prevalent HD patients, which is then implemented by the ESRD Networks across the nation. Monthly data reporting from individual dialysis units includes the summary counts of the type of vascular access used at patients’ last monthly HD treatment.

A full description of data preparation is available on the FFBI website [20]. The implementation of the FFBI guidelines have resulted in several programs demonstrating an impressive growth in the AVF use (Table 2). [21]

**Increase in Prevalent AVF Use**

The initial target of 40% AVF in the prevalent HD population was reached by August 2005, 10 months ahead of schedule. The implementation of FFBI has resulted in a steady increase in AVF at an annual rate of approximately 1.3 – 3.3% [20,27]. As of July 2011, the prevalent AVF rate in the United States is 59.2%. The annual trends of prevalent AVF, AVG and CVC are shown in Figures 1 and 2.

Figure 3, 4 and 5 shows the overall prevalent AVF use rate by individual ESRD Network between 2003 and 2011. At an individual Network level the prevalent AVF use ranged from 30.5% to 54.1% in 2004, this improved to 52.3% - 65.9% by October 2010. A total of 13
Networks had AVF usage between 50 and 60% by October 2010. The success of achieving the target has resulted in increasing the AVF goal for prevalent HD patients to 66%.

Table 2. Examples of programs with a documented increase in AVF following K/DOQI guidelines or Fistula First

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Description</th>
<th>% AVF Before (Incidence/Prevalence)</th>
<th>% AVF After (Incidence/Prevalence)</th>
<th>Main Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascher et al. 2000 [22]</td>
<td>Retrospective, 1996 to 1999, n = 247 patients with 99 AVF and 122 grafts</td>
<td>5% use in 110 patients</td>
<td>68% use in 137 patients</td>
<td>Application of K/DOQI recommendations</td>
</tr>
</tbody>
</table>

AVF, arteriovenous fistula; CVC, central venous catheter; K/DOQI, Kidney Disease Outcomes Quality Initiative; PDSA, Plan–Do–Study–Act. Percentage of AVF+ graft at initiation over noncatheter accesses placed that year (CVC excluded). (Reprinted with permission from article by Lok [21].)

Decrease in Prevalent CVC Use

The chronic CVC use, defined as CVC in place for ≥ 90 days, has declined since the implementation of FFBI. As shown in figure 1, the chronic CVC use has declined by about a third from 13.8% to 8.8% and is consistent with the KDOQI guideline recommending <10% use [28]. The total CVC use has improved only marginally between 2003 and 2011 primarily because 80% of the incident ESRD patients start hemodialysis with a CVC.
Along with the rise in arteriovenous fistula (AV) use and decline in arteriovenous grafts, total central venous catheter (CVC) use initially increased. However, in recent years both total CVC use and long-term CVC use have steadily declined. Data from Fistula First Data [20]

Increase in Incident AVF Use

The AVF use in the incident HD patients in the United States remains low. The FFBI Annual Report 2011 prepared by the Mid-Atlantic Regional Coalition highlights the continuing low number of incident HD patients starting with a functioning AVF.

Data Sources: For December 1995-1997 and 1999-2002 measures, Finelli, L., Miller, J. T., Tokars, J. I., Alter, M. J., Arduino, M. J. National surveillance of dialysis-associated diseases in the United States, 2002. Seminars in Dialysis. 2005;18(1):52–61. No measurement taken in 1998. For December 2003 – 2009 and October 2010 measures, http://www.fistulafirst.org/AboutFistulaFirst/FFBIData.aspx. AV fistula use is the percent of prevalent hemodialysis patients dialyzing with an AV fistula, regardless of the presence of another access type. AV graft use is the percent of prevalent hemodialysis patients dialyzing with an AV graft, regardless of the presence of another access type. Total CVC use is the percent of prevalent hemodialysis patients dialyzing with a CVC; the calculation includes CVC with AV fistula, CVC with AV graft, CVC < 90 days no other access present and CVC ≥ 90 days no other access present. CMS changed the denominator definition for FFBI vascular access measures in March 2010. Prior to March 2010, the FFBI vascular access denominator was the sum of patients with AV fistula only, AV graft only, AV graft with AV fistula, CVC with AV fistula, CVC with AV graft, CVC < 90 days no other access present, CVC ≥ 90 days no other access present, other access, and missing access type. Beginning in March 2010, the FFBI vascular access denominator was calculated as the sum of patients with AV fistula only, AV graft only, AV graft with AV fistula, CVC with AV fistula, CVC with AV graft, CVC < 90 days no other access present, CVC ≥ 90 days no other access present, and other access.

Figure 1. US Trends in AV Fistula1, AV Graft2 and Total CVC3 Use, December 1995 through October 2010, with Trend in AV Fistula Use Prior to FFBI Projected Forward4.
Figure 2. United States trends in prevalent hemodialysis arteriovenous fistula, arteriovenous graft, total central venous catheter and central venous catheter greater than or equal to 90 days use, July 2003–October 2010.

Figure 3. Prevalent AVF Use Rate by Network, July 2003 - July 2011.

1AV fistula use is the percent of prevalent hemodialysis patients dialyzing with an AV fistula, regardless of the presence of another access type.

Figure 4. Percent of Prevalent Hemodialysis Patients with an AV Fistula in Use1, US and Networks, October 2004 and October 2010, In Comparison to FFBI Goal of 66%.
Figure 5. Map of the United States divided by ESRD Networks with percent of prevalent hemodialysis patients with an AV Fistula in use, October 2010.

In 2009, 14.3% of incident population had a functioning AVF, which is a marginal improvement from 12.7% in 2003. ESRD patients with an AVF in place (not necessarily functioning) at the time of starting HD during this same period had improved from 24.7% to 35.0%). Figure 6 shows the growth of the incident AVF from 2003 to 2011.

Is FFBI Target of 66% AVF Realistic?

The initial success of achieving the FFBI target ahead of time in August 2005, lead to raising the target of prevalent AVF in the United States to 66%. The big concern in the nephrology community has been whether this target is realistic and achievable? A recent study evaluated the feasibility of achieving this target over a 40-month period from January 2007 to April 2010. The monthly data collected from 4064 HD facilities with at least 10 HD patients was analyzed. The mean prevalent AVF use increased by 10% (45.3% to 55.5%) and the percentage of facilities achieving the target of 66% AVF for at least 1 month increased from 6.4% to 19.0% [29]. The primary reason for achieving the goal in these facilities is from successful conversion of CVC to permanent access within the first 90 days. The study also highlights the significant role of a vascular access nurse/coordinator in the dialysis clinic.

Lessons Learned from FFBI

Individualized Approach

The goal of FFBI is to create awareness about the role of AVF and ultimately reduce the morbidity and mortality associated with vascular access. The common misconception that an “AVF at any cost” is the “optimal” approach has led to criticism and suggestions for change in FFBI approach. The primary intent of FFBI from its inception has been to evaluate every ESRD patient for an AVF, and to individualize for suitability.
The process of individualization helps in recognizing the fact that a segment of the population may either have an unsuitable vascular anatomy for an AVF or may have multiple co-morbidities increasing the risk of maturation failure [24,30-32]. The FFBI is not based on extensive evidenced based literature. The patient characteristics such as age, cardiovascular status, limited life-expectancy and multiple co-morbidities may result in maturation failures. The high primary failure rate with AVF remains a major hurdle in improving the AVF rate in the incident HD population [30,33,34].

Moreover, the number of interventions required to facilitate the maturation process needs to be evaluated further in randomized studies. An average of 1.45 to 3.3 procedures per AVF are needed to assist with the maturation process [35,36]. The risk of hospitalization in patients with primary AVF failure also remains high [37]. On the contrary, a well functioning AVF has lower complication rates and excellent long term patency rates [38].

**Fistula First, Catheter Last**

The ideology behind the 66% target is to accept that every patient is not an ideal candidate for AVF. An alternate vascular access such as AVG in the prevalent population may have a possible role, especially in reducing the CVC use. The shorter duration for AVG maturation may have a role in reducing the percentage of patients using CVC for dialysis. There is early data to suggest that cumulative patency rates of AVF and AVG may not be different if the AVF with primary failures are excluded [39].

In the event of thrombosis, the success of endovascular intervention and resultant 6-month patency rate has been reported at least in one series to be higher with AVG compared to AVF (63% vs. 22%) [36]. Similarly, the patency of AVG is reported to be superior to AVF with a second access [40]. Finally, the overall morbidity and mortality has been found to be significantly better with AVG when compared to CVC in prospective studies [41,42]. The appropriate use of AVG in the dialysis population may be justified in adopting and balancing the policy of “AVF first but CVC last” [43].

![Figure 6. Incident AVF use from July 2003 to July 2011 in the United States.](image-url)
Improve Pre-Dialysis Care

The AVF rate in the incident ESRD population in the United States has remained low despite a minimum of 6 months of follow up with a nephrologist [44]. Several hurdles that need to be crossed and include: patient denial, lack of vascular access education, delay in referral process and evaluation, and variable surgical skills [45-47]. There is an urgent need to improve support and education of the primary care physicians for early referral, develop a national level consensus to create trigger points to improve the referral process and involve the surgical community to standardize the training program [44]. A recent proposal from FFBI to initiate a “30-20-10” mnemonic as an appropriate trigger point for referral is under consideration [44].

A referral to the nephrologist at an estimated glomerular filtration rate (eGFR) of 30ml/min, referral for permanent vascular access creation at eGFR of 20ml/min and initiation of dialysis at around a eGFR of 10ml/min [44].

Additional Leadership Role for Nephrologist

The nephrologist needs to play a lead role in the management of vascular access. The nephrologist can make certain that a proper surgical referral process is in place and continue to follow up even after the access has been placed, thus can appropriately intervene if there is a delay in the maturation process. The nephrologist can assist with the selection of patients for referral for AVF or AVG as a primary access, especially in elderly patients with limited life expectancy [18] or those with a likelihood of requiring multiple interventions to achieve a successful functioning AVF, thus reducing the number of patients being treated long term with a CVC [37,48]. As a medical director of a dialysis center, the nephrologist can develop and implement quality assessment and performance improvement measures to impact the vascular access targets [44].

Conclusion

The AVF use in the prevalent HD population in the United States increased significantly since the inception of K/DOQI Guidelines in 1997 and FFBI in 2003. The provision of education resources, implementation of the policies and “change concepts” and creating an awareness of the benefits of AVF have all contributed to this success. The lessons learned from the ongoing evaluation and analysis of the data will certainly help identify the ideal population that will benefit the most with this strategy of ‘fistula first’. The role of AVG as an alternate access in select group needs to be better defined with the ultimate goal to reduce the CVC use. The need to improve AVF placement in incident HD population remains a continuing challenge.
References


IV. ARTERIOVENOUS GRAFT
**Introduction**

Arteriovenous graft (AVG) is considered as the second choice for hemodialysis vascular access after arteriovenous fistula (AVF) due to the common concept of higher risk of infection and possibly shorter lifespan. The AVG is usually reserved for patients that lack proper superficial veins for the creation of AVF. However, some argue that the AVG should be considered as a first choice in subsets of end stage renal disease patients such as those with multiple comorbidities, octogenarians [1], short life expectancy, and those requiring initiation of dialysis within a short period of time in order to avoid the insertion of a tunneled dialysis catheter. Although the AVG also carries the advantage of early cannulation, ease of needle insertion, and lesser incidence of early failure, it is plagued with long term complications including most commonly dysfunction related to stenotic lesions that, if not treated promptly and properly, restrict the flow within the graft leading eventually to complete cessation and thrombosis. Other common complication is the development of pseudoaneurysms. Other less common complications include infection, seroma and hand ischemia. Our focus in the following discussion will be on stenosis and thrombosis.
I. Stenosis

A. Incidence and Location

A review of 309 patients receiving hemodialysis via an AVG, the cumulative likelihood of symptomatic stenosis at 2 years was 67% for the vein-graft anastomosis (VGA), 19% intragraft, 16% venous outflow, 13% central vein stenosis (namely in those with prior history of ipsilateral dialysis catheters) and 5% for the artery-graft anastomosis (AGA) [2].

A review of 2,300 angiogram cases revealed the following anatomic distribution of stenoses: VGA 60%, peripheral vein 37.1%, intragraft lesions 38.4%, central veins 3.2% and mixed lesions 31.3% [3]. Inflow stenosis were considered uncommon in earlier reports with prevalence of <5%, however, more recent ones showed inflow stenosis to be as high as 29% [4].

B. Clinical and Non-Clinical Indicators

There are often clinical indicators of stenotic lesions along the inflow, graft or venous outflow. A diminished pulse and thrill along the graft and decreased arterial chamber pressure on dialysis are usually indicative of inflow stenosis. Difficult cannulation along the graft or increased pulse and diminished thrill along the juxta-arterial segment of the graft associated with diminished thrill and pulse along the rest of it are suggestive of intragraft stenoses. An increased pulse throughout the graft and diminished thrill usually indicate an outflow stenosis (VGA and/or outflow veins). A diffuse swelling of the upper extremity suggests central vein stenosis. A high-pitched bruit is usually heard over severe stenotic lesion (see also chapter “The Role of Physical Examination…”).

A non-clinical indicator of graft dysfunction includes increased venous pressure (dynamic or static) and usually indicates an outflow problem. A decreased access flow (Qa) to <600mL/min and namely the rate of drop in the Qa by >25% can indicate either inflow and/or outflow problems.

C. Pathology

It has been well established that the stenotic lesion that affects the VGA and juxta-anastomotic vein in the AVG stems from neointimal hyperplasia. This consists of an amalgam of 1) \(\alpha\)-smooth muscle cells further characterized as myofibroblasts, 2) abundance of extracellular matrix, 3) angiogenesis within the neointima and adventitia, 4) macrophage layer lining the perigraft and 5) an increased expression of mediators and cytokines [5].

D. Therapeutic Options

These include either percutaneous intervention or surgical revision. According to the Kidney disease -Dialysis Outcome Quality Initiative (K-DOQI) guidelines, treatment of the
stenotic lesion is recommended when there is >50% decrease in the luminal diameter AND association with one of the following: abnormal physical findings, decreased access flow to <600mL/min and increased static pressure. Additionally, if angioplasty of the same stenotic lesion is required >2 times within 3 months, a surgical revision should be considered. The elective correction of symptomatic stenotic lesions may reduce the rate of thrombosis, however, it does not appear to increase the useful lifespan of the AVG.

Figure 1. a) Left upper arm brachial artery to brachial vein loop AVG with initial angiogram showing a severe stenotic lesion at the VGA involving juxta-anastomotic brachial vein (dashed black arrow). The graft itself was exempt from stenosis (full black arrow). The brachial vein (solid white arrow) proximal to the VGA had poor filling prior to angioplasty.

b) Post-angioplasty (7mmx4cm balloon) image: Note the better filling of the outflow vein (solid white arrow) and the good response to angioplasty at the stenotic lesion (dashed black arrow).

Figure 2. a) Inflow lesions noted on the initial arteriogram with the tip of the angiogram catheter (*) in the axillary artery. Note the stenotic lesions along the brachial artery (solid black arrow) proximal to the AGA (dashed black arrow). b) Post-angioplasty (5mmx4cm balloon) image of the inflow lesions along the brachial artery (solid black arrows) and AGA (dashed black arrow).
E. Description of the Percutaneous Angioplasty Procedure and Outcomes

Based on the clinical background, the AVG is accessed with an 18g needle in an antegrade direction if the problem appears to be with the outflow or in a retrograde fashion if the problem appears to be with the inflow. If there is suspicion of both inflow and outflow lesions, the graft is then accessed close to the tip of the loop in a way that the sheath can be flipped in one direction or another. The alternative is to cannulate the AVG with 2 sheaths in opposite direction. After the cannulation with the 18g needle, a guidewire is introduced followed by the insertion of either a 6Fr or 7Fr sheath. An angiogram is then performed to identify the stenotic lesions. A guidewire is passed beyond the stenotic lesion. A 7mm or 8mm angioplasty balloon is usually used for the VGA unless it is a freshly inserted anastomosis (<4 weeks old) where the balloon should match the inner lumen of the graft (i.e. if it is a 6mm graft, we then use a 6mm balloon; personal opinion). The venous outflow lesions should be angioplastied with a balloon that is tailored to the caliber of the vein proximal and distal to the lesion. The balloon can be oversized by 1mm in the veins or within the well incorporated graft, however, it should be tailored to the caliber of the graft at the AGA level since some grafts are tapered (4 to 6mm or 4 to 7mm) and taking into account the caliber of the juxta-anastomotic artery (figures 1 and 2). The expected results of the angioplasty are: <30% residual stenosis and primary patency of 50% at 6months. The expected result from a surgical revision is a primary patency of 50% at 1 year according to the K-DOQI guidelines.

F. The Role of Stenting of the VGA

The role of stenting of the VGA still needs further evaluation before its adoption. Comparative studies between percutaneous transluminal angioplasty (PTA) alone and PTA with stent deployment mostly showed no significant difference in the cumulative patency between the 2 groups as summarized in table 1 [6-12]. The study by Haskal et al. has received much publicity due to significant impact on primary patency of the access circuit at 6months in the stent graft group but failed to report on the cumulative patency of the access circuit that showed no difference between the 2 groups at 6 months. This study has also other limitations that are discussed separately (see chapter on “Endovascular Stents” for further discussion). Two ongoing studies have completed enrolment of patients with dysfunctional AVG that were randomized to either angioplasty alone or angioplasty with stent graft deployment. The phase IV RENOVA study on the Flair™ stent (C.R. Bard, NCT00677235) will report on access circuit patency at 12 and 24 months and primary and secondary patency at 6,12 and 24 months. The phase III REVISE study on the Viabahn® stent (W.L. Gore and associates, NCT00737672) will report on target lesion primary patency, assisted primary and secondary patency at 24 months. While we are waiting for the results of these studies, it is recommended to follow the K-DOQI guidelines with the reservation of the use of stents for: 1) surgically inaccessible lesion, 2) contraindication to surgery or 3) angioplasty induced vascular rupture. References from top to bottom: 6 to 12; AVG: arteriovenous graft; DE: duration of efficacy; N/A: not available; NR: non-randomized; NS: not significant; PTA: percutaneous transluminal angioplasty; rec. periph.: recurrent peripheral; RT: randomized trial; st.: stenosis.
G. Prevention

The focus of the prevention of stenosis is on the prevention of neointimal hyperplasia. There is a large number of reports incriminating the graft material (bovine carotid artery vs. polytetrafluoroethylene) and design (cuffed vs. non-cuffed, externally supported vs. non-externally supported etc.), graft caliber (6mm vs. tapered 6-8mm, etc.) and surgical technique (namely the type of sutures at the anastomosis and the angle formed by the graft at the VGA and AGA) with some potential impact on decreasing the rate of neointimal lesions and providing better primary and secondary patency, however, no specific recommendation has been adopted to date.

Local therapy (i.e. addressing the neointimal hyperplasia at the VGA directly with disease modifying agents) has been tackled in the last decade with some promising short term results in animal models.

However, NO breakthrough has been achieved in humans to date using different agents. External beam radiation has failed to produce any positive result [13].

Vascular endothelial growth factor D (VEGF-D) gene therapy was terminated for “strategic reasons” (NCT00895479). Drug eluting perivascular wrap study on Paclitaxel-eluting mesh (Vascular Wrap™) was terminated for “imbalance in the number of infected grafts” (NCT01033357).

Another study on endothelial cell loaded gel foam wraps (Vascugel®) was supposed to be conducted in multi-center randomized-controlled trial has not been launched due to the lack of funding.

There are pending results on Recombinant Elastase (PRT-201) local therapy on AVG and AVF as well as on Sirolimus eluting wraps. (See also chapter “What the General Nephrologist Needs to Know about Neointimal Hyperplasia”).

<table>
<thead>
<tr>
<th>Study Year (Type)</th>
<th>Stent</th>
<th>Indication for stent deployment</th>
<th>Stent group n/Control group n/PTA only n</th>
<th>Procedural success Stent/PTA</th>
<th>1st patency post intervention/6mos</th>
<th>1st patency post intervention/6mos Stent</th>
<th>1st patency post intervention/6mos PTA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bechard 1993 (prospective RT)</td>
<td>Gianturco</td>
<td>Venous anastomosis stenosis &gt;50%</td>
<td>28/30 + historical EVS</td>
<td>N/A</td>
<td>N/A</td>
<td>DE</td>
<td>DE</td>
</tr>
<tr>
<td>Quinn 1995 (prospective RT)</td>
<td>Gianturco</td>
<td>Venous anastomosis stenosis &gt;50%</td>
<td>40/47</td>
<td>N/A</td>
<td>N/A</td>
<td>27%</td>
<td>51%</td>
</tr>
<tr>
<td>Hofer 1997 (prospective RT)</td>
<td>Wallstent</td>
<td>Recurrent within 6mos</td>
<td>1/2/20</td>
<td>100%</td>
<td>100%</td>
<td>56%</td>
<td>53% [p=NS]</td>
</tr>
<tr>
<td>Sroka et al. 2005 (observational)</td>
<td>SMART + plaxcell</td>
<td>Thrombosed AVG with elastic recoil or rec. periphe/neointima</td>
<td>34/35</td>
<td>N/A</td>
<td>N/A</td>
<td>63%</td>
<td>12%</td>
</tr>
<tr>
<td>Vogel 2005 (prospective, NR)</td>
<td>SMART</td>
<td>Elastic recoil or venous rupture or rec. periphe/neointima</td>
<td>25/35</td>
<td>100%</td>
<td>97%</td>
<td>67%</td>
<td>8.2/mos</td>
</tr>
<tr>
<td>Ekele 2009 (observational)</td>
<td>Wallstent</td>
<td>Failed PTA or rec. stenosis within 3 mos</td>
<td>25/34</td>
<td>93%</td>
<td>97.7%</td>
<td>39.3%</td>
<td>72.4% [p=0.02]</td>
</tr>
<tr>
<td>Haskal 2010 (prospective, RT)</td>
<td>Flair</td>
<td>Dysfunctional AVG</td>
<td>97/83</td>
<td>94%</td>
<td>79%</td>
<td>38%</td>
<td>20% [p=0.003]</td>
</tr>
</tbody>
</table>
H. Complications of Angioplasty

Bleeding at the angioplasty site of the graft, VGA or venous outflow is usually graded based on the impact on the flow within the access circuit and expansion of the peri-vascular extravasation or vascular rupture. The mild extravasation usually responds well to balloon tamponade. The moderate to severe extravasations that do not respond to balloon tamponade are usually treated with stent graft.

II. Thrombosis

A. Incidence and Causes

Schild et al. reported a thrombosis rate of 25% in AVG compared with 9% in AVF in 1,700 consecutive accesses with significantly better salvage rates in AVG than AVF [14]. The identification of a flow limiting stenotic lesion is prevalent in the majority (>85%) of thrombosed grafts. A small number of thrombosed grafts could be attributed to dialysis-associated or post-dialysis hypotension and the rest due to unknown causes. The association of thrombophilia and graft thrombosis has not been established [15].

B. Clinical Exam

The thrombosed graft should be assessed prior to pursuing a thrombectomy procedure. The history of present illness and access history including prior intervention(s) and orientation of the graft are first reviewed. Caution should be exercised in patients with severe cardiopulmonary disease and low oxygen reserve to minimize the clot migration to the pulmonary circulation and avoid massive radiocontrast and fluid volume administration. The graft is then examined. Beside the absence of thrill to palpation and bruit to auscultation, the inspection of the graft is important with attention to the surgical incisions, presence of extension grafts and pseudoaneurysms that may interfere with the cannulation of the graft or present a challenge in clearing the clot burden from within their lumen. More importantly, the presence of erythema (usually with tenderness to tapping) and/or purulent drainage from the clotted graft, suggestive of infection, is an absolute contraindication to percutaneous thrombectomy. Patients with infected graft should be referred promptly to a vascular surgeon for the resection of the infected graft material along with the administration of intravenous antibiotic.

C. Prevention

Although the prevention of thrombosis seems tightly linked with the prevention of stenosis, other therapies have been attempted to address directly the thrombus formation. Different agents such as anti-platelets and anticoagulants have been used for that purpose. A
combination of dipyridamole and aspirin has been the subject of a large multi-center randomized double-blind placebo-controlled trial with a modest clinical improvement but statistically significant difference in 1-year primary unassisted patency (28% in the treatment group vs. 23% in the placebo group). However, the cumulative patency did not differ between the 2 groups with an additional cost of around $2,700 per annum in the treatment group [16]. In a small-randomized controlled trial, 12 patients were assigned to 4g of fish oil after graft insertion and 12 patients were assigned to 4g of control oil [17]. One year primary patency rate was significantly higher in the treatment group (75.6% vs. 14.9%). This led to the design of the FISH study that is a multi-center randomized double blind placebo-controlled trial that involves 232 patients with newly inserted grafts that will be assigned to either fish oil or placebo with primary end point of primary patency at one year [18]. The results of this completed trial are pending (see also chapter on “Medications and Vascular Access Patency”).

In summary, it is still premature to make a recommendation for any specific prophylactic therapy to date. The role of surveillance compared to monitoring alone in the prevention of thrombosis is a fairly controversial subject of discussion and debates [19]. However, in my opinion, although equally effective, when a clinical monitoring program cannot be reinforced, a surveillance program shall then be an accepted alternative and is often easier to implement in some dialysis centers.

D. Different Methods of Thrombectomy of AVG

Earlier reports from the 1980’s and 1990’s showed better outcomes with surgical thrombectomy over percutaneous thrombectomy as reviewed in a meta-analysis by Green et al. [20]. However, data since 2002 showed similar results in both techniques [21]. The percutaneous thrombectomy can be offered more expeditiously (if available), prevents the need for unnecessary dialysis catheter insertion or hospitalization and allows a simultaneous assessment/treatment of the access circuit stenoses in a rather short period of time without the need for general anesthesia. Hence, the percutaneous thrombectomy has gained more popularity over the last decade. The two different modalities should still be regarded as complementary to each other. If one fails, the other can be attempted, although it is important to note that surgical salvage of a thrombosed AVG after an unsuccessful percutaneous intervention is rarely feasible and often leads to the revision or insertion of a new AVG [22].

The surgical thrombectomy involves an incision close to the VGA followed by the clearance of the venous outflow from the clots. An embolectomy catheter is then passed through the same incision across the arterial anastomosis and used to sweep the entire length of the graft. Additional interventions are also performed including intra-operative angiogram and angioplasty, patch angioplasty of the VGA stenosis or revision of the VGA with an extension graft.

The percutaneous thrombectomy has evolved over the last 3 decades from the 1) use of thrombolytic therapy alone, also known as pharmacologic thrombectomy that consisted of using prolonged systemic infusions of Streptokinase and later Urokinase (associated with poor results, prolonged infusion time and increased bleeding complications) [23] to the 2) use of local thrombolytic therapy in conjunction with other techniques such as “lacing-maceration” [24] and “lyse-and-wait” [25] also known as pharmacomechanical
thrombectomy that consisted of using intragraft instillation of thrombolytic agent (Urokinase and later Retavase, Alteplase, etc.) with or without Heparin through either single hole catheters or pulse-spray catheters (noted to be more successful yet still time consuming with less bleeding complication) coupled with angiogram/angioplasty of stenotic lesions and the use of an embolectomy balloon (for the “lyse-and-wait” technique) to 3) mostly the abandonment of the thrombolytic therapy and reliance on the mechanical thrombectomy using embolectomy balloons/catheters with over the wire option (e.g. 4fr Fogarty Embolectomy Catheter, Edwards Lifesciences, Irvine, CA, US) coupled with thromboaspiration, and/or the use of a thrombectomy device that either macerates (e.g. Arrow Trerotola PTD, Arrow International/ Teleflex, Research Triangle Park, NC, US), or microfragments and simultaneously aspirates the thrombus using either a high velocity normal saline jet (e.g. Angiojet Ultra Xpeedior or Angiojet Ultra AVX, Medrad Interventional/ Possis, Warrendale, PA, US) or an encapsulated impeller (e.g. a rotating helical screw/Thrombex PMT, Edwards Lifesciences).

There is a plethora of reports on these different techniques and their outcomes as well as randomized controlled trials comparing the different percutaneous techniques or percutaneous versus surgical that are beyond the scope of this chapter. Hence, I will focus on describing the mechanical percutaneous thrombectomy.

E. Description of Percutaneous Thrombectomy Procedure

The commonly performed procedure by the interventional nephrologists utilizes an embolectomy balloon and less commonly an adjunctive thrombectomy device. Although different centers have special and modified ways of doing the thrombectomy procedure, these are the usual steps that are followed in our center without any claim of superiority over other approaches:

- The graft is initially cannulated with two 7fr sheaths pointing in opposite direction. One is antegrade pointing toward the venous outflow and one retrograde pointing toward the arterial inflow. The latter is usually placed along the graft close to the VGA.

- A guidewire is then passed via the antegrade sheath, manipulated through the VGA and passed to the central veins. A 5fr straight angiogram catheter is then mounted on the wire and advanced to the central veins followed by the removal of the guidewire. A central venogram is performed to assure the patency of the central veins. 5,000 units of Heparin and sedatives are then administered. A “pull back” angiogram is sometimes performed to study the venous outflow in the upper arm namely if there is suspicious anatomic problem or to assess the clot burden.

- An angioplasty of the venous anastomosis and venous limb of the graft is then performed followed by the use of the angioplasty balloon as a “dam” at the VGA. A 4fr embolectomy balloon (typically 9mm in inflation diameter) is then passed across the AGA, inflated to minimal pressure and then pulled into the graft, sweeping its entire length and while aspirating simultaneously from the sheath(s). This procedure is repeated until a pulse is noted along the graft with good flow through the sheaths. The 4fr embolectomy catheter is then reintroduced and used to occlude the inflow
along the arterial limb of the graft. The angioplasty balloon that was used as a dam at the VGA is then pulled back toward the graft sweeping in a retrograde fashion the clots along the VGA and juxta-anastomotic graft and while aspirating from both sheaths (figure 3). The angioplasty balloon is then removed, followed by a final antegrade sweep with the 4fr embolectomy balloon.

- If there are remnant/adherent intra-luminal thrombi within the graft or outflow veins that cannot be extracted by the technique described in the previous step, a mechanical thrombectomy device (Arrow Trerotola PTD in our center) is then used to clear these thrombi. We do NOT advocate the “polishing” of the remnant thrombi in an antegrade fashion into the pulmonary circulation i.e. deliberate embolization (see complications paragraph below) (figure 4).

- Following this step, further venous angioplasty could be performed if deemed necessary. Attention is then shifted to the inflow. An arteriogram is then performed with a catheter placed in the feeding artery to rule out stenotic lesions along the arterial system, AGA and arterial limb of the graft that are then dilated with appropriately sized angioplasty balloons. The arteriogram is also important for ruling out distal arterial embolization, namely in the forearm branches that should always be studied including in patients with upper arm AVG.

- After the establishment of flow and treatment of the anatomic lesions, the guidewires and sheaths are removed. The cannulation sites are then covered with a special band-aid and occasionally a figure 8 suture is applied for hemostasis.

![Figure 3](image)

Figure 3. a) During the thrombectomy procedure of a curved left upper arm brachial artery to proximal basilic vein AVG, the embolectomy catheter is passed past the AGA (solid black arrow), inflated to minimal pressure followed by the sweeping of the graft in an antegrade fashion (direction of the black dashed arrow) to the sheath while applying thromboaspiration from the side ports of the sheath. b) The embolectomy balloon is reintroduced to occlude the inflow (solid black arrow) while pulling back the angioplasty balloon (solid white arrow) that was inflated initially as a dam at the venous outflow/VGA and later pulled back into the graft while applying thromboaspiration. The angioplasty balloon is then removed and while the embolectomy was still inflated at the inflow, it is pulled out in an antegrade fashion for the final sweep. c) An arteriogram shows great flow within the graft with no further residual clots or stenoses.
Figure 4. a) A filling defect consistent with a thrombus (solid black arrow) noted along the left subclavian vein (SCV). b) A thrombectomy device (Arrow Trerotola PTD) is used to clear the thrombus during a thrombectomy procedure. c) Central vein venogram post removal of the thrombus.

F. Outcomes of Percutaneous Thrombectomy Procedure

Between December 2001 and end of June 2011, we have performed 3,387 thrombectomies on AVG out of 31,245 encounters (10.82%). 3,128 (92.35%) were successful in achieving at least 1 dialysis session (i.e. clinical success), 111 (3.28%) were aborted mostly due to the inability to cross the anastomoses (namely VGA), and 148 (4.37%) were unsuccessful.

The goal set by K-DOQI for clinical success rate of at least 85% with primary patency of 40% at 3 months after percutaneous thrombectomy and 50% at 6-months/40% at 1 year after surgical thrombectomy. Percutaneous thrombectomy of AVG within 60 days from its insertion (i.e. AVG with early failure) has been associated with poor secondary patency, very poor technical success and fairly high rate of stenotic lesions that are not amenable to angioplasty (62% and 33% in the <30 and <60 days old AVG, respectively) [26].

G. Complications of Thrombectomy Procedure

Bleeding complications are not uncommon and are managed in the same fashion as delineated under complications of angioplasty. The most concerning complications of the thrombectomy procedure are pulmonary embolization and distal arterial embolization of the limb. A right to left heart shunt with severe pulmonary hypertension, although uncommon and often unrecognized by the patient upon the provision of medical history, adds an additional risk of systemic embolization. The embolization of the pulmonary circulation is a well-recognized complication but often asymptomatic.

We strongly feel in our center that the deliberate embolization of the pulmonary circulation should not be a common practice despite the “reassurance” from different reports on the “relative safety”. Our concern stems from the lack of proper studies on the long-term impact of this practice on the cardiopulmonary system especially in patients with severe cardiopulmonary diseases or the cumulative burden in those with frequent graft thrombosis [27].
The arterial embolization is uncommon (1-7%). Despite this low rate, it is important to evaluate the arterial branches post thrombectomy. There are different techniques we use to extract these emboli. We primarily rely on direct catheter aspiration or the use of over the wire low profile angioplasty balloon or regular embolectomy catheter to extract these emboli coupled with aspiration.

**Conclusion**

In conclusion, the AVG remains an important hemodialysis access that many lives of patients afflicted with end stage renal disease depend on. Challenges remain ahead of us in regards to the maintenance of this lifeline. Despite the advances in the pathophysiology of the AVG dysfunction and targeted therapy, there is no breakthrough remedy that has emerged to abate the occurrence of neointimal hyperplasia-induced stenotic lesions and thrombosis. Hence, we should continue to be well educated, prepared and well equipped to deal with these complications with a concerted effort between nurses, nephrologists, interventionalists and surgeons that should work as a team and address each and every dysfunctional AVG on an individual basis in order to provide the best access patency and avoid dialysis catheters.

**References**


Chapter XVIII

Pseudo-Aneurysms in Dialysis Access

Karn Gupta
Wake Nephrology Associates, Raleigh Access Center, NC, US

Introduction

Vascular access is considered the lifeline of hemodialysis patients. It has also been referred to the Achilles heel of such patients. Of the various options available, arterio-venous fistulae (AVF) and arterio-venous graft (AVG) remain the preferred choice for long-term AV access. Proper functioning of these vascular accesses are essential for ESRD patients.

Both AVF and AVGs are at risk of developing pseudo-aneurysms due to multiple factors. These pseudoaneurysms can lead to access failure secondary to thrombosis, infection and acute rupture. These could also limit the cannulation sites available for dialysis needle insertion. Incidence rates have been reported to range from 2% to 10% [1,2] Given the fact that only limited sites are available for creating a vascular access, it is extremely important to preserve an existing access for as long as possible.

Definition

Pseudoaneurysms arise from a disruption in vascular wall continuity resulting from trauma, inflammation or iatrogenic causes such as repeated trauma from dialysis needle cannulations. Under the influence of sustained arterial pressure, blood dissects into the tissues around the damaged vessel and forms a perfused sac that communicates with the vascular lumen. The perfused sac is either contained by the vascular adventitia or by soft tissue structures around the vessel.

Pseudo-aneurysms should be differentiated from true aneurysms which are abnormal vascular dilatations formed secondary to weakening of the vessel wall (Figure 1). In contrast pseudo-aneurysms are perfused sacs formed secondary to vascular wall disruption and would usually have a “neck” communicating with the vessel.
Etiology of Pseudo-Aneurysm Formation

Multiple factors could lead to the development of pseudo-aneurysms in AV accesses used for hemodialysis. These could develop either from multiple infiltrations during needling of the AV access, or repeated trauma from needle insertion at same site which causes wall thinning, leading to wall weakness, expansion and pseudoaneursym formation.

Venous outflow stenosis leading to increased intra-access pressure and inflammation/infection could also lead to further development and enlargement of pseudo-aneursyms. Pseudo-aneursyms are more commonly seen in AVG’s as compared to AVF’s.

Clinical Signs/Symptoms

Pseudo-aneursyms could present as a silent, visible, pulsatile mass over or around a AVF or AVG and could have localized signs due to mass effect. Systemic features could include distal ischemia, embolization or sepsis. Vascular rupture is another life threatening complication which could lead to profound blood loss and even death.

Diagnosis

Pseudoaneurysms are usually diagnosed by clinical examination, which reveal an abnormal enlargement or dilatation of the AVG or AVF with palpable thrill. Doppler US could also be used to confirm the diagnosis, which would show a cystic dilatation.
communicating with the AV access with a characteristic “ying-yang” flow of blood. Angiography is the gold standard for diagnosis and is the preferred modality as diagnosis and treatment could be achieved at the same time. A pseudoaneurysm would appear as an “outpouching” of the vein/graft with concomitant flow of contrast into the “pouch” on an angiogram (Figure 2).

**Management**

Asymptomatic pseudo-aneurysms are usually managed by careful observation and follow up. Further evaluation and management is usually needed if either the integrity of overlying skin is compromised leading to high risk of spontaneous rupture or the aneurysm size limits the sites available for dialysis needle cannulation. Rapid expansion of the pseudo-aneurysm should also prompt further evaluation.

Various modalities have been used for management of pseudo-aneurysms needing repair. These include ultrasound compression [3], ultrasound guided percutaneous thrombin injection [4,5,6], endovascular options [7-13] or open surgical repair [14].

Ultrasound compression of the pseudoaneurysm is done using a ultrasound probe for about 20-30 minutes for pseudoaneurysms with a narrow “neck”. This should be done carefully, ensuring that only the pseudoaneurysm sac is compressed sparing the main AVF or AVG (as this could lead to graft or fistula thrombosis).

Ultrasound guided percutaneous thrombin injection has also been used in some centers. Thrombin converts inactive fibrinogen to fibrin leading to thrombus formation in the pseudoaneurysm. This modality is usually not preferred by most interventionalists as the thrombus formed could lead to further propagation of the thrombus into the access circuit and lead to eventual clotting of the AVG or fistula.

![Figure 2. Pseudoaneurysm of a thigh AVG.](image_url)
Figure 3. Pseudoaneurysm of thigh AVG after deployment of covered stent.

Also, wide neck pseudoaneurysms are not suitable for this modality given the risk of thrombin embolization and distal arterial thrombosis. Endovascular options include covered stent (stent graft) exclusion of the pseudoaneurysm, detachable balloons, coil embolization or balloon inflation during injection of percutaneous thrombin. Endovascular treatment carries the benefit that the AV access can be used immediately. Of all the endovascular options; covered stent exclusion of the pseudo-aneurysm is the most commonly used modality these days and has excellent success rates (Figure 3). Exceptions to the use of covered stent grafts are active infection and location of pseudo-aneurysm at a site which would lead to placement of the stent across a bone joint.

Open surgical repair is usually reserved for large pseudo-aneurysms which cannot be treated with endovascular or minimally invasive modalities [15]. The major drawback of this modality is delayed use of the access after surgery and need for central venous catheters in the interim. Surgery also has potential associated complications including bleeding, wound infection, seroma formation and prolonged recovery time.

**Prevention**

Pseudo-aneurysm formation could be prevented by utilizing a careful needle puncture technique and rotating needle sites. Doxycycline [15] has also been suggested to prevent pseudoaneurysm formation but has not been proven in randomized trials.

**References**

Pseudo-Aneurysms in Dialysis Access


V. CENTRAL VENOUS CATHETERS
Chapter XIX

Tunneled Hemodialysis Catheters – Infection and Dysfunction

Hemender Vats and Micah Chan
University of Wisconsin School of Medicine and Public Health,
Division of Nephrology, Madison WI, US

Introduction

Chronic hemodialysis will likely remain the predominant renal replacement therapy and vascular access will probably continue as the Achilles heel of hemodialysis. The National Kidney Foundation / Kidney Disease Outcomes Quality Initiative (NKF/ KDOQI) vascular access guidelines recommend that all patients with chronic kidney disease with glomerular filtration rate (GFR) less than 30 ml/min/1.73m² should be assessed for placement of an arteriovenous fistula (AVF) or graft (AVG) and all attempts should be made to avoid initiating hemodialysis with a central venous catheter.[1]

Despite these recommendations, hemodialysis catheters have been and will remain an important modality of providing vascular access. This Chapter will discuss the epidemiology, benefits, complications and their management and future trends in the field of hemodialysis catheters.

Epidemiology

While the technique of hemodialysis has been described since the early 1900s, the modality could not be developed as an effective means of renal replacement till safe and reliable means for vascular access were developed in the 1950’s. The first form of central venous catheters (CVCs) for hemodialysis access were described in 1959 by Teschan which required venous cutdown into the saphenous vein to the inferior vena cava. [2] Subsequently in the early 1960’s Teflon based double lumen catheters were developed for insertion in the femoral vein and percutaneous methods of cannulation gained wide acceptance. These initial
“temporary” catheters were stiff and had significant complications. The tunneled dialysis catheters (TDCs) with a subcutaneous tunnel and a Dacron cuff were developed in the 1980’s. [3,4] These were softer and more pliable and provided better blood flows while significantly reducing the risk of bloodstream infections. After the initial enthusiasm for these catheters, they have since lost popularity due to a multitude of problems associated with their use, predominantly high risk of catheter related bloodstream infections and inadequate blood flows.

Based on the USRDS data, in 2008 65% of all patients initiated hemodialysis with catheters while only 15% patients had a maturing fistula at the same time. [5] (Figure 1) In the past decade the NKF along with Centers for Medicare and Medicaid services (CMS) have taken significant initiatives to promote the use of AVF for hemodialysis. The Fistula First initiative has laid a target of 65% patients to have an AVF by 2012. In some reports, these efforts have reduced the prevalence of catheter use to 17-18% of hemodialysis patients. [6] Interestingly the rates for use of fistula at the initiation of hemodialysis in other developed countries across Europe and Japan are much higher.

Outcomes

Despite the popular consensus against the use of catheters, they do have some inherent advantages that have ensured dependence on them. These include the ease of placement, availability for immediate use and ease of use from the patient’s perspective as they avoid needle cannulations for every dialysis treatment. [4]

However, the overwhelming disadvantages of their long-term use deserve urgent attention.

There is now sufficient data to suggest that the use of hemodialysis catheters is associated with higher mortality. The initial data from the 1990's had reported a strong association of catheter use and increased hospitalization and morbidity. However Dhingra et al reported an approximately 80% higher adjusted relative risk of death in the TDC group as compared to the AVF group on two-year follow-up.

Figure 1. Modality of vascular access at initiation of dialysis based on 2008 USRDS data.
Table 1. Advantages and Disadvantages of TDC

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Ease of placement</td>
<td>a. Increased Mortality</td>
</tr>
<tr>
<td>b. Can be utilized immediately after placement</td>
<td>b. Mechanical dysfunction</td>
</tr>
<tr>
<td>c. Painless to use as no cannulations necessary</td>
<td>1. Kinks in the catheter</td>
</tr>
<tr>
<td></td>
<td>2. Improper Tip placement (e.g. SVC)</td>
</tr>
<tr>
<td></td>
<td>3. Catheter port breakage</td>
</tr>
<tr>
<td></td>
<td>c. Thrombosis</td>
</tr>
<tr>
<td></td>
<td>d. Fibrin Sheath development</td>
</tr>
<tr>
<td></td>
<td>e. High risk of infection and catheter related bacteremia</td>
</tr>
<tr>
<td></td>
<td>f. Inadequate dialysis</td>
</tr>
<tr>
<td></td>
<td>g. Difficult maintenance</td>
</tr>
<tr>
<td></td>
<td>a. Concern for personal care of patients as the site has to be kept dry</td>
</tr>
<tr>
<td></td>
<td>b. Requires high level of hygiene by health care workers for use</td>
</tr>
</tbody>
</table>

This was based on an observational study with over 5000 prevalent dialysis patients from 550 dialysis units across the US. These results have since been reproduced in subsequent much larger studies that also showed the relative risk of death associated with catheter use is 1.4-3.0 fold greater than patients using autogenous AVF [7-10].

The higher risk of infection certainly contributes to this increased risk of mortality. Besides this, there may be a multitude of reasons for this observation including higher levels of inflammatory mediators, decreased dialysis dose delivery, subacute microbial seeding, underlying immune dysfunction or pre-existing risk factors more prone to catheter patients. TDC use is plagued with many complications including catheter-related bacteremia (CRB), catheter thrombosis, venous stenosis, and dialysis inadequacy. (Table 1) These complications not only contribute to the increased risk of mortality as described above but also tremendous morbidity and cost to the health care system. Based on the US Renal Data System (USRDS), catheters as vascular access type have the highest overall cost per person per year in 2006 with $77,093 in expenditures; a large proportion of this cost is due to catheter-related infection which rose 21% in 2005 [5].

The complications of TDC use are discussed in detail below.

1 Catheter dysfunction: The NKF KDOQI published guidelines state that dysfunction is defined as failure to attain a sufficient extracorporeal blood flow of ≥ 300 mL/min with a prepump arterial pressure more negative than -250mm Hg [2]. This can be due to many reasons including mechanical causes like “kinking” or improper positioning of the catheter tip, patient positioning, drug precipitation, thrombotic occlusion or development of fibrin sheath.

   a Mechanical dysfunction. Kinking or acute bends in the catheter were common in the past with catheters made with stiffer materials. However with the use of silicone elastomers and PTFE, the catheters are fairly pliable and are able to
maintain integrity in the subcutaneous tunnel. The tip of the catheter should be ideally placed either at the SVC –right atrium junction or in the right atrium. Catheter tips in the SVC or the innominate vein often lead to poor flows as the tip may lie against a vessel wall.

b Thrombosis. Thrombosis, whether intraluminal or periluminal, has been reported as the primary reason for CVC dysfunction with 17% to 33% requiring untimely removal of the catheter [11]. This consequently is attributed to access loss in 30% to 40% of patients. In a large study from the Strategic HealthCare Programs National Database, over 50,000 patients with CVCs were studied and thrombotic occlusion was the principal cause of catheter dysfunction representing 28% of patients in this group, the thrombosis occurring after 30 days of placement in the majority. [12] The pathophysiology of catheter thrombosis can be explained by the principles of Virchow’s triad that explain intravascular thrombosis as a sequela of alterations in the vascular endothelium, blood flow and coagulability of blood. [13,14] The initial trauma to the endothelium and vessel wall during catheter placement and subsequent turbulence created in the blood flow by the position of the catheter intravascularly often explains the central vessel, mural or atrial thrombi that may cause catheter occlusion. The catheter ports are usually locked with an anticoagulant solution (heparin or sodium citrate) and a slow leak of those from the catheter tips may precipitate thrombosis. Anything which slows the flow through the catheter (e.g. mechanical causes, fibrin sheath etc.) may lead to thrombosis. The fibrin sheath management is discussed in detail below. Treatment of catheter thrombosis typically utilizes saline flushes or instillation of a thrombolytic agent such as recombinant tissue plasminogen activator (r-tpa), reteplase or urokinase (not available in US). While initial studies showed success with Urokinase, it has been largely replaced with t-pa due to safety concerns with use of Urokinase. Using these measures patency can often be restored in approximately two thirds of the patients.[15-19] More recently, however, research has focused on exploring methods for prevention of the thrombosis. Various anticoagulant combinations have been studied. Heparin, the traditional port locking solution, has recently shown to be no better than use of sodium citrate in randomized controlled studies. Citrate in addition may provide some benefit in reducing the risk of catheter related bacteremia by as much as 75%. Recent data has also shown some benefit of using r-tpa once a week (1 mg in each port) along with heparin twice weekly. The use of r-tpa as a port lock was also associated with lower incidence of CRB. [20-24] Use of systemic anticoagulation or aspirin has not been shown to offer any significant benefit in preventing thrombosis.

c Fibrin Sheath formation. Fibrin sheath refers to a sleeve of fibrin and proteinaceous material that surrounds the catheter starting at the point where the catheter enters the blood vessel. With the passage of time the sheath will incorporate collagen, smooth muscle and inflammatory cells. It is a fairly common occurrence in centrally placed catheters in response to the body’s mechanism of reacting to a foreign object injuring and irritating the vessel wall. The incidence has been reported from 42% to 100% depending on the design of the study. The sheath eventually grows to engulf the length of the catheter and cover the tip. At that point it creates a one-way valve, allowing administration of
fluid but preventing any aspiration of blood, hence compromising its function as a dual way catheter. The fibrin sheath usually forms within weeks to months; however, interestingly initiation of the formation of the sheath has been seen as early as 24 hours after the insertion of the catheter. (Figure 2) A fibrin sheath should be suspected if treatment with thrombolytics do not succeed in restoring blood flow from the catheter or the problem recurs very frequently. A diagnosis can be made relatively easily by withdrawing the catheter slightly and doing a radiographic study by injecting some contrast in the catheter.

Treatment of the fibrin sheath has evolved over the past two decades. Initial studies with the use of thrombolytics using Urokinase and recombinant tissue plasminogen activator (r-tpa) as continuous infusions had shown initial successes, however long term outcomes have not been very encouraging. In the past decade endovascular procedures including fibrin sheath stripping and balloon angioplasty have been used with considerable success. Fibrin sheath stripping involves accessing the tip of the internal jugular catheters with a snare that is introduced from a femoral access. Under fluoroscopy, the snare is advanced over the tip of the catheter and the fibrin sheath is removed by grasping the sheath mechanically with the snare. Another technique used more frequently is the balloon angioplasty and disruption of the fibrin sheath. This is achieved by dissecting the cuff of the indwelling catheter free from the subcutaneous tunnel followed by withdrawal of the catheter marginally. A radiographic image using iodinated contrast is obtained to identify the extent of the fibrin sheath. The catheter is then removed and angioplasty of the sheath is done by inflating a balloon in the sheath at approximately 10-20 atmospheres. Once sheath disruption is confirmed by repeat imaging, a new catheter is inserted in the same tunnel.

Various studies have been conducted to compare the different strategies for the management of fibrin sheath. Initial studies did not reveal any difference in outcomes between use of thrombolytic infusions (Urokinase) or fibrin sheath stripping, or sheath stripping as compared to catheter exchange and sheath angioplasty and disruption.

Figure 2. Radiological imaging of a fibrin sheath associated with a left IJ catheter. Arrow- tip of catheter, arrowhead- fibrin sheath.
However, more recent well-designed prospective studies have shown the superiority of catheter exchange over sheath stripping and catheter exchange with sheath angioplasty over catheter exchange alone. In light of this supportive evidence, expert opinion from the KDOQI Work Group recommends exchange of catheter and disruption of the sheath by balloon angioplasty as the preferred method for treatment of catheter dysfunction caused by fibrin sheath.

There are anecdotal reports of other methods that have been used to remove the fibrin sheath. These include use of endoluminal brushes to remove the occlusive thrombi and nitinol wire loops that are advanced into the catheter tip from the ports and manipulated to disrupt the sheath. These are minimally invasive procedures; however there is not enough evidence to recommend their use on a regular basis. [24-32]

2. Infection

Catheter related bacteremia (CRB) is the most common and indeed, the most dreaded complication of catheters. The incidence of CRB has been reported by various studies at 2.5-5.5 episodes/1000 catheter days or 0.9-2.0 episodes/person/year. This risk is 2-3 fold higher for temporary HD catheters. In fact, the cumulative incidence of the first episode of CRB has been reported at 35% in the first three months and 48% after six months. In addition to the need for removal or replacement of catheters, infections necessitate the use of antibiotics for extended periods of time, frequent and prolonged hospitalizations all contributing to the substantial medical expenditures attributable to hemodialysis vascular access. [33-36]

It has been well established that CVCs are strongly associated with an increased risk for infection-related death compared with AVF and AV grafts with the relative risk (RR) for death being 1.4 to 3.4 fold greater. Using the USRDS Dialysis Morbidity and Mortality Study Wave 1 (DMMS), Dhingra and colleagues reported in 2001 that in diabetics, the associated risk for infection-related death was 2.3 times higher for CVC compared with AVF. The mortality was 1.8 times higher in the non-diabetic patients also. Similar results have been reported by many other larger studies since then. [7-10]

There are multiple risk factors for CRB including previous episodes of bacteremia, older age, diabetes, malnutrition, iron overload, longer duration of catheter use and peripheral atherosclerosis. Besides these classical risk factors, other factors exclusive for hemodialysis related catheter infections include frequent manipulation of catheters, colonization with bacteria and contamination of the dialysis solutions. Multiple studies have demonstrated that good catheter and exit-site care with body substance isolation and prophylactic topical antibiotics decrease catheter colonization and CRB. [36]

It is postulated that the insertion and continued presence of an indwelling vascular device like a catheter disrupts the delicate balance of the fibrinolytic system rapidly initiating the coagulation and inflammatory cascade. This sets the stage for development of a thin film of polysaccharide matrix that lines the catheter surface and acts as a nidus for attachment of pathogens that usually colonize the skin and the catheter ports- hence labeled as “biofilm”. [37] A new catheter does not have biofilm at the time of placement, but it is formed soon thereafter, in some cases as early as 24-48 hours after placement of the catheter. Bacteria can then shed from the biofilm episodically and cause systemic bacteremia. The biofilm often is
impenetrable to systemic antibiotics and hence may prevent complete eradication of infection even with prolonged courses of antibiotics (for example, *Escherichia coli* requires >500 times the minimum inhibitory concentration of ampicillin; *S. aureus* requires >10 times the minimal bactericidal concentration of vancomycin to provide a three-log reduction).

In addition, host-related factors such as immunocompromised state of dialysis patients and malnutrition–inflammation complex syndrome have been implicated in the pathogenesis of CRB by decreasing the threshold of developing overt bacteremia. The risk of infection is also higher with catheter thrombosis and fibrin sheath formation, possibly by providing an interface for adherence and colonization. [37-42]

The causative organism often varies from region to region. In the United States 40 - 80% of CRB are caused by gram-positive organisms, 30-40% by gram-negative and 10-20% by multiple organisms. Regardless of the organism involved CRB can be complicated by metastatic infections such as endocarditis, osteomyelitis, septic arthritis and epidural abscess. The risk of metastatic infection is highest with *Staphylococcus aureus*. [43]

**Definitions**

There is considerable inconsistency in literature for a uniform definition of Catheter related infection. However, based on the Centers for Disease Control and Prevention (CDC), CRB should be suspected in a patient with positive blood cultures with or without fever and no other localizing signs.

1. **Definite CRB** consists of the same organism cultured in the catheter tip and the peripheral blood draws in a symptomatic patient (fever or chills).
2. **Probable infection** is defined as the alleviation of symptoms after antibiotic therapy for positive blood cultures with or without the removal of the catheter.
3. **Possible infection** is defined as the alleviation of symptoms after antibiotic therapy or removal of the catheter despite negative blood cultures in the absence of another infection. [5]

**Management**

While removal of an infected catheter has long been accepted as the only way of eradicating blood stream infection, the paucity of vascular access sites in hemodialysis patients has encouraged discussion on methods of treatment of CRB with salvage of the catheter and preservation of the vascular access site.

The National Kidney foundation KDOQI and IDSA have developed guidelines with an algorithmic approach to CRB. [44] This is summarized in Figure 2.

Treatment is usually initiated with empiric antibiotics that are often determined based on the prevalence of organisms in the dialysis unit or health facility. While third generation Cephalosposins are preferred for their broad-spectrum coverage, addition of Vancomycin is recommended if the incidence of Methicillin resistant *Staph aureus* (MRSA) is high. Antibiotics should be tailored to the culture and sensitivities as soon as they are available.
Hemodialysis catheters should be removed if there is a complicated CRB, which include severe sepsis (hemodynamic instability), osteomyelitis, endocarditis, suppurative thrombophlebitis, or persistent positive blood cultures more than 72 hours after appropriate antibiotic therapy after susceptibility testing. Treatment of uncomplicated bacteremia depends on the organism involved. In uncomplicated bacteremia with coagulase negative Staphylococcus epidermidis or Gram-negative organisms, an attempt to treat with two weeks of IV antibiotics with antibiotic locks with or without a catheter exchange over a wire can be made.

There is now increasing data for the efficacy of use of antibiotic locks for these situations with possible salvage in 65-70% cases. (discussed in chapter 21). However, if the infecting organism is S. aureus or a fungal organism, the catheter should be removed. The NKF guidelines strongly recommend exchanging catheters over a wire for vascular access site salvage to preserve the limited number of access sites in chronic hemodialysis patients. Indeed the approach of removing the catheter completely and giving a line free holiday is being adopted only for the most serious or recurrent staphylococcal or fungal infections. Indeed, prevention of infection by good hygiene, proper handling of catheters, clean dressing, the use of antibiotic impregnated discs at the catheter exit site may be the best approach for decreasing the incidence of infectious complications of catheters. [39-42,44]

Figure 3. Approach to a patient with tunneled catheter related bloodstream infection.
3. Central Venous Stenosis (CVS)

Prolonged use of hemodialysis catheters has been associated with increased incidence of central venous stenosis. The incidence has been reported to be 20-50% in patients receiving hemodialysis through catheters. Incidence tends to be higher with the duration of the use of catheters, number of catheters that have placed and duration of hemodialysis (dialysis vintage).

Moreover the incidence is highest in the subclavian catheters, followed by left IJ and then RIJ catheters. The etiology of development of stenosis is not very clear. Possible causes include constant trauma to the endothelium and vessel wall, turbulence of blood flow in a uremic milieu, platelet aggregation and thrombosis which sets off the inflammatory cascade with release of profibrotic cytokines eventually leading to fibrosis and stenosis. Due to the high incidence of CVS, subclavian catheters have fallen out of favor and are now used only as a last resort when all other vascular access sites have been exhausted. Similarly, catheters placed in the left IJ are also fraught with a high incidence of CVS. This possibly is from the long intravascular length of the catheter, the multiple turns in the catheter (three as confirmed by the three dimensional models of the left IJ vein) to achieve the successful placement of the catheter tip in the right atrium, the smaller caliber of the left IJ and the external compression of the vein by the brachiocephalic artery. Of all the vascular sites, the RIJ approach is associated with the lowest incidence of CVS mostly because this approach has the least amount of contact between the catheter and the vessel wall. Indeed, development of central stenosis by use of catheters decreases the chances of having a successful AVF or AVG placement in the limb on that side.

The treatment options for CVS include percutaneous angioplasty (PTA), percutaneous angioplasty with stent placement (PTS) and surgical correction. Various studies have been done comparing the outcomes of PTA versus PTS, however they failed to show superiority of one method over the other. Current recommendations suggest attempting PTA first and then using PTS if PTA alone is unable to restore patency or if stenosis occurs on a recurrent basis with PTA alone. Surgical correction is resorted to only in resistant cases that cannot be corrected with percutaneous interventions. Overall, the long-term results are discouraging from either modality and avoidance of a catheter placement remains the best solution to this problem.

In the recent years the use of the right external jugular vein has been attempted when the RIJ is stenosed or thrombosed with good success. This allows use of right side vessels before moving over to the left IJ hence reducing the chance of developing central venous stenosis in the left arm, which in most individuals is the preferred site for placement of AVF or AVG. [45-48]

4. Inadequate Dialysis

Hemodialysis catheters have been associated with inadequate dialysis, a reflection of the poor blood flows associated with the catheters and the frequent thrombotic and occlusive complications encountered with them. A higher chance of recirculation with the use of
catheters has a possible role in providing ineffective dialysis. This problem has been overcome by the use of larger bore catheters and better catheter design.

Recent Innovations

Most innovations in TDCs have focused on the most common factors that cause catheter dysfunction, namely CRB, thrombosis, fibrin sheath and poor dialysis adequacy. Since CRB is the most common and as discussed above, the most serious complication, a lot of attention has been directed towards developing catheters with catheter surface treatments. Initial studies revealed a benefit with antimicrobial-coated catheters in non-tunneled dialysis catheters though similar results could not be derived in tunneled catheters. Most catheters have a silver derived antibiotic coating (mostly silver sulfadiazine) that acts as an antimicrobial. Other catheters with various antibiotics (ciprofloxacin, rifampin, minocycline) have been developed, though their commercial availability is limited by lack of FDA approval and proven benefit in preventing recurrent CRB.

Other surface coated catheters were designed to combat catheter thrombosis and fibrin sheath formation. All these types of catheters have some amount of endpoint-bound or covalently bound heparin which is approved to reduce thrombus, platelet activation and fibrin sheath. Their benefit in preventing these thrombotic episodes is yet to be proven. Interestingly heparin coating has shown benefit in reducing the rate of CRB by an unexplained mechanism. [49-52]

Other advances in technology have focused on newer TDC designs. The conventional catheter tip design includes a step tip. One new design has a split catheter tip (SplitCath®). This split-tip catheter provides side holes so that if it lies against the surface of the vessel or atrium, the flow dynamics of blood does not cause as much shear stress or blood recirculation. It is theoretically meant to provide a better blood flow and lower rate of recirculation. Studies have however shown mixed results for both the proposed improvements. Other design innovations include symmetric spiral-z tip design with biased ports (Tal PALINDROME) and the Centros™ (Ash Access Technology, Lafayette, IN) catheter with curved tips designed to position the ports away from the vessel wall.

Initial studies on the Centros catheter have shown some promise in providing better blood flows and reducing the incidence of fibrin sheath development.

Despite all of the advances in technology of dialysis catheters in the last 50 years, the long-term issues of catheter dysfunction, namely infection and thrombosis have not been conquered. Whether there will be an invention of the “ideal” dialysis catheter has yet to be seen, but it is undeniable that catheters are an essential role to establishing immediate vascular access and as a bridge to AVF or AVG.
References


Central Venous Stenosis in Dialysis Patients

Micah R. Chan
University of Wisconsin School of Medicine and Public Health, Division of Nephrology, Madison, WI, US

Abstract

Despite aggressive efforts to increase autogenous fistula prevalence, catheters remain an essential access modality to a large percentage of the hemodialysis population. Central venous stenosis most commonly caused by previous catheter use has become a significant complication in dialysis patients especially in the Fistula First era. These complications contribute to the enormous costs of vascular access-related expenditures from hospitalizations and procedures to treat the condition. This chapter focuses on the pathogenesis, epidemiology of the problem, causes, preventive measures and treatment strategies.

Introduction

Central venous stenosis (CVS) in hemodialysis patients represent a major cause of morbidity and mortality in the United States which contributes to the more than one billion dollars in vascular access related expenditures for Centers for Medicare and Medicaid Services (CMS). [1] Given the era of Fistula First, CVS in hemodialysis patients has become a paramount issue because the maturity and long term patency of the autogenous fistula is dependent on unobstructed blood return to the heart. In essence, the arteriovenous fistula (AVF) is a complete circuit starting with the heart and aorta supplying the inflow and continuing through the fistula and outflow veins to the right side of the heart. Any obstruction whether it be in the anastomosis of the fistula or an outflow vein such as the central vasculature will affect the access resulting in pain, poor dialysis, edema of the extremity or SVC syndrome. Although dialysis patients can rarely have de novo CVS in the absence of a
Micah R. Chan

history of lines or device wires, the most common cause of CVS still remains catheters. Unfortunately, despite aggressive efforts to decrease catheter rates in the US, according to the Forum of End Stage Renal Disease Networks, 21% of prevalent hemodialysis patients were dialyzing with a CVC for 90 days or longer. [2] This is far greater than the National Kidney Foundation’s Dialysis Outcome and Quality Initiative (NKF K/DOQI) published recommendations of less than 10% CVC prevalence. Even though arteriovenous fistula (AVF) rates are improving with NKF K/DOQI and the Fistula First National Vascular Access Improvement Initiative recommendations, since 1998, the placement of CVCs continues to be sustained at an alarmingly high rate. [3] In this chapter we will review the definition, pathophysiology, epidemiology, prevention, and treatment of CVS, with an emphasis on recent contributions to the literature.

Definitions

Central venous stenosis has a variety of definitions reported in the literature and can be synonymous with a number of names including central vein occlusion, superior vena cava (SVC) syndrome, total venous obstruction and even central vein thrombosis in some cases. In general, CVS involves the intrathoracic veins, ie subclavian, innominate or SVC, or it involves the veins of the lower trunk, ie the inferior vena cava (IVC) or iliac. CVS has been described for over a century and in general is identified with clinical features of extremity edema, face or breast swelling, pain, and collateral vein formation. In patients on dialysis it can present the same with varying levels of severity usually on the side of a functioning arteriovenous access but often causing decreased dialysis adequacy and failure of AV access. [4] CVS in dialysis patients have been described since the late 1970s and typically are caused by previously placed central catheters. [5-7] Other causes of CVS not related to catheters include mediastinal mass, radiation therapy, or fibrosing mediastinitis. [4] There has been a dearth of information that prevalence of CVS in dialysis patients without previous access or device wires have been on the rise. Whether this is due to better detection or surveillance on the part of interventionalists and general nephrologists is unknown. This so-called idiopathic CVS could be due to a variety of factors including the uremic milieu, malnutrition-inflammation complex or predilection to thrombosis formation. For example, a 54 year old male with hypertension and diabetes mellitus with end stage renal disease (ESRD) on dialysis for the last two years presents to dialysis with a progressively swollen arm (Figure 1). This is the ipsilateral arm where he has a functioning brachiocephalic AVF. On physical exam, the AVF is pulsatile and the dialysis nurses have noticed increased bleeding times at cannulation sites. The patient’s urea reduction ratio (URR) has dropped from 70% to 60% and his transonic ultrasound access flow (Qa) showed a drop of 30% from the month prior. The nephrologist referred the patient to the interventional nephrologist who did a fistulagram showing a 95% cephalic arch stenosis with multiple collateral veins (Figure 2).

On history and medical record review, the patient never had a peripherally inserted central catheter (PICC) nor temporary or tunneled catheter on that side. Again, this phenomenon of CVS in dialysis patients without previous catheters seems to be on the rise. Morosetti and colleagues reported on late symptomatic venous stenosis in three dialysis patients without previous catheters and concluded that the mechanism could be due to the
stenosis developing at a site where there is a venous valve or venous curve. They state that because it is not typically under high pressure due to arterialization of the vein, this turbulent flow could explain a thickening of the segment. [8] The authors recommend that angiographic evaluation should be performed prior to creating a new proximal AVF when there has been a previously working AVF. Although diagnosis of CVS can be made by careful history and physical exam, angiography is the gold standard for screening and is superior to duplex ultrasound. [9]

**Pathophysiology**

One hundred and fifty years ago, Dr. Rudolf Virchow published his book, "Cellular Pathology" in which he described the interplay of blood flow, coagulability, and disruption in vessel walls as an impetus for thrombosis formation. [10]

Figure 1. Extremity edema on ipsilateral side of AVF.

Figure 2. Cephalic arch stenosis.
This process begins with the initial insertion of the catheter with endothelial damage of the vessel wall and then stasis of blood intraluminally in the interdialytic period, coinciding with patient-related factors whether inherited or acquired which ultimately forms clot. However, despite all of the advances in biomedical research, the precise mechanism of CVS in dialysis patients remains largely undefined. In animal models, structural changes in the veins occur after 24 hours of endothelial damage resulting in platelet microthrombi and smooth muscle cell migration within a week. [4, 11]

Contemporary knowledge in human subjects have refined our understanding of the mechanisms of injury demonstrating that the trauma of insertion as well as continual turbulence of blood flow (Qb) may further lead to endothelial damage. This cycle is perpetuated with chronic catheter use and dysfunction as “dialysis dose decay” becomes evident and processes such as lumen reversal or catheter manipulation are used to improve dialysis adequacy. [12] Suojanen et al. eloquently describes that the CVC upsets a delicate balance of the fibrinolytic system and these events may rapidly initiate the coagulation and inflammatory cascade. [13] Histologic examinations of atherectomy specimens from subclavian vein stenoses demonstrate this fibrous tissue and endothelial hyperplasia. [14] The uremic milieu hypothesis cannot be understated which likely contributes to this endothelial damage and inflammation cascade. One group compared the cephalic veins between normal and patients with renal failure prior to AVF creation. They showed that patients with renal failure had significantly more intimal hyperplasia, fibrous tissue infiltration and loss of internal elastic lamina. [15] They concluded that pre-existing disease inherent in renal failure patients seem to predispose to stenosis formation and not entirely as a direct result of arterialization.

Catheter design has evolved over the last two decades to help improve biocompatibility with heparin coating or ion implantation and protein conditioning, though results remain suboptimal. The polymer material most catheters are made of and its minute surface irregularities seem to be enough to activate an inflammatory cascade and the intrinsic pathway of coagulation to cause platelet attraction and adhesion. [13, 16] Leblanc et al. suggest that the stiffness of the catheter may be more important than the surface composition in terms of chronic endothelial injury and vessel wall abrasion and irritation. [16] One study demonstrated that soft pliable silicone catheters have less thrombogenic potential than regular stiff polyethylene dialysis catheters. [17]

In addition, fibrin sheath formation is a common biologic response of the body to a foreign object inserted in the bloodstream. Whether this contributes to development of central venous stenosis or is a sequela, is unknown. Hoshal et al. in 1971 first demonstrated in autopsy studies that this fibrin sleeve formed around catheters within 5 to 7 days of placement. [18] Later studies showed that the fibrin sheath can form as early as 24-hrs within insertion and was composed of fibrinogen, albumin, gamma-globulin, lipoproteins, and coagulation factors. [19, 20] It then evolves over weeks to months to form collagen and recruit smooth muscle migration. [19] These complex interactions, perpetuate the clotting process that occurs with the insertion of the CVC, and offer an explanation of the role of the fibrin sheath. One study examined fibrin sheath specimens from 8 patients and surprisingly found that although the histology showed mainly laminated proteinaceous material, it also showed several other different patterns. [13] It also showed eosinophilic matrix with inflammatory cells throughout and evidence of different evolutionary stages of acute and chronic organizing thrombus. Perhaps this protein sheath acts as a chemokine of sorts by
Central Venous Stenosis in Dialysis Patients

attracting platelets and coagulation factors and also promoting leukocyte adhesion and the inflammatory cascade. The authors suggest that the fibrin sheath initiates clotting in excess of what the body’s endogenous fibrinolytic system can overcome. [13] Furthermore, patients with hypercoagulable states or the malnutrition-inflammation complex syndrome may succumb to an even lower threshold for thrombus formation and central venous stenosis.

**Epidemiology and Risk Factors**

CVS in dialysis patients most often occurs in relation to a previous central venous catheter. It is this “catheter conundrum” which describes the contrasting symbiosis of the simultaneous disdain and utter dependence on catheters that causes the problem. This disdain stems from the multiple complications from catheters such as catheter related bloodstream infections, poor dialysis adequacy, thrombosis, and central venous stenosis.

Again, CVS in the era of Fistula First has become a paramount issue given the fact that the rates of prevalent AVF use is still below 60% and the total percentage of catheters remains at greater than 20% based on Fistula First dashboard data. [21] Evidence that CVS is directly responsible for this is debatable however based on empiric evidence when there is an ipsilateral arteriovenous access along with CVS, primary and secondary patency is diminished significantly. Macrae et al. demonstrated in a study of 133 patients referred for access dysfunction that 41% of the patients had significant central venous stenosis on venogram. [22]

Interestingly, this study also showed that risk factors for patients with CVS had a longer duration on HD and a history of a previous HD catheter insertion (52/55 patients vs. 59/78 patients, p =0.0039). In those with any history of previous HD catheter insertion, multivariate analysis showed that the number of catheters is a significant risk factor (OR 2.69, p =0.0004) even after excluding subclavian insertions. Previously, it was thought that subclavian venous catheters were the only types of catheters that caused significant CVS. In the 1980s, multiple studies showed subclavian stenosis rates of 40-50% which shifted the placement of dialysis catheters and other central catheters toward the jugular veins. [23-25] The internal jugular route, however has not fulfilled its promise of minimal central venous stenosis with recent evidence showing comparable CVS prevalence as the subclavian route. This may be due to the increased use of the jugular vein access for central venous catheters in current clinical practice. One study showed that under ultrasonography of 143 patients with right internal jugular dialysis catheters that 25.9% had thrombosis and 62% of these patients had total venous occlusion. [26]

The left sided internal jugular (IJ) approach also seems to confer higher risk for CVS than on the right. Anatomically, there can be up to three sharp angles the catheter must traverse prior to its tip in the right atrium which would include the left internal jugular vein with the brachiocephalic, the brachiocephalic with the superior vena cava and even the brachiocephalic vein with the aorta or brachiocephalic artery. These angulations are common places where CVS may develop in the setting of a left sided catheter (Figure 3). One study showed that 50% of patients with left sided IJ catheters developed CVS vs only 0.9% in the right IJ group. [4]
Figure 3. Left innominate vein stenosis.

Peripherally inserted central catheters (PICCs) have likely contributed to the rise of CVS not only in dialysis patients but non-dialysis patients as well. For one, use of PICCs have increased dramatically in the US since the 1980s with estimates of up to 10 PICCs per bed/yr in certain institutions. [27-29] Their increased use seems to stem from the relative ease of insertion, cost effectiveness and reported lower infection rates than other chronic catheters. One study by Gonsalves et al. demonstrated that there was a 7% incidence of central venous stenosis in 154 patients who underwent PICC placement and venography before and after insertion. The caliber of the catheter did not have an association with development of CVS but the duration of catheter dwell time had a significant influence on new CVS (p=0.03) as compared to patients without central vein abnormalities. Transvenous cardiac rhythm device (CRD) leads can also cause CVS in the dialysis patient. [30]

It is well known that a large proportion of dialysis patients will have these devices given the burden of cardiovascular disease inherent in the population and higher mortality due to sudden cardiac death. The true incidence of CVS in these cases have not been reported but in non-dialysis patients up to 70% of patients may develop complications associated with these leads including central venous stenosis. [31] Dialysis patients who often have ipsilateral arteriovenous access develop more pronounced symptoms given the high blood flow in comparison with patients without dialysis access. Therefore, if a CRD needs to be placed in a dialysis patient, it is recommended to place it on the contralateral side of the dialysis access.

Finally, catheter infections have also been associated with the development of CVS likely due to the proliferative inflammatory response from monocyte recruitment to activation of a variety of cytokines. In a study of 54 patients with 80 subclavian catheterizations, those with definite subclavian vein stenosis (SVS) on venogram had a 3-times more likelihood of having a previous catheter-related infection (75% vs 28%, p<0.01). [32] The same authors then
showed in a study of 42 incident dialysis patients who initiated with a subclavian catheter, that on venography 24-48 hrs after catheter removal, 1, 3, and 6 months there was a higher number of catheter-related infections observed in patients with definitive SVS (66.6% versus 33.3%; P < 0.05). [33] In fact, 52.4% of patients even 24-48 hrs after catheter removal had definitive SVS. Again, this association with subclavian catheters and catheter-related infection is likely due to a combination of endothelial injury which initiates both the coagulation and inflammatory cascade.

**Prevention of CVS**

Despite significant technological innovation in catheter design throughout the years, there has been no “biocompatible” catheter that has prevented the problem of central venous stenosis. [34] As outlined previously, a history of a catheter is the greatest risk factor for developing CVS. Therefore, the most prudent method of achieving prevention in this case is a policy of strict catheter avoidance. How a program gets there is another question as we deal with the issue of the “catheter conundrum”. Astor, et al. eloquently demonstrated in the Choices for Healthy Outcomes in Caring for End-Stage Renal Disease Center (CHOICE) Study that patients who were referred late to nephrologists prior to initiation of dialysis had a much higher likelihood of using a catheter than an AVF or AVG. [35] They showed that among 356 incident dialysis patients, that those referred at least 1 month (75%) before starting hemodialysis therapy were more likely than those referred later to use an AVF or AVG at initiation (39% versus 10%; P < 0.001). This also persisted 6 months after starting hemodialysis therapy (74% versus 56%; P < 0.01) respectively. Moreover, patients referred within 1 month of initiating with a dialysis catheter had a median usage of 202 days compared with 64, 67, and 19 days for patients referred 1 to 4, 4 to 12, and greater than 12 months before initiating hemodialysis therapy, respectively (P trend <0.001). These same authors of the CHOICE study reported later that patients who initiated hemodialysis with a central venous catheter had an adjusted relative hazard ratio of death 1.5 times that of those with AVF. [36] Recently, a group examined barriers to AV access creation and showed that a lack of formal policy for patient referral, long wait times for surgical review and access placement, and lack of a patient database for management purposes were major issues. [37] The eGFR based referral thresholds were considerably lower than appreciated in both AVF and catheters, (median eGFR of 7 mL/min/1.73 m2), with median wait times for access creation of only 3.7 weeks. Those centers that performed the best included the presence of a formalized predialysis pathway with a centralized patient database and low nephrologist and surgeon to patient ratios.

The NKF/KDOQI updated vascular access guidelines recommend under CPG 1.1 and 1.2 that patients with glomerular filtration rate (GFR) less than 30 ml/min/1.73m² be referred in a timely fashion to nephrologists and in patients with CKD stage 4 and 5, that venipuncture and catheters should be avoided. [38] Nephrologists need to gain appropriate “buy-in” from hospital administrators, surgeons, and interventionalists to establish policy to limit use of catheters in CKD patients especially PICC lines. Institutions should develop continuous quality improvement projects which review best practice and evidence to guide physicians in
adopting catheter last programs. If a catheter is absolutely necessary, then a small bore, single lumen tunneled catheter can be placed in the IJ or external jugular (EJ) veins.

Transvenous cardiac rhythm devices have also become a major problem in dialysis patients as aforementioned. Not only is there a greater risk of central venous stenosis, but “vascular access real estate” has been taken and the maturation of AVF can be compromised especially if CRD is on the ipsilateral side of access (Figure 4). Asif et al. have recommended the use of epicardial devices as opposed to the transvenous approach given the decreased risk of infection, central venous stenosis, tricuspid valvular dysfunction and the preservation of vascular access. [39] Though the epicardial device requires placement by a cardiac surgeon as opposed to an interventional cardiologist, the downstream benefits of avoiding the central veins altogether make it a very attractive alternative.

Increasing utilization of peritoneal dialysis can be another way of preventing central venous stenosis because precious vascular access sites are completely avoided. As of 2008, the incident peritoneal dialysis population was only 6 percent which has dramatically declined since the 1980s at its peak of 15 percent. [40] Only 7 percent of prevalent dialysis patients are receiving peritoneal dialysis, however when given a free choice, almost 50% of patients would choose PD and when practicing nephrologists were asked what an ideal distribution of dialysis modality would be, they stated 60:40, hemodialysis vs PD respectively. [40, 41] It has been shown that PD can be initiated acutely in the hospital and safely if there is an effective educational program in place. [42, 43] Low volume automated peritoneal dialysis (APD) done overnight can be used effectively in acute kidney injury and limit the use of temporary and tunneled dialysis catheters in these patients. These types of patients as well as CKD stage 4 or 5 can even have an AVF placed later, thereby using PD as a bridge to fistula creation.

**Treatment of CVS**

The treatment of CVS in dialysis patients will depend on whether there are development of clinical signs and symptoms that require intervention. Often times in patients with functioning AV access there may be a decrease in dialysis adequacy, poor flows or venous pressure alarms especially in patients with an ipsilateral access of the stenosis. There are essentially three options in terms of what to do: observation, percutaneous intervention or surgical approach.

First, the conservative approach of observation involves elevation of the extremity and anticoagulation if there is a thrombus associated with the stenosis. The development of collaterals typically will relieve symptoms however if there is an ipsilateral AV access, given the higher venous pressures and increased blood return, these symptoms may not dissipate. Levit et al. studied a group of dialysis patients with high grade stenosis (>50%) of the central veins but who were asymptomatic. [44] In their retrospective cohort of 35 patients with 38 AVGs, they found 86 separate CVS lesions. In the untreated group of 24 out of 86, the mean degree of stenosis was 72% whereas in the treated group (percutaneous transluminal angioplasty or PTA) of 62 out of 86, the mean degree of stenosis was 74%. In the untreated group, no patients progressed to symptoms, required intervention, or developed new CVS. In the treated group 6 out of 62 developed arm swelling, required intervention or developed new
Central Venous Stenosis in Dialysis Patients

CVS. The authors conclude that PTA in asymptomatic patients with CVS may accelerate stenosis and possibly access failure. One major limitation was that in the treated group, mean residual stenosis was 40% which would be considered refractory and may have benefited from stent placement.

The NKF/KDOQI guidelines recommend PTA with or without stent placement in dialysis patients with CVS. [3] Guideline 6.1 states that the preferred treatment for central venous stenosis is PTA. Stent placement is considered when there is acute elastic recoil of the vein (>50% stenosis) after angioplasty or when the stenosis recurs within a 3-month period. These clinical practice guidelines are deemed to be Level B evidence according to the vascular access work group.

PTA in the treatment of CVS in dialysis patients has never been evaluated in a formal randomized clinical trial. In fact, the first reported angioplasty in dialysis access including central veins was described by Gordon et al. in 1982. [45] They described a case series of 15 patients with 17 lesions in which they used the polyvinyl chloride, double-lumen Gruntzig balloon of various sizes to achieve immediate success after inflation by measuring pressure gradients. Their longest patency was 18 months after PTA but most only were patent for less than 2 weeks. More recently, due to the work of Gerald Beathard and others, immediate results from PTA have improved to 85-100%, however longer term patency is still to be much desired. [3, 46] In a seminal study of 862 venous stenoses referred for venography of which 50 were CVS and the rest peripheral, he reported initial success rates of 89% and 94% respectively. [46] However, central lesions had the worst secondary patency with 6-month primary patency of only 25% as compared to peripheral lesions which had a patency of 77%. The author suggested this is due to the greater elasticity and recoil of the central vasculature. More recently, Bakken, et al. showed in 47 patients with 49 lesions of CVS an initial success rate of 77% with PTA and 6-month primary patency of 45% and secondary patency of only 62% at 6-months. Therefore, even after more than 20 years of data and innovation, the dismal patency rates of PTA in CVS have not changed significantly.

Figure 4. Pacemaker wire CVS.
a) Number of PTA and stent procedures performed in the US 1998-2005.

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of PTA procedures</th>
<th>Number of stent procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td>52,280</td>
<td>3792</td>
</tr>
<tr>
<td>1999</td>
<td>66,235</td>
<td>4953</td>
</tr>
<tr>
<td>2000</td>
<td>70,602</td>
<td>5468</td>
</tr>
<tr>
<td>2001</td>
<td>82,550</td>
<td>6318</td>
</tr>
<tr>
<td>2002</td>
<td>98,148</td>
<td>8514</td>
</tr>
<tr>
<td>2003</td>
<td>111,825</td>
<td>10,801</td>
</tr>
<tr>
<td>2004</td>
<td>128,745</td>
<td>12,327</td>
</tr>
<tr>
<td>2005</td>
<td>139,024</td>
<td>15,260</td>
</tr>
</tbody>
</table>

b) Figure 5. Increase in stent placement.

In 1999, Haage, et al. first analyzed the notion of primary stenting as a treatment of CVS in dialysis patients. [47] They placed 57 Wallstents in 50 patients and reported seventy-three episodes of re-obstruction and nineteen cases that required additional stent placement. However, their primary patency rates were 84% at 6-months and secondary patency of 97%. Even after 24 and 48-months, secondary patency was maintained at 89% and 81% respectively.
This study and a number of recent reports have shown that while stent placement can offer excellent immediate results in symptomatic CVS, long term patency is still an issue and therefore controversial for primary placement of stents. [25, 48] Nevertheless, while the total number of access interventions increased from 52,380 to 98,148 (a 1.8 fold increase), the number of stent placements has increased from 3792 to 8514, a 2.2 fold increase (Figure 5) in dialysis patients. Even though there are no randomized trials comparing stent vs PTA in CVS, observational trials suggest that as compared to PTA, stent placement may not be any better (Table 1). [25] However, there is one randomized clinical trial comparing bare metal stents

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study Design</th>
<th>Year of Publication</th>
<th>Number of Central Lesions</th>
<th>Primary Patency</th>
<th>Secondary Patency</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rajan DK</td>
<td>Observational</td>
<td>2007</td>
<td>6</td>
<td>83.3% (95% CI 0.5-1.2) at 3-mo and 66.7% at 6 and 12mo (0.2-1.1, 0.1-1.2)</td>
<td>Secondary patency was 100% at 12mo with 3 pts censored over that time period n/a</td>
<td></td>
</tr>
<tr>
<td>Rajan DK</td>
<td>Observational</td>
<td>2007</td>
<td>89</td>
<td>In the fistula group the rates were 88.5±4.8%, 50±47.6%, 40±7.9%; At 3, 6, 9mo respectively In the graft group the rates were 78±17.3%, 40±7.9%, 16±7.9% respectively</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maya ID</td>
<td>Observational</td>
<td>2007</td>
<td>23</td>
<td>19% at 1 yr</td>
<td>64% at 1 yr</td>
<td>All stents had restenosis on D. venogram</td>
</tr>
<tr>
<td>Sprouse LR</td>
<td>Observational</td>
<td>2004</td>
<td>n/a</td>
<td></td>
<td>n/a</td>
<td>Symptoms related to central stenosis were controlled for 6.5mo on average</td>
</tr>
<tr>
<td>Aytekin C</td>
<td>Observational</td>
<td>2004</td>
<td>14</td>
<td>1, 3, 6, and 12mo primary stent patency were 92.8%, 85.7%, 50%, and 14.3%</td>
<td>3, 6, 12mo, and 2-yr secondary patency rates were 100%, 88.8%, 55% and 33.3%</td>
<td></td>
</tr>
<tr>
<td>Chen CY</td>
<td>Observational</td>
<td>2003</td>
<td>18</td>
<td>3, 6, 12, and 18mo primary stent patency were 100%, and 89%, 73% and 68%, 49% and 42%, 16% and 0% respectively</td>
<td>100% after 3mo, 93% and 100% after 6mo, 85% and 91% after 12mo, 68% and 72% after 24mo</td>
<td></td>
</tr>
<tr>
<td>Hatzimpaloglou A</td>
<td>Observational</td>
<td>2002</td>
<td>15</td>
<td>70% at 12 and 24mo</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Smaira T</td>
<td>Observational</td>
<td>2001</td>
<td>9</td>
<td>56% at 1yr</td>
<td>75% at 1yr</td>
<td></td>
</tr>
<tr>
<td>Haage P</td>
<td>Observational</td>
<td>1999</td>
<td>50</td>
<td>3, 6, 12, and 24mo were 92%, 84%, 56% and 28%, 100% after 3mo, 93% and 100% after 6mo, 85% and 91% after 12mo, 68% and 72% after 24mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vessely TM</td>
<td>Observational</td>
<td>1997</td>
<td>20</td>
<td>1, 3, 6, and 12mo were 90%, 67%, 42% and 25%, 3, 6, 12, and 24mo were 89%, 64%, 56% and 22%,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mickley V</td>
<td>Observational</td>
<td>1997</td>
<td>15</td>
<td>1 yr at 100%, 2 yr at 85%</td>
<td>1 yr at 70%, 2 yr at 50%</td>
<td></td>
</tr>
<tr>
<td>Lumsden AB</td>
<td>Observational</td>
<td>1997</td>
<td>25</td>
<td>84% at 1mo, 42% at 6mo, 17% at 1yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gray RJ</td>
<td>Observational</td>
<td>1995</td>
<td>32</td>
<td>46% at 6mo, 20% at 12mo</td>
<td>76% at 6mo, 33% at 12mo</td>
<td>Peripheral and central lesions were mixed in the data reporting.</td>
</tr>
<tr>
<td>Breathard GA</td>
<td>Observational</td>
<td>1992</td>
<td>24</td>
<td>n/a</td>
<td>70.4% at 1mo, 62.1% at 2mo, 49.6% at 3mo, 28.9% at 4mo</td>
<td></td>
</tr>
<tr>
<td>Matthews R</td>
<td>Case report</td>
<td>1992</td>
<td>2</td>
<td>n/a</td>
<td>n/a</td>
<td></td>
</tr>
</tbody>
</table>
and covered stents in CVS. [49] Shemesh, et al. showed in a study of 25 patients that had recurrent cephalic arch stenosis that 3 and 6 month primary patency was 82% in the stent graft group and 39% in the bare stent group. One-year primary patency was 32% in the stent graft group and 0% in the bare stent group (P .0023). The study had major limitations though, including small sample size, early termination, and short term follow-up. When percutaneous options fail, surgical techniques can also be used to treat CVS. Although many times these surgeries will require claviculectomy and result in higher morbidity to the patient, symptoms can be resolved and often times dialysis access can be salvaged. These surgeries can range from axillary vein to IJ bypass, IJ to axillary vein transposition, axillary to saphenous bypass, patch angioplasty of axillosubclavian stenosis or even right atrial bypass grafting. [50] El-Sabrout et al. showed in nine patients with CVS from bilateral subclavian CVCs that a PTFE bypass from obstructed vein to the right atrial appendage could provide a functional access for up to a year after surgery. [51]

**Conclusion**

Central venous stenosis has become a central issue in the field of nephrology due to the efforts of increasing the number of autogenous AVF placement with the enduring problem of catheter use. Despite a variety of treatment options to provide symptomatic relief for CVS, long term patency is still a problem for these patients. To diminish the morbidity and cost associated with access dysfunction and CVS, catheter avoidance strategies remain a national priority.

**References**


Central Venous Stenosis in Dialysis Patients


Catheter Locks for Prevention of Infection and Maintenance of Access Viability

Sanjeev Shah
University of Wisconsin School of Medicine and Public Health, Division of Nephrology, Madison, WI, US

Introduction

Despite efforts by the National Kidney Foundation and their Fistula First initiative, tunneled hemodialysis catheters remain an important form of vascular access for hemodialysis patients in North America. Unlike their native access counterpart the fistula, the tunneled catheter has two major drawbacks for the patient: catheter thrombosis and the risk of blood stream infection (BSI) [1]. Both points severely affect quality of life as well as mortality for patients. In fact, after cardiovascular causes of death, infection is the second most common cause of death in the hemodialysis population [2]. In light of these facts, a variety of novel strategies have been implemented to address both risk of thrombosis and risk of infection in tunneled hemodialysis catheters. This chapter will highlight important developments in the prevention of both clinical problems by examining the use of catheter lock solutions.

The development and rationale of catheter lock solutions is best understood by examining the pathogenesis of thrombosis and catheter associated BSI in the dialysis population—both are often linked [3]. Catheter infection can happen through one of three potential mechanisms: extraluminal colonization, intra-luminal colonization or hematogenous spread from an unrelated focus of infection [4]. Unlike temporary dialysis catheters, where extraluminal colonization is often the predominant factor in initiating infection, tunneled catheters are often spared this mode of infection due the presence of a subcutaneous cuff which helps to retard the migration of organisms from the skin surface to the underlying vein. By contrast, intraluminal colonization secondary to hub/lumen contamination is often the
predominant form of infection in patients with tunneled catheters [5]. Hub contamination eventually leads to the formation of a “biofilm” of organisms adhering to the catheter lumen, a process that is accelerated by the formation of a fibrin sheath. Insertion of a foreign object in the blood necessarily activates the coagulation cascade and leads to deposition of fibrin, platelets and polymorphonuclear leukocytes along the catheter lumen, leading to a network of scaffolding that can help bind further bacteria as well as provide protected sanctuaries for growth [21]. In such cases, thrombus formation and subsequent catheter related infection become intimately linked, necessitating a strategy that not only addresses sterilization but also effective protection against thrombus formation.

The process of a “catheter lock” describes placing a solution within the catheter lumen and allowing it to dwell there for a period of time. This strategy has obvious benefits as it allows high concentrations of solution to be in contact with the catheter lumen without theoretically subjecting the patient to the systemic effects of the solution. An ideal catheter lock solution would be one that sterilizes the lumen, does not lead to bacterial resistance, has low side effects if systemically released as well as one that helps to break the cycle of re-infection by preventing thrombus formation. Prior and current attempts for production of catheter lock solutions have strived to reach these ideals—with mixed results. The following will be a review of some of the major catheter lock solutions in use and their efficacy.

### Heparin

The most common catheter lock solution today is heparin. Heparin, by virtue of inhibiting the intrinsic coagulation cascade, has been used for decades to prevent interdialytic catheter thrombosis and has obvious evidence for efficacy in preventing thrombosis. Despite its widespread use, however, very few guidelines exist for standardized use as evidenced by its conspicuous absence from the KDOQI guidelines [6]. Although felt to be generally safe, a recent randomized trial has shown evidence of systemic leak and increased risk of serious bleeding [7]. In addition, there have been reports of heparin-induced thrombocytopenia (HIT), with estimates of the clinically important form of HIT up to 3.9 % in hemodialysis patients whose catheters are packed with heparin [8]. To date, *in vitro* studies have shown some slight, short term antibacterial action of heparin although *in vivo* clinical studies have failed to show any benefit in this regard [9]. In fact, there is now some evidence that heparin may actually promote biofilm formation. When used, heparin is usually given at a dose of 5000 units/ml although concentrations as low as 1000 u/ml and as high as 10,000 units/ml have been used with success [10].

By contrast, recent publication of a RCT comparing intermittent use of tissue plasminogen activator (tPA) along with heparin in comparison to heparin alone has shown benefit [11]. Unlike heparin, tPA has theoretical benefit for management of catheter dysfunction in that it can actively treat thrombus formation—not just prevent its formation—by dissolving fibrin clot. Such dissolution of fibrin also has benefit for preventing bacteremia by reducing the presence of sheltered niches for bacterial growth. The above mentioned trial tested this hypothesis by comparing use of tPA locks once weekly (using heparin locks for the remaining two other HD sessions) with the use of heparin alone as a locking strategy. Investigators in this Canadian trial were able to show a 14% relative risk reduction in degree
of catheter malfunction as well as an 8.5% relative risk reduction in prevention of bacteremia. Adverse effects— including overall risk of bleeding—were not statistically different in both arms although the heparin arm did show a higher rate of intracranial hemorrhage. The major limitation to widespread use of this technique may be cost: estimates based on this trial revealed that tPA use cost $13,956 per episode of catheter related bacteremia prevented. No data was forthcoming as to the potential cost savings in regards to prevention of catheter malfunction.

Citrate

The coagulation cascade requires the use of calcium for adequate hemostasis. Citrate, by virtue of its ability to chelate cations, theoretically can prevent thrombosis by sequestering calcium ions. This idea has been exploited in catheter lock solutions as a means of maintaining catheter patency. To date, seven randomized controlled trials (RCTs) have looked at citrate as a catheter lock in comparison to heparin, the current standard. A meta-analysis of trials prior to 2007 examining citrate based lock solutions suggests that, surprisingly, citrate seems to have little efficacy in terms of improved catheter patency in comparison to heparin [12]. This lack of improved efficacy persisted even when accounting for study heterogeneity and different concentrations of citrate, suggesting that citrate is at best non-inferior to heparin for preventing thrombosis. More recent trials have actually showed a higher rate of thrombosis as noted by higher use of thrombolytics [13, 14]. It is unclear if this difference is due to differing patient characteristics in older vs. newer trials (i.e. AKI patients vs. chronic hemodialysis patients) or types of catheters used, suggesting that catheter type and vintage may play a role in predicting efficacy of a given solution.

In addition to theoretical anti-thrombotic properties, there is in vitro evidence that citrate may independently have antimicrobial properties against gram positive and gram negative bacteria as well as Candida species. This effect is attributed to three potential properties related to microorganisms and divalent cations [9]. First, divalent cations appear to be intimately involved in the crosslinking of polysaccharides in bacteria—as such, chelation of ions such as Mg$^{2+}$ by citrate appears to induce permeability in the cell wall and enhance cell death. Second, calcium is involved in the expression of various genes required for bacterial growth—chelation and subsequent lowering of calcium levels could interrupt such growth. Lastly, calcium is involved in the lattice structure of the glycocalyx slime layer that forms “biofilm” on catheters. Chelation of divalent cations may thus disrupt protected sanctuaries for bacterial growth and allow for better clearance of organisms [9, 15].

RCTs involving citrate locks prior to 2007 have shown much lower rates of infection, with up to a 75% decrease in relative risk of infection in comparison to heparin based on meta-analysis [12]. Notably, the trials that showed benefit also strictly adhered to aseptic technique with use of topical antimicrobials at the exit site as well as use of mupirocin for those patients screened to be S. aureus carriers, although some benefit (up to a 10% decrease in BSI) occurred even without explicit use of these additional prophylactic measures. Also notable was the fact that these trials used higher concentrations of citrate (up to 30%). While a Dutch trial did not show any higher degree of side effects with the use of citrate and did
show a lower incidence of bleeding in comparison to heparin [7], there have been other reports of fatal arrhythmia with higher citrate concentrations [16].

More recently, RCTs looking at citrate have failed to show the same difference in benefit as it relates to prevention of catheter thrombosis or catheter related BSI [13, 14].

Variation in the data for citrate has led to varied practice patterns: a large proportion of European dialysis units have begun to use citrate preferentially over heparin [15], although the majority of North American units continue to use heparin given concerns about the safety of citrate.

Ethanol

Ethanol has antimicrobial properties via a mechanism of protein denaturation [17]. It is thus theoretically attractive as lock therapy as it has low potential to breed microbial resistance, is relatively inexpensive, readily available and has a low toxicity profile in comparison to other agents such as antibiotics, citrate or heparin. Basic science data has confirmed that concentrated ethanol (>30%) has activity against a wide variety of organisms including gram positive, gram negative and Candida species with the ability to kill both planktonic as well as sessile organisms [18]. The latter is an important point to keep in mind as in vitro susceptibility testing of various antibiotics is often misleading when looking at comparable efficacy of specific antibiotic lock therapy (e.g. gentamicin): often concentrations >1000 times the MIC is required to kill sessile organisms within the biofilm. Unlike various antibiotics, ethanol has been shown to convincingly kill all organisms (including Candida) within the biofilm at a concentration of 70% within 4 hours of exposure [19]. Moreover, ethanol has been shown to be safe with both silicone and polyetherurethane catheters, with no loss of structural integrity of the catheter type despite exposure to high concentrations of ethanol up to 70% for 10 weeks [20].

Multiple reports have looked at the efficacy of ethanol as a potential lock therapy in both adults and children, often in the form of case reports or retrospective series [21]. More recently, a prospective, randomized controlled trial has also revealed the improved efficacy of ethanol in comparison to heparin in the prevention of tunneled catheter infections. Ethanol was shown to cause a greater than four-fold decrease in BSI as compared to heparin in a hematology patient population [18]. Authors from the same trial also published a case series examining the efficacy of alcohol locks in the treatment of established BSI. They noted an 80% clearance rate of established bacteremia in 19 patients using a combination of 70% ethanol locks and organism specific antibiotic therapy, although admittedly there was no control group [17]. As salvage therapy using antibiotic lock therapy in the dialysis population has had a much lower published clearance rate for treatment of established BSI (32%), this result suggests the need for further prospective trials looking at this lock modality, specifically targeting the dialysis population.

To this end, a RCT looking at ethanol locking as preventative modality is underway. The HEALTHY-CATH trial—an Australian trial—will specifically look at the efficacy of 70% ethanol locks in comparison to heparin in the prevention of catheter associated BSI [22]. This trial will be important as prior trials looking at ethanol have all used short daily locks, something that is impractical in a hemodialysis population that dialyzes (and therefore uses
their catheters) three times a week. A prospective look at adverse effects will also be helpful as current data suggest that ethanol, while efficacious, may cause significant short term catheter dysfunction [23]. An important endpoint to examine will be to see if the use of ethanol causes clinicians to trade improved bactericidal action at the expense of catheter dysfunction.

**Antibiotic Locks**

Clearance of adherent biofilm within the catheter lumen requires concentrations of antimicrobials such that they can penetrate within the biofilm and not only kill planktonic organisms but sessile organisms as well. In this setting, use of antibiotic locks as opposed to systemic antibiotics is theoretically attractive as it allows for high concentrations to be employed without subjecting the patient to risks of toxicity.

Antibiotic lock regimens tested in RCTs thus far in the hemodialysis population have included use of the following antibiotics: gentamicin, vancomycin, cefazolin, cefotaxime, and minocycline [24]. These antibiotics have often been used in combination with each other (most often with gentamicin), with other antimicrobials and also with heparin to prevent intraluminal thrombosis. Trials thus far have looked at both non-tunneled and tunneled catheters with the majority of trials examining incident patients more so than prevalent patients on hemodialysis. Three systematic reviews/meta-analyses have convincingly shown antibiotic lock therapy appears to reduce the rate of catheter related BSI, almost by a factor of 3 [12, 24, 25]. While both gentamicin alone or in conjunction with other antimicrobials appeared to be protective against both gram positive and gram negative organisms in general, gentamicin locks alone did not seem protective against *S. aureus* bacteremia whereas use of other antibiotics did show benefit in this regard [12]. Gentamicin dosing has been varied in trials, being as high as 40mg/ml and as low as 4 mg/ml. Vancomycin concentrations used have been as high as 25 mg/ml whereas cephalosporin dosing has usually been 10 mg/ml [24].

Concern has been raised about use of antibiotic lock solutions as it relates to two issues: risk of systemic toxicity as well as the development of resistant organisms. While theory would suggest that there should be minimal risk of systemic toxicity, there is often some degree of leak as evidenced by significant gentamicin levels as high as 2.8 mg/L in one trial [26]. Such high levels portend risk of ototoxicity as well as risk of loss of residual renal function. Almost 10 % of patients in one trial complained of vestibular symptoms or deafness; as formal audiometry was not performed in this trial, further subclinical damage could not be excluded. Previously, there had been no reported cases in dialysis patients with gentamicin resistant organisms, although as of 2010 reports have begun of gentamicin resistant *S. epidermidis* and *Enterococcus* [27, 28]. As of now, there has fortunately been no emergence of antibiotic resistance when using vancomycin locks or other antibiotics [12]; admittedly, follow-up in most of these randomized controlled trials has been short—a fact which does not preclude development of resistant organisms if long-term use is contemplated.
The above mentioned discussion suggests that there is a need to move beyond antibiotic lock therapy; rather the focus should be on antiseptic antimicrobial therapy that meets the parameters of being non-toxic and highly bactericidal, able to penetrate biofilm and effectively prevent thrombosis and fibrin sheath formation. Trials examining ethanol and various antimicrobial combinations (i.e. N-acetylcysteine, tigecycline and heparin) will go a long way towards helping to answer this question in the future [29]. In the meantime, a novel catheter lock solution containing citrate, methylene blue and parabens has been tested in the recently published AZEPTIC trial [10]. As mentioned previously, citrate has proven efficacy as an antimicrobial agent at high concentrations as well as a comparatively robust antithrombotic agent. Methylene blue similarly has antimicrobial properties via redox reactions that inactivate bacterial cell walls as do the compounds commonly found in preservatives called parabens. While low concentrations of each individually are not particularly effective (e.g. citrate at lower concentrations of less <10%), the combination solution of all three components has surprisingly robust synergistic antiseptic properties. A current solution of 7% citrate, 0.05% methylene blue, 0.15% methylparaben and 0.015% propylparaben effectively killed 99% of all planktonic bacteria tested within minutes, prevented biofilm formation and also killed sessile organisms within established biofilm in preliminary tests [30]. The recently published AZEPTIC tested this solution. This trial— a multicenter, RCT— examined the effect of this novel citrate/methelene blue and paraben solution (C-MP-P) in comparison to heparin in 407 hemodialysis patients using endpoints of catheter patency as well as risk of catheter associated BSI (Maki, Critical Care Medicine). The results of the trial showed an impressive 71% risk reduction in catheter related BSI in comparison to heparin and also showed improved efficacy in preventing death from any cause. All major organisms causing catheter associated BSI were represented including S. aureus (with the exception of fungi). Catheter patency was maintained equivalent to that of control using heparin locks. Importantly, the C-MP-P did not have an adverse effect profile that was inferior to that of heparin.

Conclusion

These results in aggregate suggest that there are many potential avenues to prevent catheter related BSI as well as maintain catheter patency using lock therapy. As hemodialysis catheter related complications are a major cost expenditure in an already overburdened health care system, these simple measures have the potential to bring huge cost savings to medicine. More importantly, through the use of strict aseptic technique, new catheter designs and now novel lock therapy, we may finally be able to close the gap in mortality and morbidity that has been strikingly apparent when comparing hemodialysis patients utilizing catheters and those using native fistulas.
References


Bosma, J., Siegert, C., Pearbooms, P., and Weijmer, M. Reduction of biofilm formation with trisodium citrate in hemodialysis catheters: a randomized controlled trial. *Nephrol Dial Transplant* 2010; 25:1213-1217

FDA. FDA issues warning on TriCitrasol dialysis catheter anticoagulation FDA Talk Paper T00-16, 14 April 2000


Chapter XXII

Catheter Surface Coatings – Do They Make a Difference?

Vandana Dua Niyyar¹ and Alexander Yevzlin²
¹Division of Nephrology, Emory University, Atlanta, GA, US
²University of Wisconsin, Madison, WI, US

Abstract

Vascular access dysfunction is a major cause of morbidity in hemodialysis (HD) patients. An upper extremity autogenous arteriovenous fistula (AVF) that preferentially involves the cephalic vein is the access of choice for hemodialysis patients, followed by autogenous AVF utilizing the basilic vein and the use of prosthetic arteriovenous grafts (AVG). Despite these recommendations, central venous catheter (CVC) use is widespread among both incident and prevalent HD patients. Long-term use of CVC’s for HD is complicated by a high rate of infection and thrombus-related dysfunction. The use of surface treated catheters has been advocated to minimize catheter-related infections (catheters with antimicrobial coatings) as well as catheter thrombosis (catheters with antithrombotic coatings), and thereby, to mitigate the impact of these complications. This review will discuss the role of catheter surface coatings with respect to these two complications and discuss emerging trends in this field.

Introduction

The predominant modality for renal replacement therapy for patients with end-stage renal disease (ESRD) in the United States is hemodialysis (HD) [1]. The lifeline for these HD patients is their vascular access. The access of choice for hemodialysis patients remains an upper extremity autogenous arteriovenous fistula (AVF) that preferentially involves the cephalic vein, followed by autogenous AVF utilizing the basilic vein and then the use of prosthetic arteriovenous grafts (AVG) [2, 3].
Despite these recommendations, central venous catheter (CVC) use is widespread among both incident and prevalent HD patients [1], with little change in CVC use despite the efforts of the Fistula First Breakthrough Initiative. Their ongoing use can be attributed to a multitude of factors, including a rise in the prevalent HD population, an aging HD population [4] and multiple co-morbidities affecting the vasculature. Moreover, the high primary failure rate of AVFs and the increasing placements of marginal AVF in an attempt to achieve the recommended targets, have led to prolonged use in some patients. Though central venous catheters have the distinct advantage of providing immediate access for use [5], they are primarily intended as bridge therapy. The long-term use of central venous catheters is fraught with complications including a high rate of infection [6] and thrombus-related dysfunction [7, 8].

The use of surface treated catheters has been advocated to minimize catheter-related infections (catheters with antimicrobial coatings) as well as catheter thrombosis (catheters with antithrombotic coatings), and thereby, to mitigate the impact of these complications. This review will discuss the role of catheter surface coatings with regards to these two complications and emerging trends in this field.

**Catheter Related Bacteremia**

A serious complication limiting the use of central venous catheters is catheter-related bacteremia (CRB) [9]. Major risk factors for catheter related infections include contamination of the catheter hub, subsequent colonization of the catheters by intra-luminal spread and the formation of a biofilm by bacteria. Bacteria enter the lumen through the flora of the surrounding skin or the hands of health-care workers during catheter-hub manipulation for dialysis. They then attach to the HD catheter and extensively propagate into bacterial colonies. A coating of exopolysaccharide and a sticky glycocalyx matrix called the biofilm is generated. The biofilm stabilizes and attracts other microorganisms to adhere to each other as the bacterial colonies mature (Figure 1).

Biofilm formation is an adaptive strategy that shields the bacteria and prevents diffusion of antibiotics to them and allows them to survive in a hostile environment [10]. In addition, though a clear link between biofilms and fibrin sheaths has not been established, it has been shown that infectious complications increase the risk of catheter-related thrombosis [11] and also once a peri-catheter thrombus or fibrin sheath is formed, the patient is predisposed to infections (Figure 2) [12].

**Catheter Thrombosis**

Central venous catheters were first introduced for dialysis access in the 1980’s [13, 14]. Catheter design has since evolved over the years [15], with continual alterations in an attempt to minimize intimal trauma leading to thrombosis while at the same time providing maximal blood flow [5]. Thrombus formation was initially reported in an in-vivo study from Belgium, where the investigators placed silicone catheters in rats and studied histological changes in their veins at scheduled intervals [16].
Catheter Surface Coatings – Do They Make a Difference?

Figure 1. Biofilm can lead to infection. A) Drawing of bacteria producing adhesive biofilm which may eventually form into a fibrin sheath around catheters. B) The fibrin sheath may become infected, which can be especially difficult to manage in the setting of pacer leads.

As a result of endothelial damage to the cell wall at the site of catheter insertion, a pericatheter thrombus formed as early as 24 hours within placement. With the continued presence of the central venous catheter, and ongoing injury, the researchers noted smooth muscle migration and the addition of collagenous matrix, transforming the thrombus into an organized sheath. They thus described a continuum from clot formation to an organized sheath that disrupts flow through the catheter.

The pathophysiology of thrombus formation in CVC’s used for HD can be further explained by Virchow’s triad – endothelial injury (initial insertion of catheter leading to endothelial damage of the vessel wall), coagulability (initiation of the coagulation and inflammatory cascade) and changes in blood flow (intra-luminal stasis of blood in the interdialytic period), all three of which exist in many hemodialysis patients (Figure 3) and which lead to eventual fibrin sheath formation (Figure 4). Each one of these factors has been addressed so as to minimize catheter dysfunction. Changes in catheter design have evolved over the years – individual catheters, placed side by side; dual-lumen catheters; step-tip vs. spilt-tip catheter which showed no significant differences in flow and re-circulation, though
the split-tip catheters had a significantly longer half-life (78% vs. 64% at 120 days) [17]; addition of side holes – which lead to higher flow rates, though they had increased adherent clots and catheter related bloodstream infections (2.54 vs. 0.254/1000 catheter days); symmetric tipped tunneled catheters [18] and the self-centering superior venacava catheter [5]. The diverse uses of catheter lock solutions – in both prophylaxis and treatment of catheter thrombosis and catheter-related bacteremia – have led to the development of a variety of solutions, none of which is “just right”. Surface-treated catheters are yet another attempt to mitigate the complications of both infection and thrombosis in central venous catheters and may either be anti-microbial or anti-thrombotic.

Figure 3. Virchow’s triad – hemodialysis patients often suffer from all three problems of the triad.

Figure 4. Fibrin sheath leading to thrombosis. A) Thick arrow points to tip of retracted tunneled catheter with long fibrin sheath from femoral vein into IVC. B) Disruption of fibrin sheath with balloon angioplasty. C) Thin arrow points to thrombosis after angioplasty can lead to pulmonary embolism.
Antimicrobial Surface Treated Catheters

The use of antimicrobial surface coatings has been studied extensively in the critical care literature. As a result, the Centers for Disease Control recommend the use of antimicrobial coated catheters in those patients in whom the rate of infection exceeds 3.3 per 1000 catheter days [19]. However, the published data, as detailed below and in Table 1, is sparse with regards to both the acute and chronic hemodialysis population.

Table 1. Anti-infective coatings

<table>
<thead>
<tr>
<th>Catheter Type</th>
<th>Coating</th>
<th>Studies</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-tunneled Femoral</td>
<td>Minocycline/Rifampin</td>
<td>Chatzinikolaou, 2003, Prospective, randomized study</td>
<td>Significant decrease in catheter-related infections in the antibiotic-coated catheters.</td>
</tr>
<tr>
<td>Non-tunneled, Subclavian</td>
<td>Bismuth</td>
<td>Schindler, 2010 Prospective, randomized, double blinded study</td>
<td>No improvement in catheter survival, but a decrease in colonization in the bismuth-coated group.</td>
</tr>
<tr>
<td>Non-tunneled compared to catheters with attachable cuff</td>
<td>Silver-impregnated cuffs</td>
<td>Dahlberg, 1995 Prospective, randomized, non-blinded study</td>
<td>No significant differences in catheter colonization, exit site infections or catheter-related infections in the two groups.</td>
</tr>
<tr>
<td>Non-tunneled and tunneled, Internal jugular / Subclavian</td>
<td>Ion-beam assisted deposition of silver coating or ion implantation of silicone</td>
<td>Bambauer, 2003, Prospective case-control study</td>
<td>Significant decrease in bacterial colonization in the surface treated group. Silver leaching noted, though non-toxic.</td>
</tr>
<tr>
<td>Tunneled, Internal jugular</td>
<td>Ion-beam assisted deposition of silver coating</td>
<td>Trerotola, 1998 Prospective, randomized, control study</td>
<td>Colonization and infection rates were slightly (but not significantly) higher in the experimental group as compared to the control group. Two patients required premature removal of the catheters as a result of presumed allergic reaction to the silver.</td>
</tr>
<tr>
<td>Tunneled, Internal jugular and femoral</td>
<td>Split-tip catheter with a silver sulfadiazine coating, compared to a spiral z-tip design with a silver anti-microbial sleeve</td>
<td>Kakkos, 2008, Prospective, randomized, control study</td>
<td>Infection rates similar in both groups. Primary patency improved with the silver anti-microbial sleeve, the authors attributed that to the spiral z-tip design.</td>
</tr>
</tbody>
</table>
A randomized trial of internal and external minocycline and rifampin coatings on non-tunneled femoral catheters in hospitalized adult cancer patients requiring hemodialysis for acute renal failure showed a significant decrease in the risk of catheter-related infection with coated catheters [20]. There were 66 patients in the experimental group and 64 patients in the control group; all 7 infections were in the uncoated catheters.

Another antimicrobial used as a surface coating is bismuth, which not only inhibits growth of bacterial organisms but has also been shown to inhibit biofilm formation [21]. A prospective, randomized controlled double-blind trial investigated clinical outcomes with surface-modified bismuth coated catheters (77 patients; 38 with bismuth coated catheters and 39 standard catheters). The study found no improvement in catheter survival between the two groups, though there was a decrease in bacterial colonization in the bismuth coated group [22].

Silver is theoretically advantageous as it has been shown to decrease bacterial colonization in vitro [23] as well as potentially reduce thrombogenicity. In a randomized control trial of silver-impregnated cuffs in subclavian HD catheters (101 patients; 47 with silver-impregnated cuffs and 54 with routine catheters), the authors found no reduction in catheter-related infections [25]. An analysis of 225 catheters (113 HD catheters surface-treated with silver, 112 untreated catheters) showed a significant decrease in bacterial colonization with the surface treatment (8% as compared to 46.4%) [24]. They also reported silver leaching in their patients, with increases in measured silver levels, though the levels returned to normal several days after removal of the tunneled catheters and no toxicity was found in those 21 patients who were tested.

The use of silver coating in tunneled internal jugular hemodialysis catheters was also evaluated by a randomized, control trial in 91 patients (47 in the coated catheter arm and 41 in the uncoated arm) [26]. Paradoxically, colonization and infection rates were slightly (but not significantly) higher in the experimental group as compared to the control group.

Two patients required premature removal of the catheters as a result of presumed allergic reaction to the silver and the resultant hyperpigmentation persisted long after the removal of the catheters.

A case-control study of 200 patients, 100 in each arm, evaluated two different catheter-tip designs – a split-tip with a silver sulfadiazine coating applied to the external surface of the catheter between the hub and cuff, as well as cuff to mid-catheter; and a spiral-z tip with an anti-microbial silver sleeve permanently bonded to the surface of the catheter between the hub and cuff. Though there was a significant decrease in malfunction and thrombosis in the silver bonded group, the authors attributed the improvement to the difference in catheter tip design and not the surface coating.

**Anti-Thrombotic Surface Treated Catheters**

Heparin is a sulfated polysaccharide and its major anticoagulant effect is through an antithrombin (AT)-dependent mechanism which inactivates thrombin and activated factor X (factor Xa) [27]. Surface-coated catheters, with heparin covalently bonded to the surface of catheter, have the hypothetical advantage of reducing thrombin activated factors, decreased proliferation of smooth muscle cells and reduction of biofilm, fibrin sheath and thrombus
formation. Both fibrin sheath formation and thrombus weight were reduced in unpublished animal studies from the manufacturers, but the results are yet to be validated in the HD population. There have been only three publications addressing heparin-coated catheters, as detailed below.

A case-control retrospective review of 88 tunneled internal jugular catheters (38 uncoated split-tip and 50 heparin-coated catheters) found no difference in catheter patency or catheter related infections in the two groups [28]. In another retrospective review of 60 heparin-coated catheters, the authors suggested that these catheters may be effective in mitigating thrombosis and inhibiting fibrin sheath propagation, without the systemic effects of heparin [29].

However, given the small sample size, lack of controls and the retrospective nature of their observations, the researchers recommended larger randomized clinical trials to confirm the benefit.

Another prospective database was retrospectively queried to determine outcomes of 175 tunneled internal jugular catheters (89 heparin-coated and 86 non-coated) [30]. The primary outcome was cumulative catheter survival and the secondary outcome was infection-free catheter survival.

Cumulative catheter patency was similar in both groups though interestingly, the authors found that the incidence of catheter-related bacteremia was significantly less in the heparin-coated catheters. They hypothesized that the heparin coating prevented thrombus formation, which acted as a nidus for the biofilm formation, but did not prevent the formation of a thrombus at the catheter tip.

**Table 2. Anti-thrombotic coatings**

<table>
<thead>
<tr>
<th>Catheter Type</th>
<th>Coating</th>
<th>Studies</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tunneled, Internal jugular</td>
<td>Heparin</td>
<td>Clark, 2009 Case-control retrospective review</td>
<td>No significant difference in catheter patency or catheter related infections in the two groups</td>
</tr>
<tr>
<td>Tunneled, Internal jugular</td>
<td>Heparin</td>
<td>Mojibian, 2009 Retrospective review</td>
<td>Over 16-month period, the authors reported catheter-related infections 1.12/1000 catheter days and 6/60 catheters were exchanged for malfunction, suggesting that these catheters may be effective in mitigating thrombosis and inhibiting fibrin sheath propagation.</td>
</tr>
<tr>
<td>Tunneled, Internal jugular</td>
<td>Heparin</td>
<td>Jain, 2009 Retrospective review</td>
<td>Cumulative catheter patency was similar in both groups though the authors found that the incidence of catheter-related bacteremia was significantly less in the heparin-coated catheters.</td>
</tr>
</tbody>
</table>
Future Directions

Although central venous catheters are the least preferred mode of vascular access, a surface treatment that maintains patency while minimizing catheter related infections may decrease the morbidity and mortality associated with them. Despite the theoretical advantages of surface treatments, there is a paucity of data in hemodialysis patients. There are, nonetheless, some valid concerns regarding these treatments that need to be addressed in randomized, controlled trials including long-term efficacy and systemic side-effects of both anti-microbial and anti-thrombotic coatings. In addition, it is hard to justify the increased cost [31] of surface-treated catheters for chronic hemodialysis in the absence of convincing clinical data demonstrating that they reduce catheter-related complications in this patient population.

The search is on for the perfect surface coating and though there has been remarkable improvement in the development of coated catheters, the field is still wide open for future innovation. The desired characteristics of an ideal surface coating would be one that is [31]:

- Biocompatible
- Prevents both thrombus and fibrin sheath formation
- Has broad-spectrum antimicrobial activity without inducing resistance
- Is safe and effective long-term

Until then, the best prophylaxis remains minimizing central venous catheter use in the first place.

References


Chapter XXIII

A General Nephrologist’s Approach to a Poorly Functioning Catheter

Roman Shingarev¹ and Alexander S. Yevzlin²
¹Division of Nephrology, Department of Medicine, University of Alabama, Birmingham, AL, US
²University of Wisconsin School of Medicine and Public Health, Division of Nephrology, Madison, WI, US

Introduction

Despite several national efforts to reduce catheter dependence for incident and prevalent end-stage renal disease (ESRD) patients, catheter use remains a major problem in the US hemodialysis (HD) population, with tunneled dialysis catheter (TDC) being used in the vast majority of incident HD patients and over 25% of prevalent HD patients [1]. TDCs are associated with an independent risk of mortality [2], as well as morbidity, including central venous stenosis [3, 4], infection [5, 6] and thrombosis [7]. Perhaps the most common form of catheter morbidity is dysfunction of the TDC. This requires interruption of dialysis sessions, low flow and consequent inadequate dialysis, and multiple referrals for procedures. Catheter dysfunction is defined by KDOQI as “failure to attain and maintain an extracorporeal blood flow of 300 mL/min or greater at a pre-pump arterial pressure more negative than –250 mm Hg” [8]. Left untreated, such catheters require premature removal when they become nonfunctional (i.e., with one or both lumens that cannot be aspirated) [9].

The purpose of this chapter is to describe the process of catheter dysfunction evaluation for the general nephrologist. TDC dysfunction can be conveniently divided into early or late presenting, which helps guide diagnosis and subsequent management. Dysfunction noted immediately after the catheter placement is likely due to the positioning of the catheter, preexisting vascular abnormalities (e.g., central venous stenosis) (Figure 3) or mechanical damage to the catheter (e.g., tight suture or perforation). Dysfunction developing after successful initial use is usually due to thrombosis, fibrin sheath formation around the catheter, mural thrombus adhering to the catheter tip, or new central venous stenosis. The remainder of
the chapter will describe these problems in detail and offer a comprehensive diagnostic algorithm that can be used at the bedside.

**Bedside Catheter Evaluation**

Catheter dysfunction is usually detected at a dialysis unit where several steps can be taken to evaluate and resolve the problem. Improvement of blood flows after patient repositioning is indicative of catheter tip malposition. Reversal of inlet and outlet lumens may overcome the ball valve effect of the fibrin sheath or a vessel wall in direct contact with one of the catheter tips. Dialysis equipment should be assessed for malfunction leading to activation of pressure alarms. Examples of equipment problems include line kinking, dialyzer pump failure, dialyzer clotting, etc. Instillation of a thrombolytic agent in TDC lumens for 1 hour to up to 24 hours is usually performed when intraluminal stenosis is suspected. Endoluminal fibrin analysis system (FAS) brush has been employed in attempt to improve catheter flows by few dialysis centers, however only one small study sought to evaluate its effectiveness reporting positive results [10].

Figure 1 suggests a diagnostic and therapeutic algorithm for general nephrologists and dialysis unit staff to follow when catheter dysfunction is present.

Figure 1. Diagnostic and therapeutic algorithm for catheter dysfunction in the dialysis unit.
The general nephrologist should perform a physical examination of the malfunctioning catheter as the first step in evaluation and should include aspiration of luminal contents, assessment for kinks, integrity, and tunnel infection of the TDC. Next, a radiograph should be obtained to evaluate the catheter positioning.

This may reveal a kink in the catheter, a catheter tip that migrated into the Superior Vena Cava (SVC) or even into either of the brachiocephalic veins. The latter may happen in obese patients, whose cuff-to-vein catheter length may increase considerably with movement, thereby shortening the intravascular catheter length due to immovable subcutaneous cuff position. A curved caudal portion of the catheter or a doughnut (“down the barrel”) appearance of the edge of the catheter’s tip is indicative of azygous vein cannulation. Location of the distal portion of the catheter in the midsternal or left parasternal region should raise a suspicion of intraaortic placement of the catheter. A lateral radiograph showing the catheter projecting toward anterior mediastinum may further strengthen this suspicion [11, 12]. If any of these abnormalities is discovered, tPA should not be used in an attempt to re-establish flow; in this scenario tPA will be ineffective and potentially harmful.

**Diagnostic Evaluation in an Interventional Suite**

If adequate blood flows cannot be reestablished at the dialysis unit, referral to the interventional suite is indicated. This referral should only be made after attempts have been made to diagnose the problem with physical exam and radiography at the dialysis unit. For this reason, when a patient is referred to the interventional suite for TDC dysfunction, it is assumed that efforts such as patient repositioning and tPA, when appropriate, have already been tried. If this has not been performed by the general nephrologist, it is imperative to communicate this to the interventional team so that unnecessary procedures and their attendant morbidity can be avoided. The diagnostic algorithm that is suggested for the interventional suite is outlined in Figure 2. If there’s a suspicion for a peri-catheter thrombus or fibrin sheath, angiogram can be performed by slowly injecting 10-15 ml of contrast by hand through each catheter port. In presence of a fibrin sheath, the contrast will outline the sheath flowing retrograde from the catheter tip (Figure 4). Antegrade contrast flow may also demonstrate a pericatheter filling defect consistent with a mural thrombus [13]. Alternatively, the catheter may be retracted over a wire to position its tip in the internal jugular vein. In this case, the contrast flows antegrade clearly outlining the lumen of the fibrin sheath (Figure 4) [14].

**Interventions Directed at Specific Causes of Catheter Dysfunction**

In many instances, despite a thorough physical examination and appropriate outpatient imaging, the diagnosis of catheter dysfunction cannot be made. Nevertheless, the general nephrologist should familiarize themselves with the potential causes of TDC dysfunction that can be diagnosed and treated interventionally, simply because the restoration of flow cannot be tested in the interventional suite.
Roman Shingarev and Alexander S. Yevzlin

Figure 2. Diagnostic and therapeutic algorithm for catheter dysfunction in the interventional suite.

A radiographic problem may be fixed but it does not follow that the catheter will sustain adequate flow. When the patient returns to the I unit in this scenario, it is imperative that the general nephrologist be able to have a discussion with the interventional specialist about what problem was diagnosed and to be able to judge if the problem was treated adequately.

For this reason, we briefly describe several interventional approaches that can be used to diagnose and treat catheter dysfunction in the interventional suite.

Catheter Damage

If a catheter wall integrity is compromised anywhere along its extravascular portion, either as a result of a manufacturing defect or an operator’s mistake, the patient may present with either persistent bleeding from the tunnel or symptoms of air embolism [15, 16].

Diagnostic test of choice in this case is a catheterogram that can be performed by hand-injecting 10 cc of contrast into each catheter lumen. Extravasation of contrast confirms the diagnosis necessitating exchange of the malfunctioning catheter for a new one.
Catheter Kinking

The initial radiograph taken in the IR suite may immediately expose a problem such as a catheter kink. Kinking occurs either as a result of a “high stick”, when the entry in the internal jugular vein was made high above the clavicle in the neck forcing the catheter to take a sharp turn from the tunnel and into the vein, or when the catheter gets caught in the insufficiently dissected subcutaneous tissue at the neck incision site after it has been inserted in the vein through the splitsheath or over the wire. In the first scenario, the existing TDC has to be
removed and a new one has to be placed lower in the internal jugular vein after sufficient hemostasis has been achieved. In the second scenario, an Amplatz wire placed in the IVC through one of the lumens may be used to stabilize the catheter. Next, an incision in the skin overlying the kink is made with care taken not to nick the catheter and a blunt-tip hemostat is used to dissect the tissue underneath the kink. Moving the catheter back and forth over the wire while applying pressure to the catheter bend usually allows the operator to eliminate the kink.

**Tip Malposition**

Due to complex anatomy of the thoracic veins, catheter malposition is common [17]. In the settings of SVC stenosis (itself common in HD patients) and venous aberrations that follow, such as dilatation of the azygous vein, the likelihood of incorrect catheter positioning is even higher [18]. Even if initially appropriately positioned, catheters have been described to migrate spontaneously, most commonly in the contralateral innominate vein generating an array of complications [11, 19]. TDC dysfunction in these cases is due to direct contact of the catheter tip or its’ side holes with the vessel wall causing obstruction of blood flow. A TDC placed through the left internal jugular vein may induce thrombus formation even if its’ tip only moves up into the upper portion of the SVC [20], because of the 90 degree turn the catheter has to take from the left brachiocephalic vein into the SVC. If the catheter length is too short, its’ tip will be sticking against the right lateral wall of the SVC irritating endothelium.

If the TDC is found to be malpositioned within the first week of its’ placement, attempts can be made to advance it into the lower portion of the SVC over an Amplatz wire placed through one or both catheter lumens. Older TDCs will have fibrous tissue formed around the cuff necessitating subcutaneous dissection and subsequent exchange for a new TDC. An operator may choose to advance the new TDC further into the SVC to minimize the future catheter migration, however, observations from a small patient series reported by Haygood et al. [11] suggest this strategy does not necessarily changes the outcomes. Nevertheless, this option may still be appropriate for TDCs with split-tip design, as its’ tips are preformed to separate at an angle making it more likely for the shorter tip to end up in an inappropriate position. Because of that, some experts recommend placing the tips of a split-tip catheter in the right atrium [21]. This recommendation is somewhat controversial, as there are reports of higher incidence of atrial thrombi, vessel wall perforation leading to cardiac tamponade and cardiac arrhythmias [22, 23], associated with atrial positioning of a catheter. Supporting evidence, however, is rather insufficient to advice against such practice. If the TDC is to be exchanged, an operator may also consider changing a split-tip catheter for a step-tipped one, which should theoretically lower the chances of tip migration.

**Catheter Thrombosis**

Intraluminal thrombosis remains the most common cause of TDC dysfunction despite routine use of anticoagulant locking solutions [24, 25]. After the initial evaluation ruling out a positional or mechanical problem, in instillation of a thrombolytic agent is recommended.
Several drugs, such as urokinase and streptokinase, have been used in the past, but of drugs currently available on the market only two – alteplase and reteplase have been used for TDC thrombosis. Reteplase has been purported to have superior clot penetration [26], it is rather cumbersome to use requiring frozen storage and aliquoting individual doses [27].

Therefore, use of alteplase or tPA is more common in clinical practice. The dose of 2 mg per lumen is usually instilled for about an hour, however, if blood flow is not restored, the alteplase is aspirated from the lumens and another dose may be instilled for longer duration (usually 10-24 hours), although evidence exists that prolonged dwell time may not influence subsequent rates of TDC patency [28].

In general, treatment of intraluminal thrombosis with thrombolytics is associated with 70-88 % immediate success rate of restoring adequate blood flow [28-32]. At two weeks following instillation of thrombolytics only half of the TDCs remain patent [28]. These unsatisfactory patency rates are likely explained by the fact that catheter dysfunction in many patients included in these studies was due to thrombi extending outside of the catheter lumen or fibrin sheath that require a more intensive therapy than described above.

As described above, a FAS brush can be employed in the interventional suite in attempt to mechanically remove an intraluminal thrombus, however, the outcome and complications data are limited to a small trial reported by Tranter et al. [10]. The immediate success rate of 73% and 6-week patency of 50% are comparable to those of thrombolytic use and it is unclear if this novel strategy can improve outcomes if used in combination with thrombolytic therapy.

Fibrin Sheath

Recurring use of thrombolytics should in itself raise suspicion for the presence of fibrin sheath around the catheter (Figure 4) [33] – a problem affecting 40 – 100% of central venous catheters [34-36]. While thrombolytic therapy was demonstrated to have immediate success rate of 91%, two-month patency was, expectedly, quite low at around 36% [37]. Subsequently, four other strategies for restoration of catheter patency have been evaluated. Those included TDC exchange, percutaneous fibrin sheath stripping (PFSS), angioplasty disruption, and internal snare maneuver (Table 1).

In one study, patency rates were shown to be superior with catheter exchange compared to PFSS at 4 months [14] and in another one, PFSS did not improve catheter patency rates when compared to urokinase over 45 days following the procedure [13].

Yet another study showed no differences in immediate or long-term (6 months) outcomes following TDC exchange, PFSS and angioplasty disruption [38]. Most recently, Oliver et al. [34] demonstrated significantly improved median times to recurrent TDC dysfunction associated with angioplasty disruption followed by TDC exchange compared to TD exchange alone (373 days versus 97.5 days, p = 0.22).

Based on these findings and procedure cost analysis, current KDOQI guidelines currently recommend the latter strategy for treatment of TDC-associated fibrin sheaths. A novel technique of fibrin sheath removal by an “internal snare” has been described in 2007 and has not been compared head-to-head with other fibrin sheath disruption procedures. Authors, however, report 100% immediate success and 100% patency rate at a mean follow up of 17 weeks [39].
### Table 1. Interventional options for treatment of fibrin sheath

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TDC Exchange</strong></td>
<td>One or two guide wires are placed in the IVC under fluoroscopic guidance. Subcutaneous tissue around the cuff is dissected under local anesthesia with a hemostat and the indwelling TDC is retracted over the wires that are then sterilized. A new TDC is then inserted through the existing tunnel over the wires into the appropriate position.</td>
</tr>
<tr>
<td><strong>Percutaneous Fibrin Sheath Stripping</strong></td>
<td>A standard 6-French sheath is placed in the femoral (usually right) vein and a diagnostic angiographic catheter is advanced into the SVC over a guide wire. Next, the guide wire is exchanged for a 25-mm or 35-mm diameter nitinol loop snare, which is then engaged and advanced cranially to encircle the catheter. An Amplatz wire placed in the IVC though one of the TDC lumens may facilitate this maneuver. After the snare device reaches the catheter insertion site in the internal jugular vein, it should be tightened and retracted all the way out to manually clean it thereby minimizing the risk of distal embolization of fibrin. Contrast can be injected through the catheter to evaluate the outcome of this procedure.</td>
</tr>
<tr>
<td><strong>Angioplasty Disruption</strong></td>
<td>The indwelling TDC needs to be retracted over two Amplatz wires as described in the “TDC Exchange” section above. A long (20cm) 7-French sheath is then advanced over one of the Amplatz wires into the SVC and a 12 mm balloon is inserted through the sheath and inflated several times along the fibrin sheath tract. To maximize the fibrin sheath disruption, the balloon may be moved back and forth in the SVC while inflated. Post-procedure angiography should be performed to ascertain success of the procedure.</td>
</tr>
<tr>
<td><strong>Internal Snare</strong></td>
<td>A 0.089 mm nitinol wire is folded in the middle to form a U-shaped loop and advanced through each TDC lumen under fluoroscopic guidance until the loop emerges from the catheter tip. Moving the loop back and forth around the tip of the catheter disrupts the fibrin sheath overlying the distal and proximal ports and restores the catheter flow.</td>
</tr>
</tbody>
</table>
Central Vein Stenosis

Stenosis of the brachiocephalic vein or SVC does not affect the TDC function as long as its tip remains outside the stenotic segment not in direct contact with the vessel wall (Figure 3). If patient develops SVC syndrome, however, the catheter has to be relocated. In the settings of SVC stenosis, the usual choice is either femoral vein. In many patients with long history of vascular access problems internal jugular and femoral veins may become inaccessible, either due to stenosis (Figure 3) or venous stents placed in arteriovenous thigh grafts. Uncommon approaches to cannulation of these patients have been described, including translumbar approach [40, 41] or transhepatic approach [42, 43]. Decision to undertake one approach or the other should be based on an individual patient’s anatomy and an operator experience with these procedures.

Conclusion

TDC dysfunction can be conveniently divided into early or late presenting, which helps guide diagnosis and subsequent management. Dysfunction noted immediately after the catheter placement is likely due to the positioning of the catheter, preexisting vascular abnormalities or mechanical damage to the catheter. Dysfunction developing after successful initial use is usually due to thrombosis, fibrin sheath formation around the catheter, mural thrombus adhering to the catheter tip, or new central venous stenosis. General nephrologists are critical in guiding the diagnosis and management of poorly functioning tunneled hemodialysis catheters.

References


A General Nephrologist’s Approach to a Poorly Functioning Catheter


VI. HEMODIALYSIS VASCULAR ACCESS INTERVENTIONS
Introduction

Venous angioplasty is currently the most common therapeutic endovascular procedure performed by interventional nephrologists. This is because of the high prevalence of venous stenosis in association with the arteriovenous (AV) access of patients on hemodialysis (HD). Venous angioplasty may involve peripheral veins or central veins, but in this chapter, the discussion will focus only on peripheral venous angioplasty.

General Concepts

Angioplasty of venous stenosis, in HD patients, is usually performed in the context of the AV access. Venous stenosis may be present prior to creation of the AV access, or may evolve following its creation. The creation of an AV access drastically augments blood flow to its venous outflow tract, and exerts demand for an efficient venous drainage. Thus, pre-existing silent venous stenosis is uncovered, and becomes clinically significant soon after creation of the AV access. Venous stenosis that evolves following vascular access creation will become clinically significant over time.

Two crucial technical steps need to be achieved prior to performing venous angioplasty. The first is successful cannulation of the access. This step is necessary for both diagnostic and therapeutic purposes. The second is successful passage of a guide wire across the identified venous stenosis.

History and physical exam of the AV access are crucial in determining the initial cannulation approach [1-3]. This is especially true of the AV fistula (AVF), but is also
important in the case of the AV graft (AVG). When a stenosis is suspected in the body or venous outflow tract of the AV access, cannulation should be done in the initial aspect of the inflow segment of the access, with the needle pointing in a downstream direction. However, when the stenosis is suspected to be in the initial 5 cm of the access, cannulation should be done at a more proximal site, with the needle pointing in an upstream direction. Two cannulations, pointing in different directions, become necessary when inflow and outflow venous stenoses coexist in the same access. Depending on the clinical circumstances and technical factors, they can be done in the same setting, or at different times.

AV access cannulations may prove to be difficult in the AVF with early failure or with long stricture. In general, the AVG is cannulated with an 18 gauge needle that allows the introduction of 0.035” guide wire. The same may apply to mature AVF, but the use of a 21 gauge needle and a micropuncture set (Medcomp, Harleysville, PA) allow safer cannulation of the AVF, especially when the luminal diameter is narrow.

In these instances, a 0.018” guide wire is introduced initially, but in most instances, it is replaced by a 0.035” guide wire if venous angioplasty is judged necessary. Placement of a sheath, with a side port, at the cannulation site is very useful while performing venous angioplasty as it allows insertion of the guide wire through its lumen, yet continues to allow angiography by injecting contrast agents through its side port. The size of the sheath necessary for angioplasty depends on the size of the angioplasty balloon being used.

For the same balloon diameter, it may also vary by manufacturer. In general, with current technology, a 6F sheath allows passage of angioplasty balloons up to 8 mm in diameter; whereas, in most instances, a 7F or 8F sheath allows up to 14 mm in diameter.

Diagnosis of Venous Stenosis

In general, a venous stenosis that reduces the luminal diameter of the vessel by ≥ 50% is agreed upon as an anatomically significant obstruction. Functionally, a significant stenosis reduces AV access flow (unless flow is diverted into accessory veins). Clinically, and depending on its location in the AV access circuit, it will induce one or more of the following: reduction in urea clearance rates, abnormal venous and/or arterial pressure of the HD circuit, increased HD circuit recirculation, and prolonged bleeding from AV access needle cannulation sites. At times, it causes emergence of collateral veins, and extremity swelling.

Angiography is the gold standard for diagnosing venous stenosis. The history, physical exam [1-3], AV access flow measurement [4] and duplex ultrasound [5] can also diagnose venous stenosis.

In practical terms, the history and physical exam are crucial in raising the suspicion of venous stenosis as well as suggesting its possible location [1-3]. When a stenosis in the body of the AV access is suggested, this suspicion can be further refined by examining the AV access by ultrasound. These data, taken together, will help plan and direct the initial endovascular treatment approach of the AV access.

Once the AV access is cannulated, an angiogram is done. Images of the AV access, its arterial anastomosis, and its venous outflow tract are obtained. Any venous stenosis with severity of ≥ 50% needs to be identified. Venous stenoses may have different shapes and be
Venous Angioplasty

of variable severity. They can also be single or multiple, focal or diffuse, mild or severe, and it is not uncommon to encounter complete venous occlusion.

Balloon Angioplasty

A full understanding of the AV access derangements, in the context of the troubling clinical signs and symptoms, is absolutely necessary before proceeding with venous angioplasty. This will help avoid doing unnecessary venous angioplasty in cases where other overriding derangements co-exist. An example of such a situation would be a “failing to mature” AVF that has a significant stenosis in its venous outflow tract, but its main problem is poor arterial inflow due to atherosclerotic artery and narrow arterial anastomosis. If the arterial inflow cannot be augmented, then it would be futile to perform venous angioplasty in this case. Another example would be a patient who has a stenosis associated with the initial inflow segment of the AV access, but has signs and symptoms of ipsilateral hand ischemia [6]. In this case, the benefit of dilating the inflow stenosis, which leads to enhanced AV access flow, will likely aggravate hand ischemia and should be avoided.

When venous angioplasty is judged necessary, a guide wire is advanced across the lesion. In general, a hydrophilic, steerable, flexible, 0.035 guide wire is best suited for this purpose, and is sufficient in the majority of cases. When significant tortuosity is encountered, an Amplatz superstiff guide wire (Cook, Inc. Bloomington, IN) may become necessary to minimize buckling tendencies as the angioplasty balloon is being advanced.

It is best to choose the angioplasty balloon diameter to be equal to the diameter of the vein adjacent to the stenosis being dilated. Due to compliance of the venous system, one may be able to minimally oversize the balloon diameter. However, the risk of venous rupture increases with balloon oversizing. The duration of balloon inflation time continues to be controversial and there is no clear evidence that a longer inflation time would lead to improved outcomes [7].

The length of the balloon should be chosen based on the length of the stenosis being dilated. On theoretical grounds, it would be best to choose a balloon length that allows the least physical trauma to the spasm-prone healthy vein, adjacent to the stenosis. By this token, one should choose the shortest balloon length that covers the lesion.

On the other hand, if a short balloon is not well positioned over the lesion, slipping of the balloon off the lesion may occur, thereby leading to inadvertent vessel wall spasm, trauma, or tear. Spasm is a serious problem that is commonly seen with venous angioplasty. Its untoward effects are usually transient, but can, on occasion, be sufficiently prolonged to cause vessel thrombosis. Venous spasm, frequently, but not always, responds to repeat balloon angioplasty (personal experience) using low inflation pressure and prolonged inflation time.

The intensity of pressure applied to the angioplasty balloon should be gradually increased until full balloon effacement is seen under fluoroscopy. Once this is achieved, there is no reason to continue to apply higher pressures.

Most commercially available angioplasty balloons, with 6-8 mm diameter, can achieve a maximal pressure of 16-20 atm. In general, these balloons are able to dilate the majority of venous stenoses. However, it is not infrequent to encounter stenoses that require higher pressures for successful dilatation [8, 9]. Pressures up to 35 atm, can be achieved by non
compliant, high pressure angioplasty balloons (Bard Peripheral Vascular, Tempe, AZ). An
insufflator device is very helpful in applying accurate pressure, but with experience, inflating
the balloon with a hand held syringe assembly may be sufficient in most instances.

Infrequently, a venous stenosis may resist dilatation with non compliant, high pressure
angioplasty balloon. A cutting balloon may then be considered [10]. It has sharp blades that
fan out from the balloon surface when it is fully inflated. Usually, the cutting balloon is
inflated to lower pressures (8 atm), with the idea of inducing a superficial cut in the inner wall
of the vessel, at the site of the highly resistant stenosis. This renders the lesion more
responsive to subsequent standard balloon angioplasty. Experience with cutting balloons is
still limited [10-13], but some have reported favorably on its safely and success in managing

**Complications of Venous Angioplasty**

Fortunately, venous angioplasty procedures are safe, and therefore are suitable for
interventional nephrologists in an outpatient setting [14-19]. Their complications are mostly
minor in nature. Major complications that lead to loss of the AV access, induce serious
bleeding, or serious illness are infrequent. In a review on the subject by Beathard et al., in a
large data base of interventional procedures, that included a high percentage of venous
angioplasty, total complications were 3.54%. Of these, only 0.28% classified as major [14].

Complications of venous angioplasty fall into three categories:

The first category includes a variety of technical complications either at the cannulation
site or the angioplasty site [16-18]. Venous spasm, tear, or even rupture can occur at the site
of angioplasty. Spasm usually resolves spontaneously, within few hours, but at times it can be
severe to block access flow and precipitate thrombosis.

In such cases, one should attempt to reinflate the angioplasty balloon in the spastic
segment under low pressures for 20-30 seconds. Venous tear or rupture can have devastating
effects on the AV access but in most cases it responds to conservative measures that include
external pressure and reinflation of the angioplasty balloon across the involved segment. A
stent may be necessary at times when these measures fail or when a large expanding
hematoma is seen. Pseudoaneurysm formation at the site of angioplasty can be managed
conservatively if the pseudoaneurysm is small, but when judged to be large, placement of a
stent to seal its origin, or surgical excision, would be safer considerations. Other
complications include AV access thrombosis, local pain, and infection.

The second category relates to the development of distal hypoperfusion syndrome [6] or
high flow AV access in response to successful venous angioplasty. These complications may
be immediate or delayed, and are relatively more common following AVF angioplasty in
comparison with AVG angioplasty.

The third category includes systemic reactions to intravenous iodinated contrast agents or
to sedation [19]. Serious allergic reactions can be avoided in the majority of instances with
prior identification, and the use of contrast agent prophylaxis.

However, extreme caution, including avoidance of contrast agents, should be undertaken
in those with history of near fatal anaphylactic reactions. Over sedation, leading to pulmonary
arrest, may occur, and should be avoided, especially in the elderly, and in those with preexisting respiratory compromise.

**AVF Angioplasty**

In the context of AVF, peripheral venous stenoses include lesions in the juxta-arterial segment of the AVF, the body of the AVF, and the AVF outflow tract veins. The body of the AVF refers to the segment where needle cannulation takes place. The AVF outflow tract veins extend from the body of the AVF to the outer edge of the subclavian vein. Venous stenosis may be due to lesions that existed prior to AVF creation, or due to acquired lesions. Venous stenosis is the main cause of the “failing to mature” AVF [20-23], and is also common in late AVF failure [24,25]. Venous stenosis is also almost universally present in the thrombosed AVF [26].

**Juxta-Arterial Anastomosis**

This lesion is considered the most common cause of “failing to mature” AVF. Its incidence among cases of “failing to mature” AVF can be as high as 43-64% [20, 21]. It involves stenosis of the initial 5 cm of AVF inflow tract (Figure 1). Most of the time it is distinct from the arterial anastomosis (Figure 1A), hence it is classified and coded as venous angioplasty. At times however, it is continuous with stenosis of the arterial anastomosis (Figure 1B). It frequently exhibits resistance to standard balloon angioplasty but usually responds to non compliant, high pressure angioplasty balloon. It is believed to be most common with radial cephalic AVFs. It is also common in the brachial cephalic AVFs. While it is less common in the basilic and brachial vein transposed AVFs, it can still be seen. It is my personal experience that the juxta-arterial anastomosis stenosis is common in thrombosed AVFs, and dilating it is a prerequisite for successful thrombectomy [26].

In general, dilating the juxta-arterial anastomosis stenosis requires passage of a guide wire from the AVF through the lumen of the stenosis. It is advised to advance the guide wire across the arterial anastomosis for 2 reasons: First, the lesion’s anatomic proximity to the arterial anastomosis would make it difficult to properly position the angioplasty balloon, if the end of the wire is not advanced well beyond the stenosis. Second, a well positioned guide wire is necessary due to safety reasons in case a thrombus, tear, flap, or spasm occur following balloon dilatation. Having the guide wire across the arterial anastomosis allows the angioplasty balloon to be repositioned and re-inflated to manage any of these potential complications.

It also allows other measures to be implemented as well, if necessary, such as placement of a stent, or aspiration of a clot.

In general, the size of the angioplasty balloon that is used to dilate the juxta-arterial anastomosis stenosis should be chosen so as to allow the minimum dilatation necessary to provide adequate flow rate for HD purposes. This is largely a judgment call that is refined with experience. Over dilating this segment can lead to vigorous AVF blood flow that
culminates in overgrown AVF (mega AVF), aneurysmal formation, and higher tendency for distal hypoperfusion (vascular steal) syndrome [6].

Figure 1. Angioplasty of juxta-arterial anastomosis segment of AVF: The initial 5 cm of AVF inflow is referred to as the juxta-arterial anastomosis segment. It is a frequent site of stenosis. It is classified and coded as venous stenosis since it is usually distinct from the arterial anastomosis as shown in A (arrow). However, it can involve a longer segment and extend to the arterial anastomosis as is shown in B (arrow). Early aneurysmal formation is seen in A between the arterial anastomosis and the stenosis. Both A and B are upper arm brachial cephalic AVFs. The stenosis in A led to “failure to mature” whereas the stenosis in B caused late AVF failure. Venous angioplasty using a 6 mm wide angioplasty balloon successfully dilated the stenotic segment in A. The post angioplasty fistulogram is shown in C. In this case, the injection is carried out with the catheter’s tip in the proximal brachial artery (BA), hence the BA and the arterial anastomosis (arrowhead) are visible in the post angioplasty fistulogram (C). Venous angioplasty using a 5 mm wide angioplasty balloon successfully dilated the stenotic stricture in B. The post angioplasty fistulogram is shown in D. In this case, the injection is carried out with the catheter’s tip close to the arterial anastomosis hence the BA is not visible in the post angioplasty fistulogram (D). The acute angle between the BA and the AVF made selective catheterization of the proximal BA more challenging and was felt not to be absolutely necessary in this case.

In general, a 4 or 5 mm wide angioplasty balloon is used to dilate the juxta-arterial segment of the radiocephalic AVF, whereas, a 5 or 6 mm wide angioplasty balloon is used for upper arm AVFs. Certainly, a wider angioplasty balloon may be necessary at times, in either location, depending on anatomic considerations, clinical context, and AV access blood flow rates.
Body of AVF

In the “failing to mature” AVF, venous stenosis in the body of the AVF is a common derangement [20-23] (Figure 2). In our series of “failing to mature AVF”, 21% of referred cases had occluded veins, usually in sites corresponding to the body of the AVF. A total of 59% had venous stenosis in the body of the AVF or its outflow tract. These early detectable lesions are a consequence of poorly-chosen veins for the creation of the AVF. Preoperative U/S assessment should minimize this from occurring.

In late AVF failure, the venous stenoses in the body of the AVF may have emerged from repetitive dialysis needle puncture or from slowly evolving preexisting lesions. Dilating these lesions is usually successful. The choice of the angioplasty balloon should be based on the diameter of the vein adjacent to the stenosis. Care must be taken to avoid over dilating the body of the AVF to prevent future aneurysm formation.

Figure 2. Angioplasty of multiple coexisting lesions of “failing to mature” AVF: Multiple lesions are a common finding in patients presenting with “failing to mature” AVF. This is exemplified in this case of a brachial cephalic AVF that failed to mature following 3 months after creation. In A, a fistulogram shows complete occlusion of the cephalic vein in the mid upper arm (arrow) with collateral veins (interrupted arrows) draining the AVF. Contrast is shown to reflux upstream and outline the brachial artery (BA). Management of this AVF is challenging due to the occlusion and due to lack of visualization of the cephalic vein proximal to the occlusion. In this case, it was fortunate that a 0.035 guide wire successfully traversed the occlusion and advanced into the proximal cephalic vein. The catheter was parked in the cephalic vein arch and contrast was injected in order to outline the cephalic vein arch segment. The result is shown in B revealing a stricture of the cephalic vein arch (arrow). In this case, due to AVF immaturity and severity of the stenosis, a 5 mm wide angioplasty balloon was used to dilate the strictured segments. This successfully managed the mid upper arm venous occlusion (C), and the cephalic vein arch stenosis (D). Additional time is required for this AVF to mature, and will likely need repeat angioplasty in the near future for recurrent lesions or to assist in maturity. In subsequent procedures, a wider angioplasty balloon may be necessary. Frequent clinical exams are essential to determine appropriate time of re-intervention.
Swing Point

In this chapter, the swing point refers to the segment of vein at the junction point between transposed and non transposed vein. It is usually in the proximal upper arm. Obviously then, stenosis of the swing point is particular to, and typical of, transposed upper arm AVFs.

This lesion is very common, and typically emerges around 2-3 months following transposition surgery (Figure 3). It is believed to be induced by mechanical factors. When clinically significant, it causes exaggerated pulsations of the AVF easily detected by physical exam. It frequently exhibits resistance to standard balloon angioplasty but usually dilates well with a non compliant, high pressure angioplasty balloon. Most of the time a 7 or 8 mm wide angioplasty balloon is chosen, but in overgrown AVFs, a wider balloon may be necessary. Unfortunately, this lesion has a high recurrence rate. In cases that exhibit frequent and early recurrence, placement of a covered stent may become necessary as a last endovascular management resort.

![Figure 3. Angioplasty of swing point stenosis of transposed upper arm AVF: Stenosis of the swing point of transposed AVF is very common. In this case, an upper arm transposed brachial basilic AVF was referred because of high venous pressure. In A, a tight stenosis at the swing point (arrow) is seen. A venous valve proximal to the stenosis is also noted (arrow head). The stenosis was dilated with an 8 mm wide angioplasty balloon. A tight waist (arrow) on the balloon is a reflection of the severity of the stenosis and is shown in B. With additional intraluminal pressure, there is full balloon effacement as is shown in C. In D, a final fistulogram shows complete resolution of the swing point stenosis.](image)

Venous Outflow Tract

Radiocephalic AVFs frequently encounter venous outflow tract stenosis at the level of the elbow in the form of focal stenosis, stricture, tortuosity or even occlusion. At times, advancing a guide wire across such lesions may be challenging. Angioplasty is usually successful if the lesion is successfully traversed. It is rare for a radiocephalic AVF to be hampered by venous stenosis in the upper arm because of alternative and parallel routes of
drainage that frequently utilize the cephalic, basilic and brachial veins. On the other hand, brachial cephalic AVFs, with their obligate dependence on the upper arm cephalic vein, as their sole venous outflow tract, commonly suffer from stenoses in the proximal upper arm cephalic vein, and the cephalic vein arch. These lesions are believed to be the cumulative end result of several factors that include turbulence, thickened vessel wall, calcified venous valves, and failure of vessel wall to dilate in response to increase in blood flow. The cephalic vein arch stenosis may be diffuse (Figure 2B), focal, or multifocal (Figure 4). It is also characterized by high severity, resistance to dilatation, and high rates of recurrence [27]. A non compliant, high pressure angioplasty balloon is usually necessary to dilate this lesion. Placement of a covered stent is a reasonable option in order to decrease chances of recurrence.

![Figure 4](image.png)

**Figure 4.** Angioplasty of the cephalic vein arch of brachial cephalic AVF: The cephalic vein arch is a frequent site of stenosis. The stenosis may be due to a single focus or due to multiple foci of stenosis. It can also be a long stricture involving the whole cephalic vein arch up to the outer edge of the subclavian vein. In this case, 2 distinct foci of high grade stenosis are seen (A). One of these is at the dome of the arch (short arrow) and the other (long arrow) is adjacent to its junction with the subclavian vein. In this case, both stenotic foci responded to angioplasty with 8 mm wide balloon.

It is extremely important however to avoid protruding the stent beyond the proximal end of the cephalic vein arch, into the adjacent subclavian vein, to avoid jailing the axillary vein. This can be challenging when the cephalic vein arch stenosis extends to its junction with the axillary vein. It is to be kept in mind that surgical bypass of the cephalic vein arch is an alternative treatment option, but only few vascular surgeons have experience with it. With regard to upper arm transposed AVFs, the swing point lesion, discussed above, is a special form of outflow tract stenosis. Proximal to the swing point, it is less common to encounter
outflow tract stenosis. This is especially true of basilic veins, but it is my personal experience that proximal upper arm brachial veins are more prone to venous stenosis, seen in association with branching segments and venous valves. Overall, these stenoses respond well to initial balloon angioplasty.

**AVG Angioplasty**

The AVG is a special conduit through which blood flow crosses from the arterial to the venous system across a pressure gradient. The majority of AVGs in the US are made of polytetrafluoroethylene (PTFE). It can be of different diameters (6-8 mm), and of different lengths and configurations. For all practical purposes, it is agreed upon that angioplasty of the body or venous anastomosis of the AVG are venous angioplasty. On the other hand, angioplasty of the arterial anastomosis is classified as arterial angioplasty.

**Venous Anastomosis**

Stenosis of the AVG venous anastomosis is the most common derangement that affects the AVG (Figure 5). The underlying cause is smooth cell proliferation at the surgical anastomosis between the PTFE graft material and the native vein. Turbulent blood flow is believed to be a contributor to stenosis. It becomes clinically significant in most cases between 3 and 6 months after AVG creation. This lesion may be focal and limited to the venous anastomosis, but can be associated with long segments of stenosis extending to the adjacent draining vein, and referred to as “venous stricture” [28-30]. When advanced, venous anastomosis stenosis causes several clinically detectable derangements such as high venous pressure of the dialysis circuit, prolonged bleeding from cannulation sites, and low urea clearance rates. Venous anastomosis stenosis is commonly present in thrombosed AVGs [31,32].

In thrombosed AVGs, crossing the venous anastomosis by a guide wire can be challenging if a high grade stenosis or total luminal occlusion is present. This stenosis usually dilates well with standard balloon angioplasty, but in some cases, there is elastic recoil of sufficient severity to impede AVG flow. Also, in most cases, there are high rates of lesion recurrence peaking between 3 and 6 months. Hence, placement of a covered stent across the venous anastomosis has become an attractive endovascular treatment option, in an attempt to reduce elastic recoil and restenosis [33]. Whether this approach will lead to decrease in AVG related interventions is controversial at this time.

However, no elective endovascular stent should be used in an AVG venous anastomosis, or outflow tract vein, if its placement would use sufficient length of native vein so as to prevent future AVF creation. It is important to emphasize that surgical bypass of recurrent venous stenosis is an alternative option, and that opportunities to create secondary AVFs should not be missed [34, 35].
Venous Angioplasty

Figure 5. Angioplasty of venous anastomosis stenosis of AVG: The venous anastomosis and the immediate venous outflow tract of the AVG are frequent sites of stenosis. In this case, a patient with a forearm loop AVG was referred because of forearm swelling. A high grade stenosis of the venous anastomosis (arrow) is present and is shown in A. Only the venous limb (G) of the graft is shown. The stenosis involves a short segment of venous outflow tract causing retrograde flow into multiple collaterals (interrupted arrows), which explain the forearm swelling. A tight waist (arrow) on the balloon is a reflection of the severity of the stenosis and is shown in B. With additional intraluminal pressure, there is full balloon effacement as is shown in C. In D, a final graftogram shows complete resolution of the venous anastomosis stenosis, and near complete resolution of collateral venous retrograde flow.
**Body of AVG**

Stenosis in the body of the AVG is frequent but less common than at the venous anastomosis. It is more common in older AVGs. It frequently occurs in association with needle cannulation sites (Figure 6). Smooth muscle proliferation may also track into the body of the AVG from either the venous or arterial ends. In general, these stenotic segments respond very well to standard balloon angioplasty unless the AVG wall is heavily calcified. The latter occurs in AVGs that have been in place for several years. Unfortunately, heavily calcified stenoses do not respond well to balloon angioplasty, and frequently rupture the angioplasty balloon. When dilating the body of the AVG, it would be useful to have prior knowledge of the diameter of the graft, if possible, to avoid using an angioplasty balloon that is wider than the luminal diameter of the AVG. This is a safety measure to prevent rupture of the AVG or future aneurysm formation.

**Venous Outflow Tract**

The venous outflow tract of the AVG refers to the draining peripheral veins that start at the venous anastomosis and extend to the outer edge of the subclavian vein. Most of the lesions occur close to the venous anastomosis. It is common to encounter venous stricture formation up to 5 cm, or more, starting at the venous anastomosis. In general, these strictures respond well to standard balloon angioplasty, but the longer the stricture, the higher is the likelihood of elastic recoil and frequent re-stenosis. When they exhibit elastic recoil, or high rates of recurrence, placement of a covered stent should be considered. When they fail to respond to endovascular measures, with or without stent placement, surgical bypass or creation of a new AV access becomes necessary.

![Figure 6](image6.png)

Figure 6. Angioplasty of the body of the AVG: A patient with a forearm loop AVG was referred for evaluation because of difficult cannulation on the venous limb of the AVG. On physical exam, the AVG exhibited hyperpulsatility of its arterial limb. A graftogram is shown in A, and reveals multiple foci of stenosis of the venous limb (arrows) of the AVG. These stenotic foci were successfully managed using an 8 mm wide angioplasty balloon with complete resolution as is shown in B. Incidentally, the collateral veins seen in the forearm are a result of an accidental graft to native vein fistulous tract that likely emerged from needle punctures, and grew in response to high pressure induced by the downstream stenosis of the proximal aspect of the venous limb of the AVG. These veins, which were prominent prior to angioplasty (A), seem to subside post angioplasty (B). Such fistulous tracts are not common but are occasionally seen. When large, they may need surgical ligation or walling off by a short covered stent. However, if asymptomatic, they can be left alone as was done in this case.
More proximally, the AVG venous outflow tract is subject to the same derangements that affect the AVF venous outflow tract. Stenotic lesions that are far from the venous anastomosis tend to occur in association with venous valves, turbulent flow areas, or preexisting vessel derangements. Usually venous angioplasty is successful in managing these lesions.

**Conclusion**

Venous angioplasty is an intervention that is vital to maintenance of a functional dialysis AV access. It is safe, provided it is performed diligently. Its technical success depends on AV access cannulation, passage of a guide wire across the stenosis, and overcoming lesion resistance by balloon inflation pressure. The majority of the stenoses can be successfully and safely treated by angioplasty balloon pressures less than or equal to 35 atmospheres. Despite its initial success, venous angioplasty frequently needs to be repeated at the same location due to recurrence of stenosis. In particular, stenoses of the cephalic vein arch, the swing point of transposed veins, and the juxta-arterial anastomosis segments have high rates of recurrence that affect AVFs. Recurrence of stenosis at the venous anastomosis is the most frequent lesion that affects AVGs. Diligence in physical exam and surveillance of the AV access, at the dialysis units, are vital to diagnosing AV access dysfunction, and timely referral for repeat venous angioplasty.

**References**


Endovascular Stents for Dialysis Access

Ivan D. Maya*
University of Central Florida, Nephrology Associates of Central Florida, FL, US

Introduction

The role of stent placement in the venous system of patients with vascular access for hemodialysis has evolved over the last 10 years. Several authors have advocated the use of stents in hemodialysis patients who have stenotic lesions in their vascular access for dialysis; including placing stents when the vascular access for hemodialysis has thrombosed and there is a stenosis at the venous anastomosis of an AV graft, when there is a vein rupture at the time of an angioplasty procedure, and in cases of severe refractory stenosis where simple angioplasty is not sufficient to treat the lesion (any where from the arterial anastomosis up to the central venous vessels). There are some authors who are more liberal in their use and have deployed stents for other non-approved cases i.e. treatment of pseudoaneurysms in the AV grafts. Regardless of the indication, more and more stents are being deployed in the venous system of the vascular access for hemodialysis patients. It is very important to know when and how to deploy stents and recognize when a stent placement may be detrimental i.e.: occlusion of important collateral vessels or loss of a potential secondary fistula creation in the same extremity.

Indications

K/DOQI Clinical Practice Guidelines for Vascular Access is clear regarding stent deployment and states that stents should be considered when patients present with extremity
edema that persists beyond two (2) weeks after graft placement. These patients should have a complete angiographic study to evaluate patency of the vascular access from the arterial anastomosis to the central veins. If a central vein stenosis persists after percutaneous transluminal angioplasty, then a deployment of a stent should be considered when an elastic recoil of the treated vein (>50% stenosis) is present after angioplasty and if it recurs within a 3-month period, plus the same lesion has required more than two angioplasties within a 3-month period. Initial management should include surgical revision if the patient is a good surgical candidate. If angioplasty has failed and it is surgically inaccessible, then a deployment of a stent may be useful.

The growth in clinical practice of stent deployment has outpaced that of percutaneous angioplasty alone despite very strict guidelines. The United States Renal Data System (USRDS) has reported a marked increase of stent placement in hemodialysis access. In 1998, the number of angioplasties was 52,380 and 3,792 stent placements. By 2005, the statistics showed that the relative percentage growth of stent placement was greater than angioplasty alone. The number of angioplasty cases went up to 139,024 and the stent deployment went to 15,260 cases.

**Stent Deployment Outcomes**

Investigators have attempted to evaluate the role of stent placement in hemodialysis vascular accesses looking at different outcomes, but the lack of methodology and study design have been a major limitation. We need large, multi-centered, prospective, randomized controlled studies. Unfortunately, a majority of studies have suffered from several methodological limitations, including retrospective data collection, absence of a suitable control group, combining patent and thrombosed grafts, combining stents placed at a variety of stenotic sites, type of stents and combining grafts with fistulas. There are a number of stent types available on the market, but there are no clinical trials comparing graft outcomes between stent types. It is also possible that administration of anti-platelet agents after stent placement or employment of drug-eluting stents may further improve the primary patency of the vascular access, but there is lack of literature on this important issue.

Despite K/DOQI guidelines promoting use of arteriovenous (AV) fistulas in preference to AV grafts for hemodialysis access, a substantial proportion of US hemodialysis patients continue to use AV grafts. The majority of graft failures are due to thrombosis, which occurs most commonly in the context of underlying stenosis at the venous anastomosis, followed by infection of the AV graft. Treatment of the graft failure due to thrombosis and stenosis requires mechanical thrombectomy, in conjunction with angioplasty of the stenotic lesion. The long-term success rate of this approach is quite poor, and the primary (intervention-free patency) following graft thrombectomy is only 30 to 63% at 3 months and 11 to 34% at 6 months. The primary patency of AV grafts following angioplasty is short-lived, and there is evidence that the vascular injury from angioplasty may actually accelerate myointimal hyperplasia resulting in early re-stenosis. Due to this information, there is an interest in modifying the area of stenosis to improve the patency of grafts following angioplasty. Endoluminal stents work by forming a rigid scaffold preventing elastic recoil and help to keep the vascular lumen open. They may slow the area of myointimal hyperplasia into the vascular
lumen, limiting the size of recurrent stenosis. Thus, use of stents may be of utility in preventing re-stenosis following angioplasty. Following this assertion, if we placed a stent in a stenotic area, this area will be less likely to narrow the vascular lumen. The majority of AV grafts fail due to thrombosis. Primary graft survival after mechanical thrombectomy and angioplasty is significantly worse than elective angioplasty of patent AV grafts. Most studies show primary patency at only 30% at 3 months for thrombosed AV grafts, as compared with 70% for patent AV grafts undergoing elective angioplasty.

Sreenarasimhaiah et al., reported on 34 patients who had self-expanding nitinol stents placed at the venous anastomosis following AV graft thrombectomy. Primary patency at 6 months was 63% and 36% at 12 months. Secondary patency was 88% at 6 months and 86% at 12 months. They concluded that polytetrafluoroethylene (PTFE) AV graft longevity is improved when stenosis at the venous anastomosis of thrombosed AV grafts are treated with angioplasty and stent deployment.

Maya et al., evaluated the patency of AV grafts following thrombectomy after deployment of a stent in the stenotic lesion (venous anastomosis). The authors identified 14 patients with thrombosed AV grafts treated with a stent at the venous anastomosis. The outcomes were compared with those observed in 34 demographically matched control patients whose thrombosed AV grafts were treated with PTA alone. The primary patency rate was greater for the stent group, with a median survival of 85 vs. 27 days (p=0.02). The secondary patency rate was also greater for the stent group, with a median survival of 1,215 vs. 46 days (p=0.049). The design of this study was focused to thrombosed AV grafts with only one stenotic lesion, which makes the study very selective and therefore able to give a more concise conclusion.

Haskal et al., conducted a prospective, multicenter trial on 190 patients who had a venous anastomotic stenosis lesion and randomized them to angioplasty alone or angioplasty plus deployment of the covered stent. At 6 months, the primary patency was significantly greater in the covered stent group than in the angioplasty group (51% vs. 23%, P<0.001). They also found a reduction in interventions at 6 months in the covered stent group than in the angioplasty group (32% vs. 16%, P=0.03). Adverse events at 6 months were equal in the two treatment groups. Re-stenosis occurred more frequently in the angioplasty group. They concluded that percutaneous angioplasty plus covered stent deployment in patients with a prosthetic hemodialysis AV graft and a stenotic lesion at the venous anastomosis appeared to provide longer term and greater patency than angioplasty alone.

There are no major studies on AV fistulas. There is a study performed on patients who presented with recurrent cephalic arch stenosis within three months of successful angioplasty. They were randomized to have angioplasty and stent (bare vs. covered stents). Outcome was assessed by angiography three months later. Re-stenosis rates were 70% in the bare stent group and 18% in the covered stent group (P =.024). Primary patency was 82% in the covered stent group and 39% in the bare stent group at six months. This study demonstrated the superiority of covered stents over the bare metal stents. Few more studies have shown that the use of covered nitinol stents for salvage of AV fistulas decreases the incidence of follow-up repeat intervention.

The use of covered stents for treatment of AV graft pseudoaneurysms is controversial. The largest series is on the use of 32 self-expanding covered stents in 26 patients with AV graft pseudoaneurysms. Main indication was the large size and localized pain at pseudoaneurysm site. Technical success was 100%. Most patients experienced a marked
decrease in the size of their pseudoaneurysms and successful hemodialysis was resumed. There have been some reports describing the use of covered stents in combination with percutaneous thrombin injection in the management of pseudoaneurysm associated hematoma and AV graft related seromas. The use of covered stents for treatment of vein rupture has been well-documented. Raynaud et al. reported a five-year period follow up with more than 2,000 angioplasty procedures. They have a 1.7% rate of vein rupture during that period of time. Covered stents were deployed in 37 cases with excellent results. The primary patency of the accesses at 1 year was 48% and secondary patency was 86%.

It is important to emphasize that after a fistula is created most of the veins in the outflow of the vascular access grow proportionally to the pressure. These veins can then be used later to create an AV fistula when the initial fistula fails. This is called secondary fistula and it is important because these veins are already matured and in most cases ready to be cannulated. One should be careful when thinking about deployment of a stent in an already matured vein in the outflow of an AV fistula. Secondary AV fistula is part of an armamentarium once a surgeon has created a vascular access. One should think ahead of time of what other veins are suitable for a secondary fistula. A large retrospective study by Slayden, reported on the patency rates of secondary fistula. The primary patency at 12 and 24 months was 82.5% and 60%, respectively.

The deployment of stents in the central venous system has not been researched very well. Central vein stenosis is a common observation in hemodialysis patients, which frequently arises as a complication of indwelling dialysis catheters. It may be asymptomatic, but it can manifest as a progressive upper extremity edema, sometimes manifest as a mal-functioning of the vascular access. If symptomatic, the treatment is angioplasty of the stenotic lesion. Unfortunately, these lesions recur rapidly. Some authors have advocated the deployment of stents to keep the vessel open and delay recurrent stenosis. However, in-stent re-stenosis occurs frequently, mostly at the ends of the stent, which represents a dilemma since more interventions are needed and sometimes deployment of overlapping stents to keep the access open. As a result, the primary patency of the central veins after stent deployment is quite poor, with 1-year patency of only 20% in the present study, in agreement with the 14 to 17% primary patency, which has been reported in previous series. However, in the absence of stent deployment, such patients have very limited therapeutic options. Bypass surgery is very invasive in this location, frequently. Therefore the only option without stenting would require ligation of the vascular access to relieve the upper extremity edema, which in turn would cause further interventions, i.e.: placement of a permanent catheter and creation of a new vascular access.

**Conclusion**

In summary, placement of stents (covered and bare) in the hemodialysis vascular access conduit has increased since 1998. Different studies have shown important data regarding the use of stents in the hemodialysis vascular system, but further information is needed as we cannot generalize the use of stents for every stenotic lesion we encounter. The data in AV grafts have merit and for certain instances the deployment of a stent is useful, but interventionalists need to be cautious in implementing this kind of treatment. Well-designed
studies, which include large, prospective, multicenter, randomized clinical trials, are required to solve several key issues regarding the use of stents in the hemodialysis vascular circuit. Because of the high price that a deployment of a stent adds to the cost of treating a stenotic lesion in the vascular access, a multi-center randomized study is warranted to evaluate the efficacy and cost-effectiveness of this approach.

References


Catheter failure has been responsible for a large number of patients “dropping-out” of peritoneal dialysis. Peritoneal Dialysis (PD) catheters are essential to the success of PD. This chapter lists the common problems (mechanical and infectious) encountered by the nephrologist in the management of the PD catheter and specifies different approaches to managing these issues.

Introduction

Peritoneal dialysis (PD) as a form of renal replacement therapy has increased over the years. Infection and catheter events have contributed a large extent to the reason for transferring from PD to hemodialysis [1]. The overall success of peritoneal dialysis has been largely dependent on the technical success of the PD catheter.

In this chapter, we will evaluate the reasons for PD catheter failure, and delineate a step by step approach for assessing reasons for malfunction and management of common problems encountered on PD.

Section I: Non-Infectious Complications

Non-Infectious complications have been on the rise partly because of the success associated with reduction of PD catheter-related infections. These complications arise
primarily because of an increase in intra-abdominal pressure, the technique of catheter placement and metabolic complications from the dialysate. Strategies to prevent early catheter malfunction include appropriate catheter selection, optimal surgical technique, and good postoperative care. The common non-infectious complications are listed in Table 1.

A. Catheter Related Complications

1. Impaired Draining/Filling of Catheter
A properly functioning PD catheter should allow infusion of two liters of PD fluid in ten minutes and drain more than 75% of the infused volume in fifteen minutes. [5]

Table 1. Common non-infections complications of PD catheters

<table>
<thead>
<tr>
<th>Non-Infectious Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Catheter Related</td>
</tr>
<tr>
<td>● Perioperative-perforation of viscus/hemorrhage</td>
</tr>
<tr>
<td>● Impaired filling/draining of catheter</td>
</tr>
<tr>
<td>● Pain on PD</td>
</tr>
<tr>
<td>● Catheter cuff extrusion</td>
</tr>
<tr>
<td>B. Increased Intra-abdominal Pressure</td>
</tr>
<tr>
<td>● Abdominal hernia</td>
</tr>
<tr>
<td>● Hydrothorax</td>
</tr>
<tr>
<td>● Catheter/Peritoneal fluid leak – External/Internal-Abdominal wall and scrotal edema</td>
</tr>
<tr>
<td>C. Miscellaneous</td>
</tr>
<tr>
<td>● Encapsulating peritoneal sclerosis</td>
</tr>
</tbody>
</table>

*Incidence:* This ranges from 5-20% irrespective of the technique of catheter placement and catheter type, although few independent studies have shown benefit to laparoscopic placement of the PD catheter.

The common causes and management are shown in Table 2 and the flow diagram in Figure 1 respectively.

When inflow and outflow are impaired there is either a kink or complete occlusion of the catheter with fibrin whereas if inflow is not impaired and outflow is impaired then there is catheter migration, omental wrapping, or constipation.

Table 2. Common causes of impaired draining and filling of PD catheters

<table>
<thead>
<tr>
<th>Common causes of impaired draining and filling of catheter</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Constipation</td>
</tr>
<tr>
<td>2. Catheter migration</td>
</tr>
<tr>
<td>3. Fibrin</td>
</tr>
<tr>
<td>4. Omental wrapping of catheter tip/coil</td>
</tr>
<tr>
<td>5. Fluid loculations</td>
</tr>
<tr>
<td>6. Catheter kink</td>
</tr>
</tbody>
</table>
2. Pain on Peritoneal Dialysis

Patients performing PD may experience pain associated with either the inflow or drain phases of a PD exchange. Patients may also experience generalized pain bearing no direct temporal relationship with the performance of an exchange.

**A) Inflow Pain: Pain/Cramping with Fill of Dialysate Solution**

*Causes:* The common causes of inflow pain are due to dialysate related characteristics such as temperature, tonicity and acidity, migration of the catheter, rapid inflow rates, use of large fill volumes and any underlying visceral pathology such as PID. The acidity of the dialysate solutions, especially lactate solutions with a pH 5.2-5.5 contribute to pain. Rapid inflow rates due to the “jet” effect of dialysate emerging from the distal end of the catheter at relatively high velocity could irritate the adjacent tissues and cause pain. This is more frequently seen with straight catheters than those with a curled tip.

*Management:* The following strategies can be used to manage pain such as slowly increasing fill volumes in small increments rather than rapid jumps, optimizing the temperature of dialysis solution to body temperature and reducing flow rates by lowering IV pole/adjusting cycler timings. If the above measures are unsuccessful, rule out catheter migration and visceral pathology and in extreme cases one can administer intraperitoneal 5ml/L of sodium bicarbonate pre-infusion or instill 2.5-5ml/L of 2% lidocaine.

**B) Outflow/Drain Pain**

Pain that occurs at the end of the treatment due to irritation of the peritoneum from negative pressure. This pain can be diminished with tidal PD [29, 30].
C) Back Pain
Back pain may be due to either alterations in posture induced by the presence of several liters of intraperitoneal fluid or due to the weight of the fluid itself. It may respond to exercise training. Alternatively, a change to APD with no or minimal daytime dwell volumes may be beneficial.

D) Shoulder Pain
Shoulder pain may reflect irritation of the underside of the diaphragm due to the presence of either peritoneal dialysate or intra-peritoneal free air. Placing the patient in Trendelenburg position may diminish the pain.

3. Catheter Cuff Extrusion
Erosion of the catheter cuff through the skin to the outer abdominal wall may be a sequela of exit-site infection or due to the proximity of the superficial cuff to the exit site.

Incidence: The incidence of catheter cuff extrusion ranges from 3.5 to 17 percent. [21, 22]

Etiology: Neither the method of catheter placement, surgical or percutaneous, nor the specific catheter used influences the likelihood of extrusion. Significant weight loss after PD catheter placement and excessive tension on catheter during subcutaneous tunneling could be possible causes for catheter cuff extrusion.

Management: The need for cuff shaving or catheter removal depends in part upon the presence or absence of infection. More conservative measures may be attempted in those without evidence of an infectious process. An eroding, extruding cuff may require removal by opening the subcutaneous tissue surrounding the exit site and trimming the cuff under sterile conditions and local anesthesia. Poor healing of the area or signs of persistent inflammation or infection are indications for catheter removal. [21, 22]

B. Increased Intra-Abdominal Pressure

1. Catheter/Peritoneal Fluid Leaks (Figure 2, 3)
Catheter/Peritoneal fluid leaks are due to loss of integrity of the peritoneal membrane. Leaks that occur within 30 days of placement of the PD catheter are classified as early leaks and leaks greater than 30 days are classified as late leaks.

External Leaks: External peri-catheter leaks are leaks that occur around the catheter site. The technique of catheter implantation and timing of initiation of PD, weakness of the abdominal wall due to a variety of factors predispose to peri-catheter leakage.

Internal Leaks: Internal peritoneal fluid leaks are leaks that occur through congenital (e.g. patent processus vaginalis) or acquired (e.g. peri-catheter or prior incisional site) abdominal wall defects result in dissection of dialysate through soft tissue and fascial planes.

Catheter leaks can present as abdominal wall/scrotal edema, reduced drain volumes, weight gain, abdominal hernias and hydrothorax. The common risk factors are described in Table 3.
Figure 2. Protuberant abdomen secondary to abdominal leak. Figure courtesy of Dr. Joanne M. Bargman MD FRCPC, Professor of Medicine, University of Toronto.

Figure 3. Dye-labelled dialysis fluid leaking out the catheter exit from the peritoneal cavity. Figure courtesy of Dr. Joanne M. Bargman MD FRCPC, Professor of Medicine, University of Toronto.
Table 3. A list of the common risk factors for dialysate leaks

<table>
<thead>
<tr>
<th>Risk factors for dialysate leak [8, 9]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technique of PD catheter placement</td>
</tr>
<tr>
<td>• Surgical less likely compared to peritoneoscopic/percutaneous approach</td>
</tr>
<tr>
<td>Initiation of PD</td>
</tr>
<tr>
<td>• Early initiation of PD (i.e. within 14 days)</td>
</tr>
<tr>
<td>• Large volumes rather than starting with small volumes and gradually increasing</td>
</tr>
<tr>
<td>Abdominal wall weakness</td>
</tr>
<tr>
<td>• Prior abdominal surgeries</td>
</tr>
<tr>
<td>• Abdominal hernias</td>
</tr>
<tr>
<td>• Multiple pregnancies</td>
</tr>
<tr>
<td>• Obesity</td>
</tr>
<tr>
<td>• Hypothyroidism</td>
</tr>
</tbody>
</table>

NOT risk factors: age, sex, type of catheter—although double cuff catheter is supposed to have a less likelihood of leakage.

**Incidence:** Most reports suggest that the incidence of dialysate leaks varies and is more than 5% in patients on CAPD [9]. This does not take into the account the incidence of hydrothorax and hernias in such patients and most of the studies were retrospective in nature thus under-estimating the total extent of the problem.

**Management:** It is important to conduct a thorough physical examination to look for signs of internal, external leaks and abdominal wall defects. Perform an appropriate imaging study such as a chest x-ray, CT scan, peritoneoscopy and thoracentesis if indicated followed by reducing fill volumes, monitoring abdominal girth and switching to HD if indicated.

The flow diagram in Figure 4 describes a stepwise detection and management of catheter/peritoneal fluid leak.

2. Abdominal Hernias (Figure 5)

The relative frequency by which abdominal hernias occur emphasizes the importance of early recognition and developing effective management strategies to prevent interruption on dialysis and reduction of morbidity.

**Incidence:** The incidence of hernias has decreased over the years with better surgical techniques. Hernia rates are currently reported at a rate of 0.06 to 0.08 per patient per year. [10]

**Common anatomic sites:** Umbilical hernia seems to be the most prevalent, followed by inguinal, ventral and other incisional site hernias [12, 14]. There seems to be an increased occurrence of concomitant hernias and bilateral inguinal hernias in this group of patients than in the general population.

**Presentation:** Most hernias present as a painless swelling. The most worrisome and serious of complications include incarceration and strangulation of bowel. Intestinal obstruction due to strangulation may occur in up to 10% to 15% of hernias, particularly those at the catheter site or related to other abdominal incisions.
**Diagnosis:** The diagnosis may be established via peritoneal scintigraphy or computed tomographic peritoneography.

**Prevention:** Several measures can be taken in the preoperative and postoperative periods to reduce the risk of hernia formation and dialysis leaks. These include detection and repair of preexisting hernias, detection of a patent processus vaginalis during insertion of the peritoneal catheter, paramedian versus midline catheter placement, use of a catheter break-in period and avoiding dialysis initiation for at least two weeks [12].

**Management:** Presence of hernias warrant surgical repair given the risk of bowel strangulation. The various surgical approaches to hernia repair are beyond the scope of this book.

However, the basic principles of using a propylene mesh with tension free hernioplasty followed by low volume, supine, rapid cycling PD to allow time to heal and ensure rapid return to full volume dialysis are the best approach to this problem.

**Figure 4.** Flow diagram on the management of catheter/peritoneal fluid leak.

**Figure 5.** Abdominal Hernia. Figure courtesy of Dr. Joanne M Bargman MD FRCPC, Professor of Medicine, University of Toronto.
3. Hydrothorax

A predominantly right sided pleural effusion can develop in some PD patients in the absence of heart failure likely due to a pleuro-peritoneal communication.

**Incidence:** This complication often occurs within the first month of PD initiation in about 1.6% to 6% of patients [15]. Patients with polycystic kidney disease are predisposed to develop pleura-peritoneal leaks [16]. Because of the significantly reduced abdominal capacity of these patients, a marked increase in hydrostatic pressure occurs after the infusion of dialysate, thereby favoring the flow of dialysate from the peritoneum to the chest.

**Presentation:** The patient commonly presents with dyspnea, which can be mistaken for congestive heart failure. However, if the shortness of breath worsens after infusion of hypertonic dialysate, then hydrothorax is more likely. On examination the patient has findings consistent with pleural effusion i.e. decreased breath sounds on right side of chest wall and stony dullness to percussion.

**Diagnosis:** The diagnosis of a pleuro-peritoneal defect resulting in hydrothorax can be made clinically and via radiographic techniques. Clinical methods such as thoracentesis with the dialysate fluid in the pleura having a higher concentration of glucose than plasma, and the concentrations of LDH and protein consistent with a transudate are indicative of hydrothorax. Instillation of methylene blue has given way to better radiographic techniques due to some reports of irritation to the abdominal viscera.

Radiographic methods such as peritoneal scintigraphy, CT peritoneography and MR peritoneography may be utilized to diagnose hydrothorax. Peritoneal scintigraphy involves injection of radiolabelled technetium followed by imaging in multiple projections to detect the leak. In CT peritoneography contrast is injected and the defect is visualized. Following the occurrence of nephrogenic systemic fibrosis in ESRD patients receiving gadolinium, MR peritoneography has been performed in PD patients without gadolinium. Surprisingly, the dialysate itself acts as the contrast medium showing peritoneal leakage into the abdominal wall.

**Management:** Thoracentesis is rarely required unless there is evidence of respiratory compromise. Temporary cessation of CAPD and transferring to hemodialysis remains the first-line treatment, video-assisted thoracoscopic pleurodesis (with talc/tetracycline) or repair may also be an option for patients who fail conservative management. Surgical correction of an identified diaphragmatic defect can also be performed but requires thoracotomy.

C. Miscellaneous

**Encapsulating Peritoneal Sclerosis (EPS) (Figure 6)**

EPS is one of the most serious complications of peritoneal dialysis characterized by partial or intermittent bowel obstruction, accompanied by marked sclerotic thickening of the peritoneal membrane and subsequent high morbidity and mortality. There is encasement of the bowel like a “cocoon”. It is typically associated with a progressive loss of ultrafiltration, resulting in fluid retention and edema.

**Incidence:** Multiple single center studies have shown varied occurrence of EPS. It is however, important to note the increased frequency of EPS reported among Japanese patients than in North America/Europe.
Etiology/Pathogenesis: It is unclear what the factors are that contribute to the development of EPS. There are multiple hypothesis, primarily based on rodent models that have described the probable contributing events to EPS with the most plausible being uremic milieu predisposing to fibrin deposition and encapsulation of the bowel and the “plasma-leak” hypothesis which provides indirect support for a link between the vascular alterations in peritoneal degeneration and inflammation [23, 24]. Prior episodes of severe peritonitis, the use of acetate as a dialysate buffer, a reaction to other foreign agents such as plasticizers from catheters, and an extended duration and time on peritoneal dialysis all may contribute in selected patients.

Presentation: The manifestations of EPS can be indolent and patients may remain asymptomatic for a long period. The symptoms and findings are related primarily to modification of gastrointestinal transit. The symptoms of EPS can be vague and non-specific however, they commonly present as bloody ascites, appetite loss, nausea, emesis, abdominal pain, bowel obstruction (either small or large), and ultrafiltration failure with poor solute transport.

Diagnosis: A preliminary diagnosis of EPS is usually based on a past history of PD and the existence of suggestive clinical signs and symptoms as described above. There is no established laboratory examination to confirm a diagnosis of EPS. Hyporesponsive anemia, elevated CRP and low CA-125 levels may be indicative signs of EPS, however, they are not specific. Radiologic examinations, including plain abdominal X-ray, contrast study, ultrasound study, and CT are helpful for making the diagnosis. The classic radiologic findings are depicted in Table 4.

![Figure 6. Encapsulating Peritoneal Sclerosis (EPS). Figure courtesy of Dr. Joanne M. Bargman MD FRCPC, Professor of Medicine, University of Toronto.](image)

The definitive diagnosis of EPS is confirmed at laparotomy or laparoscopy, either of which reveals the characteristic gross thickening of the peritoneum enclosing some or all of the small intestine in a cocoon of opaque tissue.

Management: The key elements in the management strategy for EPS are early diagnosis, cessation of PD with transfer to hemodialysis, sustained bowel rest with TPN, and immunosuppressive therapy/corticosteroids. If conservative therapy does not improve the
symptoms of EPS, surgical therapy must be performed by an experienced surgeon. Novel approaches such as tamoxifen, immunosuppressive agents and renin angiotensin blockers have been reported but need to be validated in larger studies. It is unclear whether renal transplantation has any benefit on EPS.

Table 4. Radiological tests and findings in EPS

<table>
<thead>
<tr>
<th>Radiologic test</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plain abdominal film</td>
<td>Dilated small bowel loops, air-fluid level and peritoneal calcification.</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>Dilated fixed loops matted together and tethered posteriorly. Intra-peritoneal echogenic strands, with echogenic “sandwich appearance” of the membrane and tri-laminar appearance of the bowel wall.</td>
</tr>
<tr>
<td>Computed tomography/magnetic resonance imaging</td>
<td>Variable diameter of bowel segments, adherent dilated bowel loops, air-fluid level with loculated ascites. Thickened intestinal wall and peritoneal membrane. Increased density of mesenteric fat.</td>
</tr>
</tbody>
</table>

**Section II – Infectious Complications**

Infectious complications are one of the major reasons for transfer from PD to HD, and for hospitalization and morbidity associated with peritoneal dialysis. The PD catheter can act as a direct conduit from the outside non-sterile environment to the sterile peritoneal cavity resulting in infection. Formation of a biofilm over the catheter predisposes to catheter infections. The majority of cases of peritonitis are due to bacteria with a small minority being due to fungi and rare organisms. The infectious complications can be classified as exit site, tunnel infection and peritonitis. This section will describe the common presentations and management of PD catheter related infections.

1. **Exit Site Infection**

An exit-site infection is defined by the presence of purulent drainage, with or without erythema of the skin at the catheter-epidermal interface. Innovations in connectology and exit site bacterial prophylaxis have led to a reduced incidence of both peritonitis and exit site infections in patients on peritoneal dialysis. However, exit site infections are still a source of morbidity in these patients.

*Prevention of exit site infection:* Acute care of the catheter after placement includes no dressing changes for 7 days and keeping the area dry for 2 weeks. Chronic care involves washing the exit site with anti-bacterial soap every other day and anti-microbial prophylaxis with either gentamicin or mupirocin [27].
There are varied opinions on the use of anti-microbial prophylaxis and the risk of developing resistance, hence, the use of prophylactic medications should be based on the local microbial pattern and patient specific indications [6].

Evaluation of an exit site infection: A method of grading exit site infections has been developed given the spectrum of presentation and to guide early recognition of infection.

A perfect exit site is usually six months old and has mature epithelium present in the sinus tract. The sinus tract is usually dry, there is no erythema or serous drainage, and crust forms no more frequently than every seven days. A good exit site has granulation tissue in the sinus tract with some epithelium and some mucosa present. The sinus may be moist and a crust forms no more often than every two days. Table 5 differentiates an acute exit site infection from a chronic one.

### Table 5. Differences between an acute and chronic exit site infection

<table>
<thead>
<tr>
<th></th>
<th>Acute Exit Site Infection</th>
<th>Chronic Exit Site Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration</strong></td>
<td>Less than 4 weeks</td>
<td>Greater than 4 weeks</td>
</tr>
<tr>
<td><strong>Drainage</strong></td>
<td>Purulent from exit site; expressible drainage</td>
<td>Purulent only at exit site; non-expressible drainage</td>
</tr>
<tr>
<td><strong>Granulation</strong></td>
<td>Exuberant</td>
<td>Exuberant</td>
</tr>
<tr>
<td><strong>Crust/Scab</strong></td>
<td>Around exit site</td>
<td>Around exit site</td>
</tr>
<tr>
<td><strong>Swelling/Edema</strong></td>
<td>More than twice the diameter of catheter</td>
<td>Lesser degree of edema</td>
</tr>
</tbody>
</table>

2. Tunnel Infection

As the infection tracks from the exit site, it can spread into the tunnel and cause a tunnel infection. Hence, a tunnel infection rarely occurs alone and is normally a continuation of an exit site infection. It usually presents as erythema, edema, or tenderness over the subcutaneous pathway but is often clinically occult, and therefore ultrasound is a useful tool in the management of exit-site and tunnel infections.

Management of exit site and tunnel infections: It is important to treat exit site infections promptly to avoid extension into the tunnel and subsequent development of peritonitis. A Gram stain of the exit-site drainage should be done and microbiological culture findings should guide initial therapy. The most serious and common pathogens found are *Staphylococcus aureus* and *Pseudomonas aeruginosa* and as these organisms frequently lead to peritonitis, such infections must be treated aggressively.

An ultrasound can be performed to guide to evaluate the location of the infection. If a sonolucent zone is detected around the external cuff (“signet ring” sign) it is likely a tunnel infection. If it persists and is over 1 mm thick following a course of antibiotic treatment and there is involvement of the proximal cuff then it portends a poor clinical outcome. Empiric treatment of *Staphylococcus aureus* and *Pseudomonas aeruginosa* should be initiated until the culture results return as shown in Table 6. Oral antibiotic therapy has been shown to be as effective as intraperitoneal or intravenous therapy. Duration of treatment should be for at least 2 weeks or until the exit site/tunnel appears normal. Refractory/relapsing exit site/tunnel infection warrants catheter removal. A patient with an exit-site/tunnel infection that
progresses to peritonitis, or who presents with an exit-site infection in conjunction with peritonitis with the same organism will usually require catheter removal. The goal in managing exit site/tunnel infections is to prevent peritonitis not save the catheter.

Table 6. Antibiotic treatment of exit site infections based on Gram stain results

<table>
<thead>
<tr>
<th>Gram stain results</th>
<th>Empiric antibiotic coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram positive</td>
<td>First-generation cephalosporin, trimethoprim/sulfamethoxazole, or penicillinase-resistant penicillin</td>
</tr>
<tr>
<td>Gram negative</td>
<td>Oral quinolone</td>
</tr>
</tbody>
</table>

3. Peritonitis

Even though there has been a steady decline in the incidence of peritonitis, it continues to be a major source of morbidity and reason for transfer to HD. Peritonitis associated with PD is primarily due to contamination from pathogenic skin bacteria. The common sources of contamination include intraluminal (touch contamination), periluminal (catheter related), visceral and hematogenous spread. Prevention strategies such as the use of aseptic techniques, nurse education and newer connectology systems (“Y” based- using flush and fill technique) have all resulted in reduction of peritonitis.

This section will highlight the updated guidelines for diagnosis and management of peritonitis.

Peritoneal-dialysis infection (exit-site and peritonitis) rates: Catheter related infections should be monitored and reported for every program annually. A goal rate of 1 episode per 18 months (0.67/year) is expected. Rates of 1 episode per 41-52 months (0.29- 0.23/year) are preferred. The rates can be reported as number of infections per organism/time period or months of peritoneal dialysis at risk/number of episodes.

Presentation: Symptoms and signs of peritonitis in PD patients may include abdominal pain, cloudy abdominal fluid, fever, nausea, diarrhea, abdominal tenderness, rebound tenderness, and occasionally systemic signs, including hypotension.

Diagnosis: At least two out of the three criteria must be present:

1. Abdominal pain
2. Cloudy effluent with WBC >100/mm³ of which at least 50% are PMN’s; one should differentiate it from other causes of cloudy effluent as depicted in Table 7.
3. Identification of organism on Gram stain

Table 7. The differential diagnosis of cloudy PD fluid

<table>
<thead>
<tr>
<th>Differential diagnosis of cloudy effluent</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Culture-positive infectious peritonitis</td>
</tr>
<tr>
<td>• Infectious peritonitis with sterile cultures</td>
</tr>
<tr>
<td>• Chemical peritonitis</td>
</tr>
<tr>
<td>• Eosinophilia of the effluent</td>
</tr>
<tr>
<td>• Hemoperitoneum</td>
</tr>
<tr>
<td>• Malignancy (rare)</td>
</tr>
<tr>
<td>• Chylous effluent (rare)</td>
</tr>
</tbody>
</table>
**Terminology for Designating Peritonitis Infections**

It is important to know the terminology highlighted in Table 8 as it is used in the management of PD catheter infections.

**Management of Peritonitis:** The general diagnostic approach to the patient suspected of having peritonitis begins with a history, physical examination, and Gram stain, culture, and white cell count and differential of the effluent peritoneal fluid. An optimal culture technique is the combination of sediment culturing of 50 mL effluent and bedside inoculation of 5-10 mL effluent in two blood-culture bottles. The differential of effluent peritoneal fluid should include secondary peritonitis which is peritonitis induced by intra-abdominal pathology and culture negative peritonitis. High peritoneal fluid amylase and/or lipase levels may suggest secondary peritonitis especially if supplemented with appropriate radiologic studies.

Occasionally, the PD fluid culture may be negative due to the culture being obtained early in the course, inappropriate use of microbiologic culture technique and antibiotics being administered concurrently for some other reason. Culture negative peritonitis patients can be managed as if they have bacterial peritonitis. With culture negative bacterial peritonitis, the patients tend to get better and the elevated peritoneal fluid cell count resolves rather quickly (two to three days) after initiation of antibiotics.

By comparison, in non-bacterial mediated sterile peritonitis, the culture will remain negative and white cell count will improve minimally despite antibiotics usage. After excluding other causes of peritonitis the algorithm in Figure. 7 can be used for initial management.

In patients with culture negative peritonitis, if the cultures remain negative after 72 hr, repeat the PD fluid cell count and differential. If the infection is resolving continue empiric therapy for 14 days and discontinue aminoglycosides if used initially. If the infection is not resolving, send cultures for unusual organisms (mycobacteria, legionella, fungi etc.) and consider catheter removal if there is no improvement in 5 days. In Gram positive peritonitis, treat *S epidermidis* for 2 weeks, *S aureus* for 3 weeks and adjust antibiotics accordingly for resistant organisms. For Gram negative peritonitis with a single organism treat for 2 weeks and for Pseudomonas or multiple organisms treat for 3 weeks.

**Mode of administration of antibiotics:** Since in PD peritonitis infection is localized to the peritoneum and bacteremia rarely occurs, and given the increased local concentration with intraperitoneal administration, intraperitoneal dosing of antibiotics is preferred to intravenous dosing. Since antibiotics are absorbed if administered in the peritoneum, serum systemic drug levels for vancomycin and aminoglycosides must be monitored to facilitate intermittent

<table>
<thead>
<tr>
<th>Recurrent</th>
<th>An episode that occurs within 4 weeks of completion of therapy of a prior episode but with a different organism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapsing</td>
<td>An episode that occurs within 4 weeks of completion of therapy of a prior episode with the same organism or 1 sterile episode</td>
</tr>
<tr>
<td>Repeat</td>
<td>An episode that occurs more than 4 weeks after completion of therapy of a prior episode with the same organism</td>
</tr>
<tr>
<td>Refractory</td>
<td>Failure of the effluent to clear after 5 days of appropriate antibiotics</td>
</tr>
</tbody>
</table>
**Continued assessment and modification of therapy based on culture and sensitivity results.** Dwell time of the exchange for intermittent therapy must be a minimum of 6 hours. Vancomycin may be considered if patient has a history of methicillin-resistant *Staphylococcus aureus* colonization/infection, is seriously unwell, or has a history of severe allergy to penicillins and cephalosporins. If the center has an increased rate of methicillin resistance, vancomycin may also be considered. If the patient is cephalosporin allergic; aztreonam is an alternative to ceftazidime or cefepime. Vancomycin and ceftazidime are compatible when mixed in a dialysis solution volume greater than 1 L; however, they are incompatible when mixed in the same syringe or empty dialysis solution bag for reinfusion. Aminoglycosides should not be added to the same exchange with penicillins as this results in incompatibility.

**Figure 7.** Initial management of peritonitis - Modified from ISPD guidelines.

dosing or prolonged aminoglycoside dosing. The intraperitoneal administration of antibiotics can be either continuous (with antibiotics given in each exchange) or intermittent (given once daily), with the antibiotic dwell being at least 6 hours in intermittent dosing. The ISPD guidelines provide detailed information for dosing of antibiotics and treatment of peritonitis once the culture results are known. If despite the initial management strategies, peritonitis does not resolve or recurs then the catheter warrants removal. Indications for PD catheter removal for PD related infections are outlined in Table 9.

**Table 9. Indications for catheter removal in PD related infections**

<table>
<thead>
<tr>
<th>Indications for Catheter Removal for Peritoneal Dialysis-Related Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory peritonitis</td>
</tr>
<tr>
<td>Relapsing peritonitis</td>
</tr>
<tr>
<td>Refractory exit-site and tunnel infection</td>
</tr>
<tr>
<td>Fungal peritonitis</td>
</tr>
<tr>
<td>Catheter removal may also be considered for repeat peritonitis and mycobacterial and polymicrobial peritonitis</td>
</tr>
</tbody>
</table>
Conclusion

Peritoneal dialysis is an underutilized form of renal replacement therapy. The ideal PD catheter is bio-compatible, easy to place and remove, provide adequate dialysis, avoid leakage and deters from infection. A multi-disciplinary approach involving physicians, nurses, vascular access coordinator and surgeons are essential for the success of PD catheter management. This chapter has highlighted the importance of recognizing mechanical failure as an important factor in determining PD success and has re-emphasized the impact of recognizing and treating infections early to prevent PD failure. This chapter has also shown a simplified and evidence based approach to the management to PD catheter related complications that a nephrologist would encounter on a daily basis.

References


Chapter XXVII

Complications of Hemodialysis Procedures

Jamie Ross
University of California-Davis, Department of Nephrology,
Davis, CA, US

Introduction

Reporting Complications

All complications which occur when initial research is performed with “new” procedures and devices are reportable by the FDA. However, unless there is a required reporting system for complications in everyday practice all data is strictly voluntary. Therefore, we can only have a partial knowledge of the frequency of the presently known complications. When discussing complications from any procedure, it is useful to agree upon the definitions of complications as well as the expected frequency. The American Society of Diagnostic and Interventional Nephrology (ASDIN) has defined the complications but these are not necessarily the same as those described by the Interventional Radiology community. [1, 2] The ASDIN has started a database collecting this information; all contributions are voluntary as well. [3] Having a national database will go a long way to improving our understanding of the frequency and type of complications resulting from interventions on dialysis access. When complications and outcomes are known it contributes to improvements and increased quality of care. Ultimately the important part of all complications is knowing what to expect and how to treat them.

Complications Common to All Procedures

The metabolic state of all CKD IV–V patients seen by interventionalists make treating them challenging. It is essential to know the effect of the procedure on the underlying
condition of the patient. In that regard the volume status, acid-base status and level of potassium can be important in the pre-operative evaluation of each patient. Discussion of the complications and reactions related to specific medications is beyond the scope of this chapter.

*Contrast* exposure is still a *high risk inherent* in endovascular procedures. Many patients are at risk for contrast reactions despite changes in the proprietary formulations. For instance, patients who have underlying asthma are at three times higher risk for contrast reactions than non-asthmatic patients. [4, 5] Those with known reactions will need to be pre-treated with prednisone and benadryl. [5] Even when contrast is non-ionic, it still can have up to 400 mOsm and is therefore still hypertonic compared to the serum osmolarity of patients. If the patient already has fluid overload an additional contrast load can result in significant pulmonary compromise. Some of these patients may require ultra filtration or dialysis prior to the procedure even if that means a temporary dialysis line must be placed. Patients who have significant hyperglycemia (blood sugar above 400 mg/dl) are at increased risk for pulmonary compromise due to intravascular shift of fluid. In diabetic patients pretreated with prednisone for a prior contrast allergy there is a significant frequency of increased blood glucose upon arrival to the procedure area. These patients may require some correction of their blood sugar prior to initiating a prolonged procedure.

With regard to the effect of contrast on renal function or the risk of contrast-induced nephropathy, there is extensive literature which may or may not support specific measures for prophylaxis to preserve residual renal function. The most generally accepted recommendations are isotonic fluids, and a minimum amount of contrast. [6, 7]

*Sedation* is of concern with these same patients due to the effect of many of the analgesic and anxiolytic medications in causing hypoventilation. When this occurs the underlying metabolic acidosis is compounded by a transient respiratory acidosis that can lead to serious hemodynamic complications. [8, 9, 10] It is good to be aware of these issues and possibly have the patient dialyzed even via a temporary dialysis catheter prior to starting a prolonged procedure requiring sedation. Some physicians will have a pH or a HCO3- mEq/L level below which they will not perform a prolonged procedure or even sedate the patient. Discussions of specific medications and the reactions of CKD IV-V patients are beyond the scope of this chapter.

*Hyperkalemia* can be an issue in patients especially with underlying cardiac disease and in patients with volume overload who are undergoing prolonged procedures with or without sedation. The patients at the highest risk for hyperkalemia are those initiating dialysis or who are under dialyzed. [11] This might include patients with poorly functioning dialysis catheters, extremely poor flows or thrombosis of their fistulas or grafts.

The highest risk for this is *the patient requiring a percutaneous thrombectomy* where the use of some devices can destroy red cells and result in an increase in the overall level of potassium in the blood stream. [12] Potassium elevation in the vascular access patient may also be due to prolonged fasting and translocation related to the contrast media itself. [13] It is worth noting that contrary what is generally believed, the ECG is an extremely poor predictor of significant hyperkalemia. [14, 15] It is important to evaluate those patients at extreme risk and know the medical treatments that are effective, such as glucose, insulin and albuterol treatments. [14, 15]

*Infections* are a risk of any procedure that breaks the skin barrier. It is an important part of each procedure to assure that the area of skin involved does not already have cellulitis or
an active infection. Knowledge of appropriate skin preparation and sterile technique is vital to maintaining good practice. [16, 17] Each of the procedures described below will have the expected rate of early and late infections associated with them. Using the standard sterile technique will keep your infection rate within those parameters.

**Bleeding** is a common risk among most of the procedures described in this text. It is important to make sure that patients have adequate platelets (usually greater than 50,000) and good coagulation (INR ≤1.5-2.0 depending on the operator). [18, 19] Patients on warfarin for dialysis related issues may need to have their level adjusted prior to the procedure if it is not emergent. Multiple medications are now available to decrease thrombosis for various indications. Each of them has a specific half-life that may be altered in renal failure. Knowledge of these medications is essential to planning a safe procedure. Patients on blood thinners for conditions not related to their dialysis access need to have this adjusted under the coordinated care of the prescribing physician. [20] There is some controversy about the need for routine coagulation profiles but there is no disagreement in obtaining the appropriate laboratory studies guided by the history and physical. [21, 22]

**Complications of Temporary or Tunneled Dialysis Catheters**

*Initial placement complications* of temporary and tunneled dialysis catheters are similar. The overall expected rates of general complications are listed in Table 1. Many of these complications have been decreased by the use of ultrasound as standard of care for all central line placement procedures. [23, 24, 25] Knowledge of anatomy can decrease many complications as well. For instance, knowing where the thoracic duct is will help avoid it. In addition, by not accessing the femoral vein at or above the inguinal ligament but slightly inferior (about 2 cm), the operator avoids the peritoneal reflection which allows passage of blood into the retroperitoneal space. [26] Using the right equipment can reduce complications. Some of the risk of air embolus has been decreased by the use of “valves” within tear away sheathes that are available with most insertion kits. It is still important for the operator to know that emergency treatment of all complications such as this. Treatment for an air embolus would be laying the patient left side down and aspirating as much air as possible. [27] Common sense can decrease other complications. Tracheal compression or bilateral pneumothorax occurred more often in the past when each side of the neck or chest was accessed without ultrasound at the same session. In addition to using ultrasound, it is prudent to avoid attempts at accessing the contralateral side of the neck or chest when a complication has arisen on the first chosen location. [28, 29, 30, 31] One can either wait a day or place a temporary access in the femoral area. While some of these complications are related to the initial placement of the needle into the vessel some are related to wire migrations into and out of the venous system. This would be mitigated to some degree by fluoroscopy and if necessary by angiographic techniques.

*Long term complications* are associated primarily with tunneled catheters. This is because the prolonged use of temporary catheters is no longer standard of care for most patients. The rate of tunneled catheter infections goes from less than 5% expected in the initial post-op period to increasing risk for infection over time that can be as high as 48% at 6 months. [32, 33] This is primarily 60% to 90% gram positive organisms. [35] With these organisms there is an increased risk up to 25% of metastatic infections. [35, 36] Eradicating these infections
can be extremely difficult. While treating these infections is beyond the scope of this chapter it is important to realize that this is the most frequent complication of prolonged catheter use. Other significant complications are stenosis or thrombosis of the central circulation. The rate or frequency of this is not well elucidated but the most reasonable statistics suggest it can occur upwards of 40% of the time. [37, 38, 39, 40] Symptoms are usually swelling on the side of obstruction especially if it is ipsilateral to a working fistula or graft. [41] (figure 1). It can also be a cause of increased bleeding, aneurysm development or just poor function of the access on the side of the central stenosis. If stenosis from previous catheters is on both sides of the central circulation then this can result in iatrogenic Superior Vena Cava (SVC) syndrome. [42, 43, 44] This can mean that the patient’s first access is a femoral one. SVC syndrome can be very symptomatic and result in shortness of breath requiring intubation, laryngeal swelling, brain swelling and even death. The rate of true SVC syndrome is not known. Fibrin sheaths can occur in some patients and be a treatable cause of catheter malfunction. The significance of fibrin sheath and fibrin sheath disruption is not clear in terms of its long term effects on the central circulation. [45, 46, 47, 48]

Table 1. Complications of Central line Placement

<table>
<thead>
<tr>
<th>OCCURS 1-2%</th>
<th>OCCURS &lt;&lt; 1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hemo or pneumothorax</td>
<td>• Cardiac, vascular injury, perforation or erosion</td>
</tr>
<tr>
<td>• Retroperitoneal bleed</td>
<td>• Nerve injury</td>
</tr>
<tr>
<td>• Air embolus or catheter embolus</td>
<td>• Thoracic duct injury</td>
</tr>
<tr>
<td>• Hematoma</td>
<td>• Trachial compression</td>
</tr>
<tr>
<td>• Sepsis/infection (may be up to 5%)</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1. Central Stenosis from a Pacemaker.
Complications Related to Angioplasty of a Hemodialysis Graft or Fistula

Angioplasty involves the placement of a wire and sheath into the access or the native vessel and then inserting a balloon through this device into the lumen of an artery or vein and inflating the balloon to anywhere from 8 atmospheres to over 25 atmospheres to breakup localized scarring, plaque, thrombus or intimal hyperplasia. The very process of performing this treatment can lead to multiple problems. In addition to an infection, placement of the wire and sheath can damage the vessel and cause bleeding, perforation, and/or scarring. [49] The inflation of the balloon, itself, can be damaging to the endothelium and can lead to accelerated scarring in the area treated either quickly in weeks or over several months or more. [50]

Inappropriate sizing of the balloon and/or excessive inflation pressure can damage or rupture the entire wall of the vessel treated. This can result in dissection and further damage to the vessel, immediate rupture or even development of a pseudo or actual aneurysm. [51, 52, 53] If the damage is extensive as in a rupture it may require the immediate placement of a covered stent to stop the bleeding. For this reason some physicians will move the balloon forward rather than remove it and then image to assure that no damage has been done with each treatment. This is important and will ensure placement and position of the wire is maintained and the balloon is still available for treatment if needed. Immediate recognition and treatment of vascular rupture is the most important part of dealing with this complication. The bleeding from a vascular rupture that is part of an arterial venous access circuit if unchecked can lead to damage to the fistula, compartment syndrome, loss of a limb and even death. [54, 55] The images shown (figure 2) give some idea of what these complications can look like. It is important to remember to save life, limb and access in that order.

As far as the treatment for this injury, there may be some place for external compression but it will not be as effective unless pressure can be placed at the exact site of injury or just proximal to it. The treatment for this is more effectively internal compression with the balloon that will occlude the vessel internally for 3 minute intervals repeating several times. At the same time the operator should be preparing to place a covered stent to secure the problem. If the balloon compression is successful then the stent can be avoided but having the

Figure 2. Extravasations.
right equipment available is essential. [55] The most concerning and difficult to treat are central stenoses. A rupture in a central vessel can result in extremely brisk life threatening bleeding and must be controlled quickly by a stent. [56] In a central stenosis it is essential to have the wire securely from the SVC and into the IVC if at all possible. It is important to have all the tools needed for treatment of any complications available prior to starting a procedure.

Complications Related to Stent Placement

The complications related to stent placement have to do with the technique and placement of the stent itself. The most important way to avoid problems with stents is to accurately image the area that is going to be treated. Pre-procedure knowledge and practice with the type of delivery system used by the stent with which you are working is extremely important. Understand the changes that occur to the stent shape as it is deployed. Make sure in your mind that a stent is the best treatment before deploying it. [57, 58] Once the stent is in, it can not by any usual means come out. Any foreign object placed into the body has a chance of causing inflammation, infection and even clotting. [59] This can be avoided by strict sterile technique and even changing gloves prior to placement. It is still somewhat unclear whether to administer an antibiotic prior to stent placement and some physicians give a few thousand units of heparin post procedure. [60]

Even after careful planning the location may not by ideal at the end of placement. The stent can be too proximal or too distal to the target lesion. Some types of stents may foreshorten and therefore not cover the lesion completely. [61, 62] This foreshortening can result in requiring a second stent to be deployed. If using a covered stent or stent graft then the risk of occluding an important branch of the vessel is significant. It is important to evaluate this prior to stent deployment so that vessels are not “jailed” or occluded.

If the stent is either narrow or the stent is not fully expanded before internal or external movement occurs then the stent can migrate. [63] This can result in the stent being caught in the heart or even pulmonary vessels. [64] This is at the highest risk when deploying a stent in the central circulation.

Table 2. Some of the Complications Related to Thrombectomy

<table>
<thead>
<tr>
<th>Category</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical</td>
<td>Adverse Drug reaction – 3%</td>
</tr>
<tr>
<td></td>
<td>Adverse Reactions to Sedation – 1%</td>
</tr>
<tr>
<td></td>
<td>Adverse event related to cardiac or pulmonary status?</td>
</tr>
<tr>
<td>Procedural</td>
<td>Subclinical extravasation of Contrast 2%</td>
</tr>
<tr>
<td></td>
<td>Extravasation not requiring treatment 1%</td>
</tr>
<tr>
<td></td>
<td>Extravasation requiring stent or prolonged balloon inflation &lt;&lt;1%</td>
</tr>
<tr>
<td></td>
<td>Arterial embolism &lt;&lt;1%</td>
</tr>
<tr>
<td></td>
<td>Pulmonary embolism &lt;&lt;1%</td>
</tr>
<tr>
<td></td>
<td>Bleeding requiring transfusion&lt;&lt;1%</td>
</tr>
<tr>
<td></td>
<td>Surgical intervention &lt;&lt;1%</td>
</tr>
</tbody>
</table>
There are several methods for treating this. First it is essential that the wire be all the way into the IVC and then the stent would tend to end up naturally into the lower venous circulation where it is safer to attempt removal. If the stent is in the heart or pulmonary vessels then it can sometimes be removed via endovascular techniques specifically developed in the cardiac catheterization laboratory. If this is not successful than open heart surgery must be performed. [65, 66] If the stent is too superficial to the skin it can erode through and extrude through the skin itself. [67] This would require surgical removal or repair.

Complications Related to Percutaneous Thrombectomy

The highest risk procedure in the usual repertoire of interventional nephrology is the percutaneous thrombectomy. [68] It is incumbent on the physician to be extremely familiar with all the techniques involved in performing this procedure. [69, 70, 71] It is important to know the signs and the treatments for each possible complication and those specific to the technique being used. (Table 2) Therefore it is essential to have all the equipment available for any complications which might occur. Anticipating these complications and knowing how to treat them if they arise is the safest option for these patients. The pre-operative history and physical are also extremely important. The access history and alternatives available if the present access can not be effectively treated with the thrombectomy procedure is very important. While many accesses are successfully treated with the thrombectomy procedure a small minority are not. [72, 73] The presence or absence of infection as well will determine if the patient will need a temporary access and admission or can safely proceed with the planned thrombectomy. The presence or absence of pulses is needed information in planning the procedure so that any changes post procedure can be recognized. As described above the patient’s coagulation state is also very important. The knowledge of their risk factors for any planned or unplanned anti-coagulation is essential in choosing the appropriate technique for the thrombectomy procedure.

There are multiple ways to perform a percutaneous thrombectomy and each method has its own unique risks. [74, 75] The procedure itself is more extensive than a focused angioplasty and therefore has a higher risk than the typical angioplasty in a flowing access. In
this setting it is most likely that the patient will be underdialyzed and fluid overloaded as well. Thus any complications for a percutaneous thrombectomy are more likely to cause symptomatic effects and require an additional intervention than with the other procedures described above. The percutaneous thrombectomy also requires increased speed which is a challenge for the operator to perform the tasks efficiently as well as without errors of judgment or mechanics. Inherent in this procedure are all the complications of the angiogram, angioplasty and sometimes stent placement. Some of the procedure has less visual information since the circuit is difficult to image without flow. Therefore, the risk of misadventures with wires and other equipment is higher.

In addition to these, add the risk of thromboembolic events to either the arterial tree or the venous circulation most specifically the lungs. Venous emboli may not need treatment at all unless symptomatic such as the case of some pulmonary emboli. Recognizing the events when they occur is the first important step in treating them. [76, 77, 78] Arterial emboli need to be treated urgently to preserve circulation. The removal of arterial thrombi can be done with some of the same techniques and equipment used in the procedure itself. There however may be a need for additional equipment and even surgical intervention. [70, 80] (figure 3) Pulmonary symptoms resulting from emboli may require the use of tPA or other anticoagulants and require transfer to the ICU or may not be symptomatic at all and may go undiagnosed. [77] It is important to recognize that if anti-coagulation is not planned as part of the primary procedure still may become necessary use these medications to treat some of the subsequent complications. Using tPA either as a primary means of dissolving the clot or as a supplement to mechanical thrombectomy devices will increase the extent of bleeding should any mishap occur. [81, 82] There is, however, an opportunity to prevent extensive bleeding in a clotted access by repairing any vascular damage prior to restoring arterial flow. Such an option does not exist in a functioning access.

**Conclusion**

Minimizing complications can be done by knowledge, preparation, common sense and a willingness to ask for assistance when needed. [83] Since our knowledge is as only as good as our reporting system, there is room for improvement. However steps are being taken to increase our database and will likely lead to improving the level of care we provide.

**References**

Complications of Hemodialysis Procedures


[50] Faxon DP et al. “Mechanism of angioplasty and its relation to restenosis.” Am. J. Cardiol. 1987 Jul;60(3); 5B-9B.


VII. HEMODIALYSIS ACCESS DYSFUNCTION AND TRANSLATIONAL RESEARCH
**Introduction**

The United States Renal Data System (USRDS) projects that the US hemodialysis population will increase to 774,000 patients by 2020 [1]. In this context, hemodialysis (HD) access dysfunction is a $1 billion per year problem currently and is likely to become an even bigger burden on our society [1]. Despite key contributions from CMS, the Networks, and the “Fistula First” Breakthrough Initiative, the US HD population lags far behind Europe in terms of arteriovenous fistula and catheter incidence and prevalence rates [2, 3]. The importance of developing a comprehensive basic science research program to meet the problem of HD access head on has been recently reviewed [4]. The purpose of this chapter is to describe the recent contributions to and future directions in epidemiology, clinical science, and translational science.

**Epidemiology**

Increasing the Use of Arteriovenous Fistulae

The National Kidney Foundation’s Dialysis Outcomes Quality Initiative (DOQI) Vascular Access Clinical Practice Guidelines in 1997 set a goal of having at least 50% of incident patients, and 40% of prevalent patients, having an AVF. The Fistula First Breakthrough Initiative (FFBI) in 2005 increased the goal for fistulae in prevalent patients to 66% by 2009. [5]
Alexander Yevzlin and Brad C. Astor

Figure 1. Proportion of incident and prevalent patients using each type of vascular access.

These initiatives have had remarkable success, with the proportion of prevalent patients using an AVF increasing from an estimated 33% in 2003 to 57.9% in March 2011 (Figure 1). [6] The proportion of patients using a synthetic graft has likewise decreased from approximately 40 to 20% over this same time. Despite these achievements, there has been only a modest increase in the proportion of HD patients initiating dialysis with a functioning AVF, from 12.7 to 17.2%. [6] The majority of patients (70-80%) still begin dialysis with a central venous catheter, and nearly one-quarter of prevalent patients use a catheter [7].

Identification of factors associated with the failure of an AVF to mature or early thrombosis, allowing better identification of patients in whom successful AVF creation or maturation is unlikely, may help avoid prolonged catheter use in incident HD patients. Improved decision-making on when and how to intervene on non-maturing AVF are also needed to optimize vascular access outcomes among incident HD patients.

AVF Maturation Failure

Estimates of the proportion of AVFs that fail to mature vary widely, but several larger studies in the US have found that approximately 40% of created AVFs are never utilized consistently. [8, 9] This has obvious implications for efforts to increase AVF use and decrease use of temporary catheters. Several non-modifiable risk factors for failure to mature have been identified consistently, including poor vessel characteristics, older age, non-white race and the presence of coronary or peripheral vascular disease. [10, 11] Lok et al developed a prediction tool for failure to mature based on age, race, coronary artery disease and peripheral vascular disease. [8] The algorithm was developed in 422 patients who had a first fistula created, using multivariate stepwise regression. This algorithm was able to classify 445 patients from an external validation cohort at 5 North American centers into 4 categories of FTM risk, ranging from 24% to 69%. The appropriate use of such prediction tools for
decision-making on whether to attempt AVF placement in an individual patient will have to take into account additional factors, including the potential success of interventions to salvage a failing AVF, the benefit of an AVF over a graft in the long-term compared to the higher risk of using a catheter as a bridge until the AVF is usable, the predicted survival of the patient, and the costs and effect on the quality of life of the patient of repeated surgical procedures.

Thrombosis is a major cause of early AVF failure. In the largest randomized controlled trial of an intervention for vascular access complications to date (n=877), the Dialysis Access Consortium tested clopidogrel versus placebo to determine whether antiplatelet therapy could reduce the rate of early AVF failure and increase the proportion of fistulae that were suitable for dialysis (Figure 2) [12]. Fistula suitability was defined as the ability to use the fistula for dialysis with 2 needles and maintain a dialysis machine blood flow rate adequate for optimal dialysis (≥ 300 ml/min) during 8 of 12 dialysis sessions occurring during a 30-day suitability ascertainment period, which began at day 120 for those who started maintenance HD within 120 days of fistula creation and began at the first day of dialysis initiation for those in whom dialysis started after day 120. Clopidogrel was able to reduce the risk of fistula thrombosis at 6 weeks after surgery from 19.5% to 12.2% (relative risk: 0.63; 95% confidence interval: 0.46-0.97). This reduction in early thrombosis, however, did not result in an increase in the proportion of AVF that were suitable for dialysis (61.8 versus 59.5%; p=0.40). The disappointing and somewhat surprising results of this trial suggest that vessel characteristics other than patency may need to be studied to identify more effective interventions.

Results from a smaller randomized trial suggest that the use of preoperative vascular ultrasound may improve the rates of AVF maturation. [13] In this study of 208 patients in whom an AVF was created, the immediate failure rate was 4% among those for whom an ultrasound report was disclosed to the surgeon, compared to 11% among those for whom the report was withheld. Primary failure at 1 year, however, was not statistically different between the two groups. Larger studies with hard endpoints are needed to determine whether this approach will have a substantial impact on AVF maturation rates. The first studies of endothelial cell implants following AVF creation have not shown a substantial effect on initial patency, but larger studies are needed. [14]

![Figure 2. Outcomes in trial of dipyridamole plus aspirin on hemodialysis graft patency [12].](image-url)
Longer-Term Vascular Access Complications

Risk Factors

Longer-term complications of AVF and AVG, including stenosis and thrombosis, remain a significant cause of morbidity and cost among HD patients. The identification of risk factors for complications and evaluation of agents to preclude or treat stenosis and thrombosis are areas of intense interest.

A recent analysis of data from the 1426 patients in the HEMO study identified intradialytic hypotension as a risk factor for AVF thrombosis. [15] Those patients in the highest quartile of kinetic modeling sessions with intradialytic hypotension (>44% of sessions) during the first 4 months of the HEMO study had a 2.5-fold higher risk of AVF thrombosis during the subsequent follow-up (median follow-up of 3.1 years). No such association was observed among patients using synthetic grafts. Lower predialysis and postdialysis systolic blood pressure also were associated with a higher rate of thrombosis in both fistulae and grafts. In addition, those patients with an AVF randomized to high-flux membranes had a higher risk of thrombosis (relative risk: 1.45; 95% confidence interval: 1.01 – 2.10) than those randomized to low-flux membranes.

The Frequent Hemodialysis Network Trial Group compared conventional, three times per week hemodialysis to frequent, six times per week hemodialysis in a multicenter randomized trial. [16] While more frequent HD was associated with better outcomes in terms of increase in left-ventricular mass and change in physical-health composite score, it also was associated with a higher risk of interventions related to vascular access (hazard ratio, 1.71; 95% CI: 1.08 to 2.73). The proportion of fistulae (approximately 64%) and grafts (approximately 17%) in the study population are similar to those of the US HD population as a whole. Further analyses of these data and additional studies should be performed to determine whether the higher risk of frequent dialysis effects both AVF and AVG, and whether the higher risk is due solely to more frequent cannulation or whether other factors may play a role.

Monroy-Cuadros et al reported results from an analysis of 831 HD patients in the Southern Alberta Renal Program with a functioning AVF. [17] In agreement with previous studies, the authors identified older age, diabetes, smoking, hypertension and peripheral vascular disease as risk factors for loss of primary patency within 6 months. The authors also found that an initial intra-access blood flow (IABF) less than 500 ml/min was associated with a substantially increased risk of loss of patency. Only 14% of the patients in this study had such a low IABF, however, limiting the ability of this characteristic to identify a large proportion of patients at risk of AVF complications.

A meta-analysis of 27 randomized trials comparing higher hemoglobin targets using erythropoietin stimulating agents, including results of the recently-completed TREAT (Treatment to Reduce Cardiovascular Events with Aranesp Therapy) trial, [18] confirmed the association between higher hemoglobin targets and outcomes, including stroke and hypertension. [19] Data from the 8 studies that included information on vascular access thrombosis, totaling 589 events in 6,844 patients, found a 33% (95% CI, 18 to 53%) higher risk of thrombosis associated with the higher hemoglobin target.

Interventions

The Dialysis Access Consortium tested the effectiveness of dipyridamole, a vascular antiproliferative agent, in combination with aspirin to prolong primary unassisted patency
Future Directions in Vascular Access Clinical Science

(defined as patency without thrombosis or requirement for intervention) of newly created AVG. [20] A total of 649 patients were randomized to extended-release dipyridamole and aspirin, twice daily, or placebo. At one year of follow-up, 23% of the placebo group and 28% of the treated group had maintained unassisted primary patency. The adjusted hazard ratio for loss of patency associated with treatment was 0.82 (95% CI, 0.68 to 0.98; p=0.03). Clinically significant stenosis (≥ 50%) was observed in 50% of treated patients and 55% of untreated patients (hazard ratio, 0.72; 95% CI, 0.57 to 0.90; p=0.005). No significant difference in thrombosis was observed. In addition, no significant difference between the randomized groups in the incidence of bleeding events was observed, in contrast to earlier studies of antithrombotic therapies. [21, 22] These results are promising, but the overall impact of the intervention was modest. The intervention improved primary patency at one year by only 5%, and the risk of graft failure (50%) remained unacceptably high in the treated group.

A secondary analyses of these study results assessed whether the use of aspirin at baseline was associated with the same outcomes. [23] Of the study participants, 43% reported use of aspirin at baseline, and 82% of these remained on non-study aspirin at one year. The use of aspirin at baseline was associated with a similar benefit to that of the combined intervention of dipyridamole plus aspirin, with a 7% lower risk of primary unassisted patency at one year (23% versus 30%; hazard ratio, 0.83; 95% CI, 0.68 to 1.01; p=0.06).

Other studies are investigating the potential for post-operative administration of fish oil to prevent AVG stenosis and thrombosis. [24] A small (n=24) randomized study reported a 5-fold increase in one-year patency of AVG in those receiving fish oil. [25]

Future Directions

The last decade has seen substantial efforts to increase the proportion of HD patients in the US with a functioning AVF. The “fistula first” initiative places even more emphasis on issues related to selection of appropriate patients for fistula placement (and perhaps more importantly, selection of patients in whom fistula placement is not the best approach) and interventions to improve fistula maturation. Inappropriate placement of fistulae and failure of fistulae to mature may lead to prolonged catheter use and its attendant risks. While some basic demographic and clinical factors that predispose patients to a higher risk of maturation failure have been identified, more complete tools are needed to allow informed decisions to be made on an individual patient level. The decision to attempt fistula placement should account for additional factors, including the likelihood of successful creation, the likelihood of successful maturation, the potential benefit over a functioning graft over the expected life of the patient, and the potential burden to the patient from repeated surgeries to salvage a nonmaturing fistula. We currently lack precise estimates for many of these factors, precluding a comprehensive, evidence-based decision tool.

Despite the publication of large, multicenter randomized trials addressing access thrombosis, no silver bullet has been identified. The results of the Dialysis Access Consortium trial of clopidogrel are disappointing, but may lead to alternative areas of research, including additional interventions of preoperative imaging and surgical techniques, as well as postoperative medications addressing factors other than early thrombosis.
Figure 3. Radiograph of dysfunctional hemodialysis access due to neointimal hyperplasia of vascular access.

Figure 4. Neointimal hyperplastic lesions in a porcine model of AVF (NH represented by black lines). Mild, moderate, and severe NH in A), B), and C), respectively.

Figure 5. Neointimal hyperplasia of vascular access can develop and progress through several pathways [9, 10]. A: Normal vein prior to access creation; B: No vascular remodeling after access creation; C: Luminal narrowing (NH) resulting in luminal compromise due to smooth muscle proliferation and inflammation; D: outward dilatation (maturation) resulting in luminal preservation of the AVF.
Clinical Science

Prevention

A number of vasoactive drugs have the potential to regulate NH in dialysis vascular access, such as platelet antagonists, calcium channel blockers, angiotensin-converting enzyme inhibitors, and fish oil. Other agents that can alter vascular remodeling include statins, peroxisome proliferator–activated receptor agonists, and immunosuppressive agents. Imatinib mesylate, a phosphotyrosine kinase inhibitor of PDGF, Bcr-Abl, and C-kit, seems to be a possible therapeutic agent. While delivery of these agents at the time of surgery could be relatively straightforward, repeat delivery, particularly for agents with a short half-life could be challenging.

Intervention

Neointimal hyperplasia (NH) has been traditionally regarded as a purely pathological entity. The approach, likewise, to NH in dialysis access so far has been clinically mechanistic (Figures 4 and 5), consisting of repeat interventions with angioplasties and stent placement. These therapies might be successful in the short term in altering NH. However, long-term patency remains elusive and the ability to regulate NH, not just eradicate or prevent it for any potential benefit is unknown. Inward remodeling (what is currently called “NH”) and outward remodeling (what is currently called “vascular maturation”), rather than distinct pathologic processes, can be viewed as two potential pathways for vascular remodeling in response to stress. As our understanding of the true role of NH evolves, broader-based investigations will refocus therapeutic efforts from “suppression” of NH to “control” (Figure 3) [4].

There has also been interest in exploring non-pharmacologic approaches to affect the course of NH including radiation therapy. Ionizing radiation can induce apoptosis and inhibit the cell cycle. SMC in their proliferative phase in neointimal tissue are likely to be especially susceptible. In tissue culture, external beam radiation to SMC inhibited growth in a dose-dependent manner. Venous SMC were less susceptible than aortic SMC [26]. Endovascular radiation therapy also inhibited NH in vitro, in porcine models of AVG, in human coronary artery stenosis, and in saphenous vein graft stenosis [27]. Local radiation therapy at the venous anastomotic site delayed site-specific graft stenosis but did not improve cumulative graft survival [28]. A prospective, randomized, controlled study of one year of far-infrared therapy improve access flow and patency in patients who received the therapy [29].

In the Beta Radiation for Treatment of Arterial-Venous Graft Outflow (BRAVO) 1 study, 25 patients with dysfunctional AVG were randomly assigned to brachytherapy or sham treatment after angioplasty [28]. Primary patency at 6 months was 42% in the intervention group and 0% in the control group. Interestingly, secondary patency at 6 or 12 months was not affected. Other non-pharmacologic treatments could include local application of physical agents such as photodynamic or ultrasonic therapy via intravascular or external application as well as percutaneous balloon cryoplasty. The last has shown promising results [30].

It is possible to deliver cells that promote healthy remodeling at the site of NH. This is especially important in considering the aforementioned novel findings from Lee and
Alexander Yevzlin and Brad C. Astor

colleagues that venous endothelium may demonstrate NH even prior to the creation of any surgical shunt. Endothelial cells embedded in absorbable gelatin have been used to wrap around arteriovenous anastomoses to augment cytokine production and control NH in porcine AVF models. *In vivo* seeding with anti-CD34 antibodies accelerates endothelialization of new AVGs in a porcine model [31]. Paradoxically, this therapy resulted in an increase in venous NH at the graft-vein anastomosis, again suggesting that regulating NH is critical and not an all-or-none process in AVG.

Gene transfer of endothelial and inducible nitric oxide synthase, cyclin-dependent kinase inhibitors, retinoblastoma protein, hepatocyte growth factor, and transcription factors such as edifoligide have all been used to inhibit NH in experimental angioplasty models [26]. Gene therapies have focused on other targets as well. In a pig model, adenoviral-mediated delivery of β-adrenergic receptor kinase reduced NH at the venous anastomosis by interfering with Gi signaling [27]. Adenoviral transfer of C-type natriuretic peptide also improved outward remodeling and thickening of venous media in a porcine AVG [28], while perivascular placement of vascular endothelial growth factor D via an adenoviral vector is currently in phase III clinical trial for the prevention of AVG venous anastomotic stenosis [30]. All of these treatments however have a) the risks of the vector *per se*; b) the unpredictability of distribution of vector and target molecule; and c) a patency-related outcome that while important, leaves us guessing as to the actual events within the dialysis access that might affect the outcome. Initial studies using endovascular balloons with sheathed needles to pierce the vessel wall suggest that repeat perivascular delivery through an endovascular approach is possible [32].

**Translational Science**

**Our Understanding of Neointimal Hyperplasia**

Several mechanisms have traditionally been implicated in the genesis of NH in hemodialysis vascular access, including proliferation and migration of smooth muscle cells (SMC) from the media, aggravation of inflammation, alteration of hemodynamic forces, and activation of the coagulation cascade [33].

Our seminal understanding of NH pathology derived from studies of coronary and peripheral arterial disease that suggested vascular SMC in media proliferate and migrate into intima. However, adventitial remodeling was also noted in studies that examined coronary arteries. NH in the arterial circulation (as in peripheral arterial grafts) can be very dissimilar to NH seen in the venous circulation (as in a dialysis fistula) [34].

Non-laminar blood flow, oscillatory shear stress, and increased turbulence following creation of an AV anastomosis result in aggressive NH; and patency of the venous conduits is generally worse than the patency of bypass grafts in the arterial circulation. In case of an arteriovenous graft (AVG), the presence of a foreign body adds further bioincompatibility and augments local inflammation that is compounded by repeat injury from dialysis needles and uremia-associated endothelial dysfunction. Changing rheology and increased blood flow actually induce regression of NH in polytetrafluoroethylene (PTFE) grafts [35]. The pathology and pathophysiology of NH has been examined both in humans and in animal
In one study, human venous tissue obtained from three patent and one thrombosed AVF was examined. NH was present together with medial hypertrophy resulting in greater than 80% stenosis. The predominant cell type was myofibroblasts by immunohistochemistry [36].

In dialysis AVG, histological and immunohistochemical analysis of NH have also revealed SMC and myofibroblast proliferation at the venous anastomosis and downstream vein [34]. Angiogenesis was prominent in the adventitia and neointima at these sites. In addition, there was increased growth factor expression by SMC, myofibroblasts, microvessels, and macrophages in these areas. In other models, cytokines related to oxidative stress have also been shown to be expressed in conjunction with growth factors [37]. A number of other inflammatory cytokines are also likely to play a role in this process of venous NH [38].

It is anecdotally acknowledged that after primary stenoses have been treated with angioplasty in AVFs, there is a significant increase subsequent stenosis (Figure 3). Recent findings confirm this clinical observation by noting an increase in the proliferative index in medial and intimal lesions [39]. This suggests that angioplasty-induced vascular injury is likely to enhance growth factor and cytokine expression. Thus, paradoxically, the very procedure performed to treat venous stenoses may in fact be responsible for aggressive dialysis access stenosis. On the basis of the pathogenic mechanisms involved in NH, a mathematical model of venous NH has also been developed [40]. The model anticipates possible access stenosis and may provide an indication for intervention. What is more difficult to track but also significant is that venous endothelium per se may be able to promote NH through one or more paracrine mechanisms [41].

Genetic factors have also been linked to the development of aggressive NH. Single nucleotide polymorphisms in the matrix metalloproteinase gene and angiotensin converting enzyme gene can alter vascular responsiveness and the latter has been investigated with regards to hemodialysis access patency. Polymorphisms of TGF-β, heme oxygenase 1 (HO-1), and the methylene tetrahydrofolate reductase gene also have been linked to AVF patency [42-45]. Among these polymorphisms, HO-1 appears to have the greatest likelihood of having a direct association with access outcomes.

HO-1 is an inducible protein that regulates vascular response to injury, decreasing NH and inflammation. HO-1 deficiency is linked with NH and inflammation with HO-1 null mice manifesting an increased number of occluded AVF through mechanisms involving matrix metalloproteinases compared with wild-type mice in experimental AVF creation [46].

Far-infrared therapy also increases blood flow and patency of AVF in HD via HO-1 presumably through activation of thermoreceptors with a concomitant reduction in endothelial inflammation [47]. HO-1 is likely the mechanism too for the salutary effects of rapamycin and paclitaxel in decreasing AVF stenosis. Thus, delivery of HO-1 into the arteriovenous anastomosis could have the potential for preventing NH or even inducing regression of NH that is already present.

Inflammation has to be considered an auxiliary if not primary stimulus for NH in dialysis access. The inflammatory activity of surgically harvested thrombosed fistulas has been measured and found to be elevated using a series of inflammatory biomarkers [48]. This finding has been corroborated by other evidence of inflammation around NH lesions, including increased expression of IL-6 and vascular cellular adhesion molecule 1 (VCAM-1).
Lee et al. recently documented significant venous NH prior to AVF or AVG creation in venous segments at the site of AV access creation [49]. These data suggest that uremia, inflammation and oxidative stress in CKD/ESRD patients could be responsible for these changes. It is as yet unclear as to whether pre-existing NH correlates with patency or a reduction in patency.

Thus, NH has been described as the primary pathologic lesion in hemodialysis access grafts and fistulas that develop stenosis as well as nonmaturation [39, 34, 36]. There is also evidence, though limited, that implicates NH in fistula nonmaturation. NH has been regarded as a purely pathologic entity with substantial research efforts have been directed at preventing and treating NH in the vascular access [50, 51]. Newer research suggests that this understanding of NH may need revision and that our efforts to “prevent” NH must evolve to “control” [4, 52].

Future Methods of Treating NH

Where do we need to go next to understand this unique form of venous biology? Fundamentally, how do we bring together the unique and interesting observations regarding NH into a synthetic thesis that begets additional and novel ideas regarding therapy and prevention? Traditionally, NH associated with hemodialysis vascular access has been viewed as a vascular SMC lesion. However, with a greater understanding of cellular responses, it is apparent that other events are also occurring. Clearly, a deeper understanding of TGF-β1 signaling is critical to understanding NH. There are studies that have described increased expression of TGF-β1, latent TGF-β1 binding protein-1 and TGF-β1 mRNA in stenotic AVF [48]. Ikegaya et al. [53] described elevated erythropoietin receptor and TGF-β1 expression in stenotic AVF in contrast to cutaneous veins and patent AVF in patients who underwent chronic hemodialysis.

TGF-β1 increases plasminogen activator inhibitor-1 (PAI-1) expression. Thus, it is not surprising that PAI-1 expression is increased in stenotic AVF [54]. Interestingly, Lazo-Langner [44] were able to demonstrate in a cohort analysis that the risk of dialysis access thrombosis was differentially associated with polymorphisms in the TGF-β1 gene that correlated with TGF-β1 production and that this risk was further modified through an interaction with the PAI-1 genotype present [44].

Interestingly, mechanisms of TGF-β1 signaling are for the most part unexamined in the context of dialysis access-associated NH or indirectly inferred. Traditional therapies that might antagonize TGF-β1, e.g. ACE-inhibition, appear to have little effect in reducing NH or maintaining access patency. However, direct antagonism of type I and II TGF-β1 receptor signaling has yet to be examined as a potential therapeutic alternative for hemodialysis access NH. It should be noted that bone morphogenic protein-7 (BMP-7) might be a therapeutic approach to limit this lesion. Choi and colleagues recently described an AVF model in mice in which BMP-7 administration reduced NH [55]. Additionally, non-traditional sources of TGF-β might also be associated with AVF NH. Jin et al. [56] induced AVF in dogs and noted that chymase- and TGF-β1 (+) mast cells were prominent in proliferating neointima and media. Chymase inhibition reduced neointimal formation.
With a solid body of literature suggesting at least a role for TGF-β1 in hemodialysis access NH, it makes sense to consider the possibility that the venous endothelium is a contributor to the process. Recent data suggest that endothelial cells undergo mesenchymal transition in certain settings [57-60]. The characteristic transformation to myofibroblasts is defined by the loss of cell surface adhesion and the de novo expression of vimentin with a resulting decline in CD31 expression. The presence of myofibroblasts in lesions of NH could well be a manifestation of not just SMC’s in transition but also endothelial-mesenchymal transition (End-MT).

This is no doubt exploratory as the majority of research in End-MT has been concentrated in embryonic tissues. Yet, it is striking to note that intimal thickening involves transdifferentiation of embryonic endothelial cells [61]. Moreover, CD40 and CD40 ligand (CD40L) have been implicated, especially the latter, at sites where endothelial cells differentiate into mesenchymal cells. CD40L is manifest in the context of platelet activation and repeated injury to an access via needlesticks could be an obvious stimulus for excess CD40L. It would be fascinating to ascertain both the presence of both CD40 and CD40L in a dialysis access at various stages of NH formation, or even immediately following access placement and then after repeated needle placements.

Other markers of potential End-MT could also be assessed in access tissue including NF-kB activated p50/p65 heterodimers, IkB, insulin-like growth factor-II (IGF-II), vitronectin, and certainly, an assessment of whether S100A4 is expressed in cells obtained from human AVFs. A constellation of such findings would suggest that End-MT is occurring and possibly contributing to the increased presence of myofibroblasts in the neointimal hyperplastic area.

As noted above, phase II studies are just beginning to examine innovative therapies directed at regulating or preventing NH in dialysis vascular access. A key feature of NH in vascular access is disruption of the internal elastic lamina. Chang and colleagues used gene expression analysis to study the impact of flow velocity and pressure on internal elastic lamina in an aorto-caval fistula model [62]. They noted an increase in cathepsin K and S and matrix metalloproteinase 2 (MMP2) mRNA levels, concomitant with increased elastase expression. Immunohistochemical studies localized cathepsin to the venous luminal endothelium lining the internal elastic lamina.

These findings should prompt additional pre-clinical and clinical studies examining elastase inhibitors including local application of recombinant human elastase to promote vasodilation after fistula creation [63]. Additional elastases and combinations of molecules may be necessary to alter or regulate the vascular transformative process of NH.

Alternatively, different agents that traditionally may not be thought of as anti-NH agents could be tried as therapeutics to affect this process. One example is the novel immunosuppressive agent, FK778. This medication exerts an anti-proliferative effect on multiple cell types. Recent work suggests it has the ability to limit NH in vein graft models [64, 65].

Similarly, discrete signaling cascades that have traditionally not been targeted for intervention merit consideration for their possible role in dialysis access NH. Inhibition of Rho kinase suppresses neointimal formation in models of vascular injury [66-69] and alters endothelial cell migration in certain cell models [70]. However, the identification of specific Rho kinase isoforms present within venous endothelial cells and whether inhibition of Rho kinase affects a true in vivo process are unknown. Furthermore, it remains to be determined if ROCK isoforms, ROCK1 and ROCK2, could be present in venous endothelium or dialysis
access NH. Indeed ROCK inhibitors are being evaluated as potential therapeutic agents for a number of vascular processes [71] and there is no reason to exclude them from possible assessment in dialysis vascular access stenosis.

The potential systemic effects of agents that target cathepsin K and S [72, 73], have stimulated study of delivery mechanisms to elucidate changes in the vascular access. Novel scaffolds, vectorially directed scaffolds and nanoparticles with periodic, concentrated delivery of molecules are all areas worthy of more in-depth investigation. Lim and colleagues expanded upon their initial work to improve control of drug release through paclitaxel (Ptx)-loaded poly(lactic-co-glycolic acid) (PLGA) nanoparticles [74]. The Ptx-PLGA-NPs were prepared and transferred to the luminal surface and inner part of ePTFE vascular grafts through a micro tube pumping and spin penetration process. This system achieved controlled drug delivery with a reduced initial burst release. The science of molecular packaging and release, targeted and measured levels of drug or molecule in the microenvironment, maintenance of drug or molecule in the microenvironment to reduce systemic side effects, and effect on true clinical outcome are all areas of needed emphasis and inquiry.

Monitoring the effects of an intervention is a difficult puzzle to solve, especially with regards to an outcome that takes time to evolve. With NH, we can measure systemic parameters or treatment parameters but the event that is of interest is happening in a vessel anastomotic area over a period of time. New imaging methodologies such as surface dissolution imaging and atomic force microscopic topographic imaging could be used for intra-vital microscopy to assess changes in animal models of venous NH over time. Other non-destructive, non-linear optical microscopy techniques using harmonic generation and fluorescence [74] are also options for experimental analyses. Intravascular ultrasound (IVUS) has been used in coronary and peripheral intervention to guage successful therapy. Since IVUS (3D imaging modality) is a fundamentally different source of information than traditional angiography (3D imaging modality), the use of IVUS represents a method of imaging cellular changes that has already entered the clinical arena [75].

It will be important to move imaging technology into the clinical setting for two reasons. More accurate and precise imaging will provide more knowledge about the evolution of lesions that afflict dialysis vascular access. Second, improvements in imaging that make it less invasive or more feasible to perform in conjunction with cannulation during a dialysis treatment might move imaging into a more precise pre-emptive or prophylactic technology.

Bioengineering-focused investigations are essential in understanding more about NH. Ex-vivo models of hemodialysis suggest that high blood flow (500 ml/min) can shear off endothelial cells and reduce nitric oxide formation [76]. Such studies represent early investigations in analyzing the impact of shear stress and needle turbulence on not only vascular mediators but also endothelial gene and protein expression in response to these treatment events. It would be interesting to determine if different techniques, e.g. buttonhole cannulation, lead to less trauma and changes in activation of various molecular mediators. Alternatively, is there a protective response mediated with some AVF through receptor signaling and desensitization via repeated needle sticks that is not manifest in other individuals who develop NH? Are there different, non-traditional receptor subtypes, e.g. cannabinoid receptors, [77, 78] activated in the presence of needle jet turbulence or shear stress? These questions are answerable and could lead to better patient predictors of access patency over time.
Summary

Numerous studies have shown definitively that a functioning arteriovenous fistula is superior to a synthetic graft or catheter in terms of dialysis flow rates and access complications. The association of prolonged catheter use and mortality has also been reported for some time. [79] More recently, several modifiable risk factors have been identified to improve access outcomes. Publication of results from several recent large, multicenter randomized trials in high-profile journals have garnered increased attention, but these results, while promising, leave much room for additional progress. A broad-based initiative that incorporates clinical, translational, and basic science to better unravel the mysteries of dialysis access is sorely needed.

References


Alexander Yevzlin and Brad C. Astor


1. Introduction

Hemodialysis vascular access dysfunction in arteriovenous fistulas (AVF) and grafts (AVG) remains a major cause of morbidity and mortality in hemodialysis patients [1-3]. Improving vascular access outcomes remains an ongoing challenge for nephrologists, vascular access surgeons, interventionists, and hemodialysis nursing staff. In AVFs and AVGs the most common cause of this vascular access dysfunction is venous stenosis resulting from progressive development of neointimal hyperplasia within the peri-anastomotic region (AVF) or at the graft-vein anastomosis (AVG) [4, 5]. Neointimal hyperplasia is defined as the thickening of the intimal layer of a blood vessel secondary to the response to vascular injury. In clinical practice, the general nephrologist is often the initial provider to be notified when vascular access dysfunction occurs in a patient. Therefore, it is crucial for the general nephrologist to have an understanding of the clinical significance, clinical presentation, and treatment options for vascular access dysfunction in order to effectively coordinate and develop an individualized treatment strategy with other members of the vascular access team (i.e. surgeon, interventionalists, vascular access coordinator, and nursing staff). This chapter focuses on vascular access dysfunction in AVF and AVG and will: (1) provide a brief overview of the clinical significance and current epidemiology of vascular access dysfunction, (2) describe the clinical characteristics of vascular access dysfunction, (2) describe the pathology and pathophysiology of hemodialysis access stenosis in AVFs and AVGs, (3) discuss current and future novel therapies for treating venous neointimal hyperplasia, and (4) suggest future research areas in the field of hemodialysis vascular access dysfunction.
2. Epidemiology and Clinical Significance of Hemodialysis Vascular Access Dysfunction

The landscape of vascular access use has clearly changed in the last decade. New vascular access initiatives (“Fistula First”) and guidelines (Kidney Disease Outcome Quality Initiative (K/DOQI)) with oversight from individual ESRD networks formed by CMS (Center for Medicare Services) have placed a renewed emphasis on AVF creation in the United States. Furthermore, the general nephrologist, along with a multidisciplinary team of surgeons and vascular access nurses, have played an important role in executing these initiatives and guidelines and ultimately in the improvement of prevalent AVF rates. However, tunneled catheter rates have remained high likely due to AVF non-maturation. This section will cover recent trends in vascular access use in the United States and discuss the clinical and economic implications of hemodialysis vascular access dysfunction.

2.1. Epidemiology of Hemodialysis Vascular Access

AVFs are the preferred vascular access for hemodialysis patients, because once mature and functional, they require fewer interventions to maintain patency and develop fewer infections compared to AVGs [6-10].

Figure 1. Trends in Vascular Access use since Fistula First Initiative. Fistula prevalence has steadily increased while graft use has steadily decreased. Catheter use has remained consistently over 20% during this same time period. Data obtained and adapted from Fistula First Dashboard, www.fistulafirst.com. All data of prevalent fistula rates (fistulas currently in use for dialysis), prevalent graft rates, and prevalent catheter rates reported is from January data except 2003, where data is from July, the first month prevalent data was available that year.
Figure 2. Trends in AVF non-maturation from 1977-2011. In general, a gradual trend in AVF non-maturation has been seen since 1970’s and has reached as high as 60% in recent reports. However, in the published reports from the literature, there has not been a standard uniform definition describing AVF non-maturation.

AVGs are advantageous because of short maturation time and relative ease of cannulation compared to AVFs [9, 11-13]. Until recently, AVGs were the most common access used in hemodialysis patients in the United States [14]. However, the main disadvantages of AVGs are development of recurrent venous stenosis, requiring frequent interventions to maintain patency, and graft infection [13, 15-18].
Due to reduced AVF use and increased AVG (70% in 1993 [19]) and central venous catheter (CVC) use in the United States from the mid-1980’s-1990’s, the National Kidney Foundation in 1997, in an effort to improve vascular access outcomes, published the first K/DOQI clinical practice guidelines for vascular access to optimize the care of vascular access in hemodialysis patients using evidenced and opinion-based guidelines [20]. Since these initial clinical practice guidelines have been published, the Fistula First Breakthrough Initiative (FFBI) [21-24] has been created and two more revised K/DOQI clinical practice guidelines and performance measures for vascular access [13, 25] have also been developed, which have clearly impacted and improved hemodialysis vascular access management. AVF prevalence has improved dramatically in the United States since 2003 when prevalent rates were reported around 33% (Figure 1). Fistula First has reported AVF prevalence of 58% in early 2011 [21] (Figure 1).

While the K/DOQI guidelines and FFBI have clearly played an instrumental role in meeting the initial target goal of 50% AVF prevalence (new goal 66% [13, 21]), the prevalence of CVC use continues to remain between 20-30% in the United States [21] (Figure 1). Published reports since 1996 have shown that 30-50% [6, 26-41] and up to 60% [42] of AVFs created never mature adequately for dialysis compared to 20-25 years ago where the non-maturation in AVFs was approximately 10-25% [7, 43-46] (Figure 2). AVF non-maturation is in large part due to aggressive venous neointimal hyperplasia [47] (Figure 3). Addressing the problem of AVF non-maturation is a current area of interest and concern, as further improvement in AVF prevalence and reduction in CVC use will be contingent on improved understanding of AVF maturation and neointimal hyperplasia.

2.2. Clinical Significance and Economic Implications of Hemodialysis Vascular Access Dysfunction

When patients develop vascular access dysfunction, due to AVF non-maturation or thrombosed AVF or AVG, they are often consigned to CVC use for prolonged periods [48]. Because dialysis with CVC is associated with increased morbidity and mortality [49-55], CVC use has significant clinical implications such as increased risk of bacteremia which has been reported to occur at a frequency ranging from 2.5 to 5.5 episodes per 1000-CVC days [8, 56], increased risk of 1-year mortality [49], and 60-70% higher risk of subsequent AVF failure [48, 57]. The cost of treating one CVC-related bacteremia in the United States has been estimated to be as high as $45, 000 per episode with an average of $22, 000 per bacteremic episode [58]. Due to the high costs of ESRD treatment and infection-related complications and hospitalizations, CMS will likely target vascular access-related infection rates as a future area of Medicare reimbursement for general nephrologists. A key area for general nephrologists to address and improve is the processes of care that lead to the creation and successful use of AVF at dialysis initiation [59-61] as currently in the United States, approximately 80% percent of all hemodialysis patients initiate dialysis with a tunneled catheter [21, 62].

Venous stenosis that occurs in both AVF and AVG is primarily due to neointimal hyperplasia. This section will provide a basic understanding of the pathology and pathophysiology of early and late AVF and AVG failure.

3.1. Pathology of Hemodialysis Vascular Access Stenosis in AVF and AVG

Venous stenosis in AVGs most frequently arises from the development of aggressive neointimal hyperplasia, characterized by (a) the presence of alpha smooth muscle actin (+) cells and myofibroblasts within the neointima, (b) an abundance of extracellular matrix components, (c) angiogenesis (neovascularization) within the neointima and adventitia, (d) a macrophage layer lining the perigraft region, and (e) an increased expression of mediators and inflammatory cytokines such as TGF-β, PDGF, and endothelin within the media, neointima and adventitia [63-68].

While the neointimal hyperplasia in AVFs is similar to AVGs in regards to pathogenesis, the venous stenosis that develops in AVFs is highly influenced by the capacity of the vein to vasodilate and vascular injury from surgical technique [69]. In AVFs the two main etiologies of failure are an initial failure to mature (non-maturation) and a subsequent (late) venous stenosis [4]. Similar to AVGs, venous neointimal hyperplasia in late AVF stenosis has been shown to be composed primarily of alpha smooth muscle actin (+) cells, together with expression of mediators and cytokines such as TGF-β, PDGF, and endothelin within the media and intima of the vein [64, 69]. However, recently, the lesion of AVF non-maturation at 6 weeks after AVF creation has also been described to have significant neointimal hyperplasia [47].

3.2. Pathophysiologic Mechanisms of Neointimal Hyperplasia Formation in Hemodialysis Access Dysfunction

The pathogenesis of venous neointimal hyperplasia in AVG stenosis and late AVF stenosis has been well described and is commonly divided into upstream and downstream events [4]. Upstream events are characterized as the initial events and insults that are responsible for endothelial and smooth muscle cell injury, which leads to a cascade of mediators (downstream events) that regulate oxidative stress, endothelial dysfunction, and inflammation (eventually resulting in venous neointimal hyperplasia). Upstream events that are believed to contribute to the pathogenesis of neointimal hyperplasia include [4, 66, 70-73]: (1) surgical trauma at the time of AV surgery, (2) hemodynamic shear stress at the vein-artery or vein-graft anastomosis, (3) bioincompatibility of the synthetic graft material in AVG, (4) vessel injury due to dialysis needle punctures, (5) uremia resulting in endothelial dysfunction, and (6) repeated angioplasties causing further endothelial injury.
Figure 4. Histopathology of vein specimens collected at time of AVF creation. (a-c) show SMA sections of patients with advanced CKD at the time of first AV access placement. Note that neointimal hyperplasia in patients is variable from minimal neointimal hyperplasia to very severe lesions. Note the aggressive thickening of the neointima and media and significant luminal stenosis in (c) which is similar to the lesion of stenotic AVF in Figure 1b. (Reprinted and adapted from Lee T et. al.: Severe Venous Neointimal Hyperplasia Prior to Dialysis Access Surgery. Nephrol Dial Transplant 26:2264-70, 2011, with permission from Oxford Press, Inc.).

The pathogenesis in AVFs that fail to mature (early failure) for dialysis, in contrast to AVG and late AVF failure, remains poorly understood. At a histological level early AVF failure is also characterized by aggressive neointimal hyperplasia (Figure 3) in both animal and human models, seen as early as 1 month in animals [67, 74] and 3 months in humans [47, 68]. The underlying factors (upstream events) which may contribute to early AVF failure, include [4, 75-84]: (1) small diameter sizes in the vein and artery, (2) surgical injury at the time of AV fistula placement, (3) previous venipunctures and pre-existing stenotic lesions, (4) development of accessory veins after surgery, (5) hemodynamic shear stress at the AV anastomosis, (6) a genetic predisposition to vascular constriction and neointimal hyperplasia, and (7) pre-existing venous neointimal hyperplasia.

Downstream events represent the response to endothelial (vascular) injury from the upstream events, resulting in the migration of smooth muscle cells from the media to the intima and eventually the development of neointimal hyperplasia [69]. The main downstream mechanisms responsible for neointimal hyperplasia are oxidative stress, inflammation, and endothelial dysfunction [4, 64, 66, 69, 85-90].

3.2.3. Pre-Existing Arterial and Venous Vessel Changes

In the specific context of vascular access stenosis, endothelial dysfunction is likely to be responsible for the development of pre-existing venous neointimal hyperplasia [80-84] (Figure 4), medial hypertrophy [80, 84] and radial artery intima-media thickening [91-93] that is present even before the creation of AVFs in uremic patients. Pre-existing arterial intima-media thickness has been correlated with future AVF dysfunction [91]. Recently, pre-existing venous neointimal hyperplasia has been linked to poor AVF maturation in a small clinical study [80].
4. Clinical Diagnosis of Vascular Access Dysfunction

Timely clinical diagnosis of venous stenosis is crucial for referral to treat the neointimal hyperplasia in hemodialysis access dysfunction. Venous stenosis can be identified using physical examination and intra-access surveillance methods. This section will provide an overview of the diagnostic methods available to detect venous stenosis.

4.1. Physical Examination

Routine physical examination of AVF and AVG plays a major role in diagnosis of venous stenosis [94, 95]. The key diagnostic elements of the physical examination for AVF include evaluation for an outflow lesion and inflow stenosis. In evaluation for outflow vein stenosis, the key features include the presence of a water-hammer pulse (hyperpulsation), abnormal systolic thrill (bruit), and abnormal arm elevation test [94, 95]. For evaluation of inflow stenosis, the key elements include the presence of a weak pulse (hypopulsation, flat access), lack of continuous thrill, and abnormal augmentation test [94, 95]. Physical examination can accurately detect and localize stenoses in AVF. A recent study demonstrated a strong correlation between physical examination and angiography in diagnosis of outflow (agreement 89.4%) and inflow stenosis (agreement 79.6%) [94]. Physical examination of AVF is a learned skill. A recent study compared the results of physical examination compared to angiography and detection of AVF stenosis in nephrology fellows with an one-month intensive training of physical examination skills by an interventional nephrologist [96]. This study reported a strong correlation between the physical examination by the nephrology fellow and detection of venous stenosis of AVF in diagnosing outflow (agreement 81%) and inflow stenosis (agreement 80%) when compared to angiography [96]. The same diagnostic elements used for physical examination of AVF should be used for detection and localization of stenosis in AVG [97]. A recent study reported that physical examination can be useful in detection and localization of AVG stenosis [97], but with less sensitivity and specificity compared to physical examination of AVF [94].

Physical examination is an important tool in diagnosis of venous stenosis. It is a skill that should be learned and utilized by nephrologists and nephrology trainees, is cost effective and does not require expensive equipment.

4.2. Intra-Access Surveillance

In most in-center dialysis centers, intra-access surveillance is commonly utilized to detect stenoses in functional AVF and AVG. The K/DOQI vascular access guidelines recommend prospective surveillance of vascular accesses to detect early stenosis with the rationale that early intervention to correct these anatomic stenosis may improve short and long-term access patency and prevent thrombosis of accesses [13]. Furthermore, these guidelines recommend surveillance with either intra-access flow with specific modalities, static venous pressure, or
duplex ultrasound in AVG [13]. In AVF the recommended surveillance modalities include direct flow measurements or duplex ultrasound [13].

The use of access surveillance, particularly in AVGs, remains a controversial issue. Among six randomized controlled trials [98-103], comparing a variety of graft surveillance methods, evaluating the impact of stenosis surveillance with preemptive angioplasty on graft outcomes, only one showed improved thrombosis-free survival or cumulative graft survival between the surveillance group and the control subjects (routine monitoring with physical exam) [102].

Surveillance will likely continue as an adjunctive measure to physical exam, which should be considered an important diagnostic skill in outpatient hemodialysis units that can be mastered by nephrologists and healthcare staff involved in the patient’s vascular access care.

5. Translating Science to Novel Therapies in Hemodialysis Vascular Access Dysfunction

There are currently few if any effective therapies to treat hemodialysis venous stenosis and neointimal hyperplasia. However, the knowledge obtained in recent years regarding the pathology and pathogenesis of vascular access dysfunction has provided a framework for development of therapies that target neointimal hyperplasia and vascular stenosis. It is important to have an understanding of the future therapies being studied as the nephrologist will play a central role, along with the surgeon and interventionalist, in the decision making process to treat vascular access dysfunction in patients. The purpose of the next section is to (1) describe current therapies for AVF and AVG stenosis and (2) novel therapies using localized delivery systems for AVF and AVG.

5.1. Current Therapies for Treatment of Neointimal Hyperplasia in AVF and AVG

This section will cover recent major studies evaluating systemic and endovascular therapies for hemodialysis dysfunction focusing on randomized-controlled trials.

5.1.1. Systemic Therapies

Systemic therapies, such as dipyridamole, angiotensin-converting enzyme inhibitors, aspirin, and fish oil, from small clinical trials and observational studies have been shown to have the potential to block smooth muscle cell proliferation and migration and to prevent thrombosis in AVFs and AVGs [104-108]. Most recently, two large randomized controlled trials, sponsored by the National Institutes of Health, evaluating anti-platelet agents in AVG and AVF to prevent neointimal hyperplasia were published [42, 109]. In the AVG study, dipyridamole and aspirin, only modestly reduced the risk of stenosis and improved primary unassisted patency [109]. In the AVF study clopidogrel reduced frequency of early thrombosis but did not improve AVF suitability for dialysis defined as cannulation with two needles, minimum dialysis blood flow of 300ml/min, successful use in 8/12 dialysis sessions, and use after 120 days from creation [42]. While these two studies have shown some
promising results, the clinical significance of these drugs used as standard treatment for hemodialysis access stenosis remains questionable and has lead to further questions and investigations regarding AVF non-maturation.

Fish oil has been shown to prevent AVG stenosis and thrombosis in one randomized, controlled trial [106]. Currently, another study evaluating fish oil and AVG stenosis and thrombosis is ongoing [110]. Other systemic agents, though not tested in randomized clinical trials, which have shown potential anti-proliferative effects targeting neointimal hyperplasia in cardiovascular and peripheral vascular disease models, include peroxisome proliferation-activated receptor γ agonist [111-113], sirolimus [114], and imatinib mesylate [113, 115, 116].

5.1.2. Endovascular Stent Therapy

Endovascular vascular therapies (angioplasty or angioplasty with stent placement) remain the only true and practical intervention available to treat vascular stenosis in AVF and AVG, but is usually reserved as a therapy after the development of a significant stenosis and neointimal hyperplasia development. The main advantage of stent therapy after angioplasty is a reduction in adverse remodeling. In dialysis access, placement of bare metal stents after angioplasty compared to angioplasty [117] alone has been shown to improve primary patency [118, 119]. However, bare-metal stents have yielded poor results due to aggressive development of in-stent restenosis. In experimental models of dialysis access in AVGs, drug-eluting stents have shown to reduce neointimal hyperplasia and improve luminal stenosis compared to bare-metal stents [120]. However, there are no clinical studies evaluating drug-eluting stents in dialysis access to date.

Stent grafts (covered stents constructed from the same material of AVGs) have received recent attention as a therapy for prevention of restenosis due to its ability to prevent elastic recoil and inability of the neointimal cells to penetrate the covered barrier [121-123]. A recently published multicenter, randomized controlled, clinical trial showed stent grafts, placed after angioplasty, to treat venous stenosis had better primary unassisted patency compared to angioplasty alone [117]. This is the only treatment to date that has shown to be effective to treat vascular access stenosis in a large, multi-center, randomized-control trial.

5.2. Novel Therapies for Treatment of Neointimal Hyperplasia in AVF and AVG

Due to the lack of current therapies to treat and prevent vascular access stenosis, there have been a number of studies evaluating “novel” therapies using the principles learned from the pathophysiology of neointimal hyperplasia development. This section will discuss the novel therapies currently being evaluated and future therapies in the pipeline.

5.2.1. Local Drug Delivery Systems for Hemodialysis Access

The rationale behind local delivery of drugs treat hemodialysis vascular access stenosis is that (1) AVFs and AVGs could be the ideal clinical model for the use of perivascular therapies since these can be easily applied at the time of surgery, (2) perivascular therapies preferentially target the “active” adventitia, (3) studies have demonstrated that lipophilic molecules when placed over the adventitia rapidly diffuse through all the layers of the vessel
wall, and (4) small amounts of otherwise toxic drugs can be safely delivered to the site of stenosis using the perivascular approach resulting in high local concentrations with minimal systemic toxicity [4]. The subsequent section will discuss local therapies to treat hemodialysis vascular access stenosis from experimental models and clinical studies.

5.2.1.1. Drug Eluting Paclitaxel Perivascular Wraps
Experimental studies have previously demonstrated the efficacy of paclitaxel eluting wraps in AVG stenosis likely due to anti-proliferative effects [124-126] (Figure 5a). In 2007, a large multi-center randomized-controlled study, evaluating the use of paclitaxel-eluting mesh wraps, Vascular Wrap™, (Angiotech Pharmaceuticals, Inc.; Vancouver, British Columbia, Canada), was initiated to study the effectiveness and safety of this therapy on primary AVG patency compared to a standard AVG. However, this study was recently suspended in 2009 following a data safety monitoring review, due to an imbalance in the incidence of infections in one of the arms (either control or treatment). An alternative approach is the use of sirolimus eluting COLL-R® wraps (Covalon Technologies Ltd; Mississauga, Ontario, Canada). An initial Phase II study demonstrated primary unassisted AVG patency of 75% and 38% at 1 and 2 years respectively with these wraps [127].

5.2.1.2. Endothelial Cell Loaded Gel Foam Wraps
The rationale behind the use of these wraps is that the endothelial cell (in addition to lining blood vessels) is also a “bioreactor” which produces a large number of beneficial mediators that reduces thrombosis, inflammation, stenosis, and increases lumen diameter. Initial experimental studies have documented a beneficial effect of endothelial cell loaded gel-foam wraps in porcine models of AV fistula and graft stenosis [128-131]. A recent Phase II study (“V-HEALTH”) was able to demonstrate technical feasibility and safety in hemodialysis patients who received a “Vascugel®” wrap loaded with treated human aortic endothelial cells at the time of AVF or AVG placement [132] (Figure 5b). A multi-center randomized-controlled study using the Vascugel® (Pervasis Therapeutics, Inc., Cambridge, MA) wraps in human AVGs is currently being designed.

5.2.1.3. Recombinant Elastase PRT-201
PRT-201 (Proteon Therapeutics; Waltham, MA) is a recombinant pancreatic elastase topically applied at the outflow vein at the time of surgery access creation which has been shown to result in both arterial and venous dilation and an increase in AVF blood flow in experimental models [133]. The clinical benefit of this approach is the potential ability to enhance AVF maturation (through rapid vascular dilation) and prevent venous stenosis in AVGs. A phase II study using this novel technology is ongoing in the United States evaluating this therapy and whether or not it improves primary patency and cumulative survival in AVG and AVF, as well as safety.

5.2.1.4. Local Gene Delivery Therapy
In animal models of angioplasty induced restenosis, the delivery of adenoviral particles encoding for vascular-endothelial growth factor C to the site of vascular injury has been shown to trigger the release nitric oxide and prostacyclin and reduce neointimal hyperplasia [134]. Preliminary studies on the use of VEGF-D gene therapy (using a packaged adenoviral
vector and a biodegradable local delivery device (collar) made of collagen wrapped at the venous anastomosis at the time of surgery), “Triam®” (Ark Therapeutics; London, UK), in patients receiving AVGs, have been able to document technical feasibility and safety (Figure 5c). A phase III study using this technology was initiated in 2009 but terminated in 2010 due to poor enrollment, likely due to the complexity of placing the local delivery device. However, the ability and feasibility to locally deliver gene therapy in dialysis access allows gene therapy to remain as a promising future therapy which needs further investigation.

5.2. Radiation Therapy

Radiation therapy has been hypothesized to be a potential therapy to treat vascular stenosis due to its antiproliferative effects and potential beneficial effects of vascular remodeling [135-138]. In experimental models, both external beam and endovascular radiation therapy has proven effective to reduce neointimal hyperplasia in AVF and AVG [65, 139]. However, in clinical studies, a recent randomized-controlled trial of 25 patients in AVGs showed that 42% of the radiated AVGs achieved the target lesion primary patency end point at 6 months as compared to 0% of the control group (p = 0.015), but this did not translate into an improvement in secondary patency at either 6 or 12 months [140].

![Figure 5. Novel local therapies for dialysis access stenosis: (A) shows an endothelial cell loaded gel-foam wrap being placed around the graft-vein anastomosis and proximal venous segment. (B) describes the placement of a paclitaxel eluting wrap around the graft-vein anastomosis. (C) is a diagrammatic representation of the biodegradable reservoir that will be used for VEGF-D gene therapy. (D) is a magnified view of the Adventa® catheter that can deliver therapies to the perivascular region through an endovascular approach. (Reprinted from Lee T et al.: Advances and New Frontiers in the Pathophysiology of Venous Neointimal Hyperplasia and Dialysis Access Stenosis. Adv Chronic Kidney Dis 16: 329-38, 2009, with permission from Elsevier Inc.).]
5.3. Far Infrared Therapy

Infrared radiation is an invisible electromagnetic wave with a longer wavelength than that of visible light. In experimental models, far infrared therapy has been shown to improve skin blood flow and endothelial function in cardiovascular disease [141-143]. The rationale for far infrared therapy to treat dialysis vascular access stenosis is that the dialysis vascular access in patients are located at a superficial site and improving access flow may improve vascular access performance. In the lone clinical study of far infrared in dialysis access in AVFs, patients who received far infrared therapy had improved access flows and longer unassisted patencies [144].

7. Future Treatment Paradigm to Prevent and Treat Hemodialysis Vascular Access Dysfunction: Individualized Therapy to Improve Care and Outcomes

The current emphasis in treating vascular access dysfunction has focused on therapies after the development of neointimal hyperplasia and vascular access stenosis (endovascular therapies). Recently, more emphasis has been placed on treatment at the time of surgical access creation (perivascular therapies). However, there are currently no therapies to evaluate treatment of vascular access stenosis in the period prior to the creation of a vascular access as progressive neointimal hyperplasia occurs in both arteries and veins before access creation. Given the complexity of uremia in CKD and development of vascular stenosis, treatment of vascular access stenosis should occur with a three-pronged approach.

First, treatment needs begin prior to vascular access placement. The most common etiology of death in CKD and ESRD patients is cardiovascular related secondary to accelerated atherosclerosis [145]. Therefore, optimizing the vasculature with therapies, such as anti-inflammatory therapies and anti-oxidants, to prevent development of arterial and venous neointimal hyperplasia may play an important role in advanced CKD patients prior to access placement.

Second, therapies need to be considered at the time of surgery to modify the hemodynamic effects and vascular injury once creation of AV anastomosis occurs and facilitate the vasodilation that is required in the vein to ensure adequate maturation.

Finally, while the goal is prevent access stenosis and neointimal hyperplasia from occurring, newer and effective therapies will be required to treat neointimal hyperplasia once it does occur. Future therapies should evaluate drug-eluting stents, as is commonly used in cardiovascular disease, and delivery of local therapy directly to the site of vascular stenosis to prevent further progression of neointimal hyperplasia (Figure 5d).
Conclusion

The magnitude and costs of dialysis access dysfunction is clearly evident, and will only become magnified in the coming years as the prevalent dialysis population continues to increase. As a general nephrologist, the care of patients with vascular access dysfunction remains frustrating because of the lack of therapies available. However, intensive research into the mechanisms of neointimal hyperplasia development is ongoing along with aggressive efforts to develop novel therapies. Understanding the role of neointimal hyperplasia development in vascular access dysfunction will be very important for the general nephrologist. In the future the general nephrologist will play an important and active role in the diagnosis of vascular access dysfunction and decision-making process regarding treatment options.

References


What the General Nephrologist Needs to Know about Neointimal Hyperplasia


Burke SK, LaRochelle A, Mendenhall HV. Local Application of Recombinant Human Type I Pancreatic Elastase (PRT-201) to an Arteriovenous Fistula (AVF) Increase AVF Blood Flow in a Rabbit Model. *Journal of the American Society of Nephrology* 2008:252A.


Catheter Design: Does It Make a Difference?

Stephen R. Ash*
Indiana University Health Arnett and Wellbound of Lafayette, Inc, Ash Access Technology and HemoCleanse, Inc., Lafayette, IN, US

Prevalence and Problems of Central Venous Catheters for Hemodialysis

In spite of the Fistula First initiative, visits to nephrologists, access planning, mapping procedures and fistula creations 82% of hemodialysis patients initiating chronic hemodialysis in the U.S. have a tunneled CVC as their first blood access device. [1] As shown by CMS and in Figure 1, at 90 days of dialysis the catheter is still the access being used in 50% of patients.

Figure 1. Distribution of access types 90 days after initiation of chronic outpatient dialysis (CMS 2006 report, Reference 2).

* Corresponding address: Stephen R. Ash, M.D, F.A.C.P. 3601 Sagamore Parkway North, Suite B, Lafayette, IN, 47904. 765 742 4813 #208.
Table 1. Advantages and Disadvantages of Tunneled Central Venous Catheters for Dialysis

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Universally applicable (functional in nearly 100% of patients)</td>
<td>• High morbidity due to thrombosis and infection</td>
</tr>
<tr>
<td>• Ability to insert into multiple sites</td>
<td>• Risks of permanent central venous stenosis or occlusion</td>
</tr>
<tr>
<td>• Maturation time not required</td>
<td>• Discomfort and cosmetic disadvantage of external appliance</td>
</tr>
<tr>
<td>• Venipuncture not required</td>
<td>• Lower blood flow rates, requiring longer dialysis times.</td>
</tr>
<tr>
<td>• No hemodynamic consequences (no CP recirculation)</td>
<td></td>
</tr>
<tr>
<td>• Ease and low cost of placement and replacement</td>
<td></td>
</tr>
<tr>
<td>• Ability to provide access over a period of months</td>
<td></td>
</tr>
<tr>
<td>• Ease of correcting thrombotic complications.</td>
<td></td>
</tr>
</tbody>
</table>
| These are patients in whom the fistula or graft has not matured, is not workable, or was not created. [2] Over the time from 2002 to 2005 the number of grafts being used at 90 days decreased and the number of fistulas increased, but the percentage of catheters being used remained about the same.

Many patients would be better served if an AV fistula were been placed some months before dialysis, and if it were fully developed and functional when dialysis was needed. However much this is the desired course, it is not often the actual course. In all of the single-minded enthusiasm of the Fistula First program, we sometimes forget that tunneled CVC are used in patients starting dialysis because they offer advantages. As summarized by Beathard [3, 4] CVC for dialysis have significant advantages as well as disadvantages (Table 1).

The requirements for a tunneled CVC for dialysis are actually multiple and stringent, unlike requirements for any other access device [5]:

- High blood flow rates at moderate pressure drops, with few instances of outflow failure and pressure alarms regardless of patient fluid status and catheter position relative to the vein wall.
- Minimal trauma to the vein intima to avoid thrombosis and venous stenosis.
- Resistance to occlusion by fibrous sheathing.
- Prevention of bacterial migration around the catheter after placement.
- Avoidance of contamination of the catheter lumen.
- Avoidance of seeding of the outside of the catheter during bacteremia.
- Avoidance of clotting at the tip or within the catheter.
- Biocompatibility of the catheter surfaces, avoiding removal of white cells or platelets.
- Avoidance of lumen collapse under negative pressure.
- Avoidance of kinking of catheter segments at points of bending.
• Physical strength and integrity to avoid breaks or disconnections of any component (ability to replace broken connectors is desirable).
• Resistance to antiseptic agents that might be applied at the skin exit site.
• Placement procedures with minimum trauma, difficulty and risk.
• Radiopaque appearance on X-ray, for evaluation of location during placement and after use.

Each tunneled CVC has a risk of failing one or more of these requirements, and each failure results in significant medical problems.

The use of dual lumen central venous catheters (CVC) for removing and returning blood during dialysis is commonplace now but in the late 1970s this concept revolutionized dialysis. [6] Before the development of CVC dialysis was possible only with a catheter within an artery, either through the internal/external arterio-venous silicone shunt or through separate catheters placed into an artery and a vein and removed after each treatment. The development of CVC for dialysis was not simple, especially for single-body catheters. Drawing blood from a central vein at 200-400 ml/min is a delicate and somewhat unpredictable process. The pressure in central veins is much lower than in arteries and vein walls are thinner and more distensible, even though the flow of blood through central veins is the same as through central arteries. Removal of blood through the ports of a CVC in a vein creates a negative pressure around these ports due to direct suction or due to the Bernoulli effect. This negative pressure can cause the vein wall to collapse around the ports and obstruct flow into the ports, even if the flow through the vein is much higher than the flow of blood through the catheter. If a fibrous tissue sheath forms around the catheter and reaches the tip or if clots form around the tip, the entry port to the catheter becomes smaller and the velocity of blood flow is increased. The increased blood velocity creates a greater negative pressure around the ports, and increases the tendency to pull the vein wall over the tip.

There are four classic approaches to the problem of providing sufficient blood outflow through dual-lumen CVC for dialysis:

• Place the removal and return lumens within the right atrium, where the tips cannot rest against a venous wall and only one lumen usually rests against the atrial wall.
• Position the catheter with the removal lumen on the inside of the catheter curve, positioning this lumen away from the vein wall.
• Use a large catheter so that the removal lumen cannot be blocked by a small clot or a small amount of fibrous tissue.
• Provide multiple blood entry ports in all directions around the circumference of each catheter tip, so that some of the ports are always facing away from the vein wall.

There are problems and limitations of each of these approaches. Positioning the tips of the removal and return lumens at the middle of the atrium is somewhat difficult, especially since the relative positions of the catheter and the heart change when the patient stands up after lying on the procedure table, and since the removal lumen is shorter than the return lumen [3]. Positioning the catheter so that the removal lumen is on the inside of the catheter curve is not always easy, as the catheter course through the subcutaneous tissue and central veins is rather complex and tortuous. Placing a larger catheter is always more difficult and
somewhat more traumatic than placing a smaller catheter, especially if the larger catheter is not round in shape. Providing multiple side holes in all directions around the catheter tips requires that two catheters be placed, or that one catheter must separate into two separate tips. Side holes in a catheter also have disadvantages. If they are too large or too many, blood will quickly flow through the tip of the catheter after placement and between uses, removing catheter lock solutions and promoting clotting at the tip. If the sideholes are too small or too few then blood will flow in and out only through the tip of the catheter, thus diminishing any advantage of the side holes. Further, any single body catheter that becomes covered by a sheath will lose function, whether there are side holes or not. Sheathing of catheters occurs only where the catheter contacts a vein or atrial wall. [7], When sheathing develops it is difficult to correct by tPA infusion, stripping or catheter replacement, [8] A newer solution to the problem of obtaining unrestricted blood removal through the catheter is to design the distal part of the catheter so that it rests against the wall of the superior vena cava (SVC) and supports the removal lumen in the center of the vena cava. This approach, used in the Centros™ catheter, is described below.

**Types of CVC for Dialysis and a Short History**

CVC for dialysis are classified into either “acute” or “chronic” catheters, depending on whether the catheters are expected to be used for only several days or months to years. Acute CVC are designed to be placed with a minimum amount of effort. Historically acute catheters for dialysis were relatively rigid, pointed catheters with a conically shaped tip that could follow directly into the vein directly over a guidewire while the catheter body dilates the entry site while the catheter is advanced into vein. Acute CVC for dialysis have no subcutaneous cuff or locking device. More recently some acute catheters soft tips similar to chronic tunneled catheters and a stylet so that the can catheter can be placed over a guidewire after some dilation, in a manner similar to a tunneled catheter.

Tunneled CVC for dialysis are soft, blunt-tipped catheters and have a subcutaneous “cuff” for tissue in-growth or a plastic “grommet” to immobilize the catheters below the skin surface. Tunneled CVC are generally placed through internal jugular veins into the SVC with the goal of placing the tips of the catheter at the junction of the SVC and the right atrium. Alternative venous access points are external jugular veins, subclavian veins and femoral veins. Due to their blunt shape tunneled CVC have traditionally been placed through a “splitsheath,” which is a cylindrical thin-walled plastic device advanced into the vein over a dilator. The dilator has a central lumen that follows the guidewire. The guidewire and dilator are then removed and the splitsheath opening is closed with a finger to prevent excessive bleeding. The catheter is then inserted through the splitsheath into the central vein. The splitsheath is split along two pre-formed grooves, and the halves are retracted around the catheter, leaving it in position within the central vein. More recently, techniques have been developed to allow placement of tunneled CVC to be performed over a guidewire placed through a previously dilated tract, in a manner similar to acute central venous catheters for dialysis.
Figure 2. (Continued)
Figure 2. (Continued)
Tunneled CVC for dialysis have a subcutaneous tunnel leading from the vein insertion site to a distant exit site. A Dacron® cuff (or sometimes a solid plastic grommet) attached to the catheter fixes the catheter in position and prevents bacteria at the exit site from migrating around the catheter. The cuff also serves as the outer limit for the fibrous tunnel that develops.
around the catheter from the central vein. The tunnel is similar to a vein wall and is contiguous with the internal jugular vein (or other vein of insertion). The tunnel stops at the Dacron cuff where it melds into the fibrous tissue surrounding the cuff. Without the cuff, as in acute catheters, this tunnel continues all of the way to the skin exit site over time, creating potential for back-and-forth movement of the catheter and potential for peri-catheter bacterial migration around the catheter.

A pictorial history of tunneled dialysis catheters is included in Figure 2, and is discussed more fully in a recent review. [5] Canaud devised a catheter system comprised of two 10 French catheters, each placed into the vena cava and with tips leading to the right atrium. Flow rate was excellent over many months of use [9, 10]. Tesio added subcutaneous cuffs and the catheter became more popular. More recent versions of the Canaud catheters have included a subcutaneous plastic grommet to fix the catheter limbs in place, and the Schon catheter has a similar device. Quinton designed the PermCath dual lumen chronic catheter, an oval shaped chronic catheter of about 20 French circumference and including two cylindrical 8 French lumens. [11, 12] Mahurkar designed a chronic CVC of soft materials and blunt tips and double-d blood flow lumens. [13] The Ash Split Cath chronic catheter has a double-d configuration in the mid-body, but separates into two separate distal tips, each with side holes in all directions. The Palindrome catheter is a double-d catheter with both lumens having the same length, but with oppositely angled and symmetrical side ports [14]. The Centros™ catheter has outward bends of the tips that contact the inferior vena cava in two places and inward bends to place the arterial and venous ports in the middle of the vena cava. No side holes are needed as the ports do not rest on the venous wall, if the catheter is positioned in the superior vena cava. [15] However, if the catheter is placed far into the right atrium as is often done with standard single-body or split-tip catheters, then the tip of the venous lumen can contact the right atrial wall and obstruct when blood is removed from the venous lumen.

Advantages and Disadvantages of Various Tunneled CVC Designs

Hydraulic Performance of Tunneled CVC versus Grafts and Fistulas with Needles

In spite of the wide variety of designs of tunneled CVC for dialysis there are few comparative studies to define advantages of one design over another. The best way to characterize the effectiveness of flow in a dialysis access is to determine the “conductance” of the access, or the flow rate divided by the pressure drop on the arterial (blood removal) limb [4, 5]. Merely indicating what the average blood treatment rate was during an entire dialysis is not very descriptive, since the actual treatment rate depends upon many factors such as number of pressure alarms, volume status of the patient, physician’s prescription, etc. There have been few comparative studies showing how the hydraulic conductance of catheters compares to needles, though one by Twardowski in 1999 was helpful. In this publication he showed that although there is considerable scatter, the hydraulic conductance of most catheters is similar to a 16 gauge needle in a graft or fistula during dialysis.
Catheter Design


<table>
<thead>
<tr>
<th>Flow division</th>
<th>Cut Straight (Reference)</th>
<th>Cut Angle</th>
<th>Cut Straight Hole</th>
<th>Cut Angle Hole</th>
<th>Cut Straight Sleeve</th>
<th>Concentric</th>
<th>Ash Split-Based</th>
</tr>
</thead>
<tbody>
<tr>
<td>End-opening</td>
<td>N/A</td>
<td>100%</td>
<td>40.6%</td>
<td>46.6%</td>
<td>18.0%</td>
<td>100%</td>
<td>6.6%</td>
</tr>
<tr>
<td>Side entrance</td>
<td>N/A</td>
<td>100%</td>
<td>51.2%</td>
<td>53.4%</td>
<td>82.0%</td>
<td>N/A</td>
<td>S4: 4.2% S3: 8.6% S2: 15.0% S1: 65.0%</td>
</tr>
<tr>
<td>Avg. SS</td>
<td>12.6 Pa</td>
<td>16.3 Pa</td>
<td>14.2 Pa</td>
<td>14.6 Pa</td>
<td>12.8 Pa</td>
<td>44.8 Pa</td>
<td>11.6 Pa</td>
</tr>
<tr>
<td>% Vol. SS &gt;10 Pa</td>
<td>41.8%</td>
<td>54.7%</td>
<td>45.8%</td>
<td>47.9%</td>
<td>41.0%</td>
<td>87.0%</td>
<td>32.2%</td>
</tr>
<tr>
<td>% Vol. RT &gt;0.015 s</td>
<td>16.8%</td>
<td>13.9%</td>
<td>9.8%</td>
<td>10.2%</td>
<td>19.7%</td>
<td>18.5%</td>
<td>60.8%</td>
</tr>
<tr>
<td>% Vol. RT &gt;0.030 s</td>
<td>0.1%</td>
<td>2.6%</td>
<td>0.1%</td>
<td>0.1%</td>
<td>2.7%</td>
<td>8.3%</td>
<td>31.4%</td>
</tr>
</tbody>
</table>

Figure 4. Measured shear rate and residence time for various parts of various catheter designs (from Reference 16). SS-Shear Stress. RT-Blood Residence Time.

Split-tip Catheters versus Single-body Step-tips

The basic concept of the SplitCath is to provide side holes around each limb of the catheter, similar to a Canaud or Tesio catheter. This assures that even if each limb lies against the surface of the vena cava or atrium that some sideholes will be facing the lumen, and away from the wall. In vitro studies demonstrate the advantage of this design, as shown in Figure 3. Mareels, Verdonckl et al. performed studies using computational flow dynamics and particle imaging and demonstrated that the Split Cath design had considerably less shear rate than any
other catheter design, with only 32% of the tip portion having a shear stress over 10 Pa as shown in Figure 4. However, the downside of the Split Cath design was that it also creates with 31% having residence time over 0.03 seconds. [16]

Clinically, which is better, catheters with a split tip or a single body? Several studies have shown a slight advantage to the Split Cath versus step-tip catheters. Trerotola et. al. performed a randomized study of 12 ESRD patients receiving 14 F Split Cath catheters placed versus 12 patients receiving 13.5 F Hickman catheters [17]. Weekly for 6 weeks the blood flow rate was measured using Transonic flow monitors, while the blood pump was set at speeds of 200, 300, 350, 400 and as high as possible with sustained flow. The measured blood flow rate at the highest pump setting was 422 +/- 12 ml/min for the Split Cath and 359 +/- 13 for the Hickman (P<0.005) as shown in Figure 5. Recirculation was significantly less at all pump settings for the Split Cath patients (P=0.01-0.06), though for both catheters it remained below 6% as shown in Figure 6.

Long term functional survival of CVC is probably the most significant data regarding success of their use. One problem with such studies is a lack of firm definitions for patency failure or CRBSI to justify removal of the catheters, and most patients end studies like these with functional catheters. In the Trerotola study above [17] the Split Cath had slightly better 6 wk survival than the Hickman catheter. Richard et. al. performed a randomized study comparing the Split Cath, Opti-Flow and Tesio catheters in 113 placements in ESRD patients. [18] Maximum (effective) blood flow rates were compared between the catheters immediately after placement, and 30 and 90 days after placement. Blood flow rate tended to be higher with the Split Cath but results were not significantly different. Failure-free survival of the catheters was analyzed with an average follow-up of 120 days. Though statistically not significant, predicted lifespan appeared higher for the Split Cath and Tesio catheters than the Opti-Flow. Placement complications occurred only with Tesio and Opti-Flow catheters. These results are shown in Figure 7.

![Figure 5. Relationship between roller pump setting of dialysis machine and actual flow rate by Transonic™ device, for Split Catheter and Bard Hickman (From Reference 17).](image-url)
Trerotola and Kraus also performed a randomized study comparing the Split Cath and Opti-Flow catheters in 132 placements in ESRD patients [19]. Complications during placement were no different for the two catheters and ranged 15-17% (mostly, kinking). Opti-Flow delivered significantly higher flow rates when tested at 1 month, but there was no significant difference in flow at 6 months. Recirculation was always lower with the Split Cath catheter but not always significantly different. The Split Cath had significantly longer half life, partly due to lower infection rate but also due to some mechanical failures of the Opti-Flow. Postulating on reasons that the Split Cath might have lower infection rates, the authors suggested that the “self-cleaning” function of the Split Cath, with continuous flow through all side holes, may diminish fibrin sheath and therefore decrease opportunity for bacterial colonization. The results of seven non-randomized studies of the Split Cath confirming catheter survival rates of about 9 months on average, are summarized in our review in Seminars in Dialysis. [5] However, overall longevity of Split Caths is not any better than with
Tesi catheters, which have been shown to have up to 5 years function assisted by a few procedures. [20]

Side Holes versus no Side Holes in Tunneled CVC

As discussed above regarding the Split Cath design, catheter side holes have advantages and disadvantages. They can decrease overall resistance and provide lower shear rate and better flow in the short run especially on the arterial side. However, they can create relative dead space at the end of the tip promoting clotting. Ironically they also allow flow of blood through the tip to wash out locking solution almost as soon as the catheter is filled with locking solution [21, 22, 5]. Side holes also allow clots to adhere to the catheter tip, due to the lumens and rough edges. Tesio/Canaud catheters have six side holes in a spiral shape. It is not uncommon for these catheters to clot completely after placement, within hours. Removing the clot with forceful irrigation, using the catheter for dialysis and then re-locking the catheter with heparin usually results in a catheter that functions for a long time. Presumably this is because the catheter becomes “biolized” or protein-coated and is therefore more resistant to clotting.

Figure 8. Relationship between flow and pressure during in vitro experiments with DD catheters. The hydraulic resistance of the venous lumen is fairly constant, but that of the arterial lumen increases with increasing flow (from Reference 23). Mean arterial extracorporeal pressure PA (O), mean venous extracorporeal pressure PV (△) and sum of both pressures (□) one day after catheter insertion.

Side holes can also increase overall catheter resistance. To understand this, it is important to understand a little more about how blood flows within a catheter. A curious phenomenon is that the relationship between flow and pressure isn’t the same on both lumens of the catheter. As shown in Figure 8, the higher the blood flow rate, the higher the resistance on the arterial side. In otherwords, the relationship between flow and pressure is not a straight line as it is on
the venous lumen. [23] The best explanation for this phenomenon is given by Fricker et al, who demonstrated that at the arterial inlet port, blood enters the catheter as “developing” flow, not parabolic or developed flow, as shown in Figure 9. This “plug” flow results in higher shear at the catheter inner surface. The higher the flow rate, the greater the distance it takes the blood to develop parabolic flow within the catheter lumen, and the greater the hydraulic resistance of the catheter.. [24] Also the more complicated the tip shape, the greater the distortion of flow and the greater the distance of developing flow, as shown in Figure 10. If the tip is blocked and all of the flow is through the side holes, then hydraulic resistance can increase markedly with blood flow rate. [24].

Do side holes provide any advantage clinically? Tal et.al. performed a prospective study of Mahurkar type single-body tunneled catheters, comparing catheters with side holes to catheters without side holes. [25] On removal, many of the catheters with side holes had adherent clots, while those without side holes had fewer adherent clots, as shown in Figure 11. In follow-up over 12 weeks there was a slightly higher flow rate for catheters with side holes, though not a significant difference. Surprisingly there was a significantly higher rate incidence of CRBSI in the catheters with side holes versus those without (2.54/1000 catheter days versus 0.245/1000 catheter days). The authors surmised that clots adherent to the catheter tip served as a nidus for infection, after seeding from systemic bacteremia or lumen contamination.

Figure 9. Depiction of the difference between fully developed and developing flow within dialysis catheters. At the arterial inlet port, blood enters as developing flow rather than parabolic flow, and this flow has high resistance. The higher the flow rate, the greater the proportion of developing flow in the catheter lumen (from Reference 24).
So side holes have advantages and disadvantages. If a catheter limb rests against a vein or atrial wall and the tip is blocked by sheath or thrombus, side holes allow continued flow though at higher resistance. However if a catheter tip can be positioned away from a wall, as in the atrium or within the SVC blood stream, then side holes would not be necessary and in fact disadvantageous.
Symmetric Tipped Tunneled CVC, the Palindrome™

In 2005 Tal reported on a new catheter design with symmetric tips and biased ports, as shown in Figure 12 [26]. In an animal study the percentage recirculation was compared to that of step-tip and split tip catheters, immediately after placement. All of the catheters were run in reverse flow and tips placed in the SVC or the right atrium. As shown in Figure 13, the Palindrome had less recirculation than any of the other catheters. Surprisingly, all catheters had slightly more recirculation when placed in the atrium than when in the SVC. The stepped tip catheters had no flow when placed in the SVC of the pig though the split tip and Palindrome allowed flow.

In the patient and over time, any catheter lying on the vein or atrial wall will be affected by sheaths, clots, and the relation of the catheter tip to the vascular surfaces, and these factors affect recirculation. In a recent survey study of recirculation in a dialysis unit, Moossavi et.al. measured recirculation in patients with step-tip, split tip and symmetrical (Palindrome) catheters, while the catheters were run in the usual flow direction. All tunneled catheters delivered the same recirculation, between 6 and 8 percent. Acute dialysis catheters however delivered blood flow with 23% recirculation. Though the Palindrome catheter appears successful, there is no clinical data yet showing that it diminishes recirculation or has higher flow rates over time than other catheters. [27]

Figure 11. Clots adherent to the side holes of Mahurkar-type step tipped catheters, in the study by Tal et al. (from Reference 25).
Figure 12. The symmetrical Palindrome catheter of Dr. Tal, with bias-cut ports. Kinetic energy carries returning blood downstream, and pressure gradient brings blood through the closest part of the removal blood lumen (from Reference 26).

Figure 13. recirculation rates with reversed flow for step tip, split tip and Palindrome catheters, in an animal model. (From Reference 26).
Figure 14. (a) catheter design of Dr. Kohler with loop to support the distal tip in the middle of the vena cava, (b) position of catheter tip of control catheters in SVC (A) and loop catheters (B), and (c) appearance of SVC in area of tip of catheter, 8 weeks after placement of the loop catheter. (from Reference 28).
Self-centering SVC Catheter, the Centros™

The idea of the Centros™ catheter is fairly simple. The best way to avoid complete sheathing of the catheter is to hold it in the middle of the vena cava. As shown in Figure 2, the Centros™ catheter has a distal end that is planar with two outward bends of the distal tips that create points of contact with the SVC, and inward pointing ports. The two contact points will center the catheter in the vena cava and place the ports in a position away from the wall of the vein wall. Side holes are not necessary since the ports should not be in contact with the vena cava wall. If fibrous sheathing near the ports is avoided the blood flow rate of the Centros™ should be maintained over months of use, and recirculation should be minimal (it measures zero, in vitro). Function of the catheter should be independent of the exact location in the SVC, so placement is easier. A gently preformed curve of the apex of the catheter can match the usual arc of the subcutaneous tract.

There is some prior evidence that a catheter supported within the SVC will remain free of sheathing and thrombosis. In 1998 Kohler and Kirkman reported an animal trial in which single lumen 3.2 mm diameter silicone catheters were placed in the SVC of pigs, and left for 1 to 8 weeks. [28]. No anticoagulant was administered and the catheters were not used for infusion or blood removal. Some of the catheters had a 2 cm diameter loop attached to the them, to center the tip in the distal SVC. During placement of the catheters without a loop, fluoroscopy demonstrated a continued relative motion of the catheter and vena cava wall with each heartbeat; however catheters with the loop remained stationary at the point of contact with the vena cava wall. As shown in Figure 14 when the loop catheters were examined at the end of the 8 week period the SVC and catheter were completely free of fibrous sheathing and thrombosis. In pigs with non-looped catheters the catheter was completely covered by sheath and thrombus, the SVC was nearly occluded and there was a much greater number and size of
Catheter Design

intimal lesions. From this study it is apparent that a catheter which is supported in the vena cava by two points of contact should have considerably less sheathing and fibrosis, and therefore more constant flow over time, versus straight, single body or split tip catheters.

In June of 2007 the FDA approved the Centros™ catheter for use in dialysis access. Catheters were produced of 28 and 24 cm length (hub to tip) with a gentle bend at the expected apex. All catheters had a self-sealing opening to allow threading over a single guidewire though this is not used for placement through a split sheath, in general. We initiated a small post-market study clinical trial to determine the hydraulic properties of the catheter and permanence of flow [29].

Nine catheters were placed through the right IJ, under local anesthesia using fluoroscopy and ultrasound, utilizing a 16 French split sheath. Tips of the catheters were placed in the lower third of the SVC rather than in the atrium. An example of a post-placement chest X-Ray is in Figure 15. The catheters were immediately used three times per week for outpatient hemodialysis. Once per week at the start dialysis, the blood pump was set to deliver a negative arterial pressure of 200 mm Hg on the arterial line. The blood flow rate associated with this modestly negative pressure was recorded (Qb₂₀₀). The same measurement was also performed on 120 prevalent DD dialysis catheters in 20 dialysis centers as part of a study of catheter locks. In the current study, reasons for catheter removal were recorded as were any significant problems with the catheters.

Figure 16 demonstrates the average Qb₂₀₀ flow rate for all 9 catheters, over the seven week study. The mean Qb₂₀₀ was 390 ml/min (SD +/- 49) at catheter insertion and was 401 ml/min (SD +/-80) at seven weeks of use (NS). By comparison, 120 standard tunneled dialysis IJ catheters being used in several dialysis units had a lower Qb₂₀₀, 348 ml/min (SD +/- 64, P<0.05). During 7 weeks of follow up, one of the nine self-centering catheters was removed due to presumed exit infection, and one was removed when no longer needed. No catheter failed to provide adequate flow for dialysis during the study.

Figure 16. Flow rate of the Centros catheters at modestly negative arterial side pressure (QB₂₀₀), over 7 weeks of dialysis use. For comparison, same measurement done on 120 prevalent DD tunneled dialysis catheters.

![Average Flow at -200 Arterial Pressure, Centros(TM) Catheters (+/- Standard Deviation)](chart)

- Standard Catheters
- P < 0.05 (n=120)
Figure 17. CT scans of the chest done 4 months after Centros placement in two patients, demonstrating that the catheter limbs form a plane within the vena cava and at least one port is separated from the vena cava wall. The SVC on the right includes two pacemaker wires.

Figure 18. CT scans of two patients with Split Cath catheters in place for several months. Note that both limbs of the catheter lie against the vena cava wall. Clot surrounds the catheter in the CT angiogram on the right.

At the end of the study catheters continued to be used for dialysis, in some patients up to 18 months. Flow rates in all patients continued at approximately 400 ml/min during each dialysis treatment for the duration of use of the catheter. Two patients volunteered for a CT scan of the chest after 4 months of catheter use. Figure 17 demonstrates that the catheters were in the expected position, limbs in a plane across the vena cava with at least one distal limb separated from the wall of the vena cava. No marked For comparison, Figure 18 includes two CT scans performed on patients with Split Cath catheters, demonstrating that both limbs of these catheters are always adjacent to the vena cava wall. One of these catheters clearly has a clot and/or sheath covering the catheter. At removal, none of the catheters exhibited any resistance to retraction, and none came out with remnants of any thickened sheath. In fact most catheters were remarkably free of any clots or evidence of sheath as shown in Figure 19. sheath was seen but of course a standard CT could not detect sheaths of less than 1 mm thickness. Also of interest, there was no sign of any SVC stenosis on these CT
studies, and none of the 9 patients ever developed clinical signs of SVC stenosis. None of the catheters needed to be run in reversed flow mode.

This preliminary study indicated that the self-centering Centros™ catheter provides optimal blood flow rate at modest negative pressure, without deterioration in flow rate over 7 weeks of use. This high flow rate occurred even in spite of the fact that the tips of the catheter were positioned in the SVC (rather than within the atrium). The study showed no evidence of any significant sheathing of the catheters or any signs of SVC stenosis, although a much larger study will be needed to confirm any benefit of this type. As the Centros™ catheter was marketed more widely, there were some complaints that catheters at the time of placement would not allow blood to be withdrawn from the venous lumen. On investigation of these problems we found almost uniformly that the catheter venous tip had been placed far into the right atrium, and the venous lumen was curved to the right. This brought us to two conclusions.

Figure 19. Appearance of Centros™ catheters after removal from patients after several months of use. Photographs were taken after a gentle rinse of the catheter with sterile saline. The only signs of any thin sheath near the jugular vein entrance and this was in very few catheters.
The Centros™ catheter should always be placed with the arterial lumen towards the patient’s left side. This directs the venous lumen into the right atrium. Further, one small side-hole near the tip of the catheter may help blood flow even if the venous tip is advanced too far into the atrium and rests against the atrial wall. One side hole near the tip may have a propensity to promote some clotting but this effect would be minimized by rapid blood flow during dialysis.

**Current Challenges and Future Directions for Tunneled CVC for Dialysis**

The advent of successful tunneled CVC for dialysis has been a great advance for patients with ESRD, both at the beginning of hemodialysis and after many years. Tunneled CVC now allow dialytic support of patients for many months if needed, allowing patients to be supported long enough for fistulas and grafts to be created, corrected, and become the best long-term access choices.

In spite of advances, tunneled CVC still have significant problems and limitations. For each of these problems, there will someday exist a solution which will advance the technology and benefits of tunneled CVC for dialysis:

- **Catheter related infections:** Catheter materials, chemical impregnation methods or catheter locks are now being investigated to kill bacteria in the biofilm layers both on the outside and inside of tunneled CVC for dialysis, in order to decrease this most common complication of the catheters. Two recent reviews have confirmed that every antibacterial catheter lock that has been studied in randomized, prospectively controlled trials has demonstrated a 50-80% decrease in incidence of CRBSI [30, 31]. A recent study of an antiseptic catheter lock (Zuragen™, a combination of sodium citrate, methylene blue and parabens) demonstrated a 70% decrease in CRBSI versus heparin catheter lock. [32] Catheter materials which resist biofilm and infection may become possible if there is some method of regeneration of the active component over time.

- **Catheter tip clotting:** As described above, catheters without side holes have some advantage in avoiding clotting but also have a tendency to obstruct if catheter tips are placed against the wall of the SVC or atrium. Catheters which open and close at the tip would allow the catheter to retain anticoagulant and completely avoid blood clotting within the ports.

- **Catheter fibrous sheathing:** As described above, one solution for catheter sheathing may be a catheter which centers itself in the vena cava (the Centros™). Other approaches include chemical impregnation of the catheter to prevent the growth of macrophages and fibroblasts around the catheter bodies, though this is likely to be difficult since the irritation of the vein wall by the catheter is such a strong stimulus for sheath formation.

- **Central venous stenosis:** Methods to distribute or diminish “wear” on the vena cava must be evolved to avoid this serious and still frequent complication. Avoiding use of acute dialysis catheters diminishes the frequency of central venous stenosis.
Catheters that are supported at only two points in the SVC diminish the contact area of the catheter to the vein and might diminish the risk of SVC stenosis in the long run but this effect is unproven at this time.

- **External component bulk**: Patients bandage and keep dry the hubs, extension tubings, clamps and connectors, but many also complain about the general bulk of the catheters components on their bodies. Also, the preclusion of showering is a real bother to many patients. Subcutaneous ports were proposed as one solution (LifeSite and BioLink) but clearly are not the answer for most long-term patients and these devices are no longer marketed. Eventually more radical skin-level “connectology” will be necessary.

- **External component breakage**: More durable yet still light-weight components are possible. Simplifying the entire catheter design to limit the size and number of glued connections is a partial solution.

With a few more improvements, tunneled CVC for dialysis could become a painless, effective and safe long term access for the majority of dialysis patients and perfectly acceptable as an alternative to AV grafts. For those patients in whom they are possible, the fistula will likely remain the optimal access for some years, in spite of patients’ concerns about insertion of needles, pain and the appearance of their AV accesses. [33]

References


[22] Polaschegg HD. Loss of catheter locking solution caused by fluid density. *ASAIO J.* 2005 May-Jun;51(3):230-


Index

anastomosis, 9, 11, 20, 41, 42, 43, 44, 54, 59, 60,
63, 64, 68, 71, 72, 97, 98, 105, 109, 110, 116,
117, 134, 135, 136, 138, 152, 174, 176, 177,
208, 210, 211, 213, 214, 218, 243, 292, 293,
295, 296, 300, 301, 302, 303, 307, 308, 309,
352, 353, 363, 365, 367, 368, 373, 374
anatomic site, 318
anatomy, 6, 9, 10, 11, 12, 13, 19, 24, 28, 69, 70,
76, 117, 118, 173, 176, 188, 190, 192, 200,
282, 285, 286, 331, 378
anemia, 81, 321
aneurysm, 55, 59, 61, 65, 191, 223, 224, 297,
302, 332, 333
angiotensin II, 163
angiotensin receptor blockers, 163
angiotensin converting enzyme, 353
angiotensin II, 163
angiotensin receptor blockers, 163
anemia, 7
angioembolism, 280, 286, 338
albumin, 246
allergic reaction, 271, 272, 294
allergy, 326, 330
alteplase, 283, 287, 339
amalgam, 208
American Heart Association, 276
aminoglycosides, 325
amputation, 186, 192
amylose, 325
amyloidosis, 123
analgesic, 330
anaphylactic reactions, 294
angiotensin II, 163
angiotensin receptor blockers, 163
anemia, 7
angiotensin converting enzyme, 353
anesthetic, 271, 272, 294
anaphylactic reactions, 294
anatomy, 6, 9, 10, 11, 12, 13, 19, 24, 28, 69, 70,
76, 117, 118, 173, 176, 188, 190, 192, 200,
282, 285, 286, 331, 378
anemia, 81, 321
aneurysm, 55, 59, 61, 65, 191, 223, 224, 297,
302, 332, 333
angiotensin II, 163
angiotensin receptor blockers, 163
angiotensin converting enzyme, 353
angiotensin II, 163
angiotensin receptor blockers, 163
anemia, 7
angiotensin converting enzyme, 353
anesthetic, 271, 272, 294
anaphylactic reactions, 294
anatomy, 6, 9, 10, 11, 12, 13, 19, 24, 28, 69, 70,
76, 117, 118, 173, 176, 188, 190, 192, 200,
282, 285, 286, 331, 378
anemia, 81, 321
aneurysm, 55, 59, 61, 65, 191, 223, 224, 297,
302, 332, 333
angiotensin II, 163
angiotensin receptor blockers, 163
angiotensin converting enzyme, 353
anesthetic, 271, 272, 294
anaphylactic reactions, 294
access device, 386
access modality, 3, 75, 243
accessibility, 176
accounting, 261
acetylation, 158
acid, 162, 166, 330, 356
acidosis, 81, 128, 337
acute renal failure, 82, 91, 123, 272
adenine, 158
adenosine, 158, 159
adenovirus, 383
adhesion, 174, 246, 247, 353, 355, 362
adipose tissue, 122, 126
ADP, 159
adults, 29, 132, 161, 262
adventitia, 20, 208, 221, 353, 367, 371
adverse effects, 263
adverse event, 159
age, 54, 63, 82, 122, 123, 124, 130, 139, 161,
186, 200, 234, 318, 346, 348
aggregation, 159
agonist, 371
air embolism, 280, 286, 338
albumin, 246
allergic reaction, 271, 272, 294
allergy, 326, 330
alteplase, 283, 287, 339
amalgam, 208
American Heart Association, 276
aminoglycosides, 325
amputation, 186, 192
amylose, 325
amyloidosis, 123
analgesic, 330
anaphylactic reactions, 294
anatomy, 6, 9, 10, 11, 12, 13, 19, 24, 28, 69, 70,
76, 117, 118, 173, 176, 188, 190, 192, 200,
282, 285, 286, 331, 378
anemia, 81, 321
aneurysm, 55, 59, 61, 65, 191, 223, 224, 297,
302, 332, 333
angiotensin II, 163
angiotensin receptor blockers, 163
angiotensin converting enzyme, 353
anesthetic, 271, 272, 294
anaphylactic reactions, 294
antimicrobial therapy, 264
anxiety, 5, 16
aorta, 23, 122, 130, 189, 243, 247, 383
apex, 402, 403
apnea, 337
apoptosis, 351
appetite, 321
arterial hypertension, 63
arterial vessels, 42
arteries, 9, 11, 12, 20, 22, 24, 27, 33, 72, 84, 85, 115, 116, 122, 129, 130, 131, 133, 134, 139, 141, 146, 182, 374, 387
arteriogram, 12, 115, 209, 215
arteriography, 116, 117, 118, 192
arteriovenous fistula (AVF), 41, 81, 133, 173, 183, 193, 207, 229, 243, 267, 361, 379
arteriovenous grafts (AVG), 95, 158, 267
arteriovenous shunt, 52
arthrits, 90
articulation, 28
ascites, 321, 322
aseptic, 261, 264, 324
aspiration, 108, 190, 217, 233, 279, 295
assessment, 9, 10, 12, 17, 28, 32, 33, 34, 38, 40, 85, 89, 92, 98, 111, 121, 124, 131, 134, 143, 183, 201, 213, 279, 297, 326, 355, 356
asthma, 330
asymptomatic, 127, 135, 216, 250, 302, 310, 321
atherogenesis, 166, 174
atherosclerosis, 130, 234, 374, 384
atherosclerotic vascular disease, 192
atomic force, 356
atrium, 232, 238, 387, 392, 393, 398, 399, 403, 405, 406
atrophy, 123
attitudes, 378
auscultation, 87, 97, 212
autoimmunity, 361
autopsy, 246, 384
autosomal dominant, 125
av fistula, 29
AVF creation rate, 31
axilla, 9, 11, 26, 33, 44, 113
bruit, 8, 87, 91, 104, 109, 110, 176, 177, 178, 191, 208, 212, 369
bypass graft, 253, 257, 352, 361

Ca++ , 362
CAD, 185, 186, 187
calcification(s), 9, 10, 12, 33, 84, 115, 116, 119, 122, 124, 127, 134, 322, 384
calcium, 116, 157, 162, 261, 351
calculus, 128
caliber, 9, 210, 211, 237, 248
calibration, 108
cancer, 272, 286, 361
candidates, 48, 71, 72, 75, 76, 93, 149
carcinoma, 124, 140, 361
cardiologist, 250
cardiac arrhythmia, 282
cardiac catheterization, 335
cardiac output, 42, 174
cardiac surgery, 337
cardiac tamponade, 282
cardiologist, 250
cardiovascular disease, 7, 162, 191, 248, 374
care model, 52, 58, 61
caregivers, 82, 195
carotid arteries, 162
carpal tunnel syndrome, 90, 120
cartilage, 22
catheterizations, 5, 248
C-C, 393
CDC, 235
cefazolin, 263
cell cycle, 351
cell death, 261
cell line, 161
cell surface, 355
cellulitis, 330
cephalosporin, 263, 324, 326
cerebrovascular disease, 185
challenges, 41, 56, 57, 58
channel blocker, 163
chemotherapy, 286
children, 262
cholesterol, 116
chronic renal failure, 129, 139, 337
circulation, 24, 52, 84, 86, 92, 115, 116, 202, 269, 332, 334, 335, 336, 352
classification, 16, 141
claudication, 7, 27, 186
clavicle, 21, 22, 24, 281
clinical diagnosis, 369
clinical examination, 38, 71, 176, 179, 180, 222
clinical presentation, 363
clinical problems, 259
clinical trials, 103, 163, 165, 204, 273, 308, 311, 370, 371
CO2, 12, 85
coagulation profile, 331
coagulopathy, 218
coatings, 267, 268, 271, 272, 273, 274
collagen, 20, 152, 174, 232, 246, 361, 373
collateral, 8, 10, 24, 84, 97, 99, 100, 103, 108, 132, 176, 177, 244, 292, 297, 301, 302, 307
colonization, 234, 235, 259, 268, 271, 272, 275, 326, 395
colostomy, 6
communication, 13, 59, 148, 320
community, 52, 54, 107, 199, 201, 287, 329
comorbidity, 14
compartment syndrome, 333
complement, 89
complex interactions, 246
complexity, 53, 124, 373, 374
compliance, 82, 293, 337
compounds, 264
compressibility, 10
compression, 12, 21, 74, 119, 134, 138, 189, 190, 191, 223, 225, 237, 331, 332, 333
conditioning, 246
conductance, 392
conduction, 90, 119
configuration, 11, 44, 52, 72, 392
congestive heart failure, 320
connective tissue, 19, 20
conscious sedation, 57, 59, 132, 147
consensus, 141, 186, 191, 192, 201, 230
constipation, 314
construction, 45, 55, 63, 68, 70, 74, 75, 85, 93, 255, 379
contamination, 234, 259, 268, 324, 386, 397
control group, 158, 159, 162, 262, 271, 272, 308, 351, 373
controlled studies, 232, 308
controlled trials, 38, 214, 261, 263, 274, 370, 406
controversial, 164, 213, 253, 282, 293, 300, 309, 370
controversies, 204, 357
coronary angioplasty, 164
coronary arteries, 164, 352
coronary artery disease, 18, 185, 346
coronary heart disease, 185
correlation, 40, 139, 140, 152, 369
cortex, 122, 127, 129, 132
corticosteroids, 321
cosmetic, 386
cost, 4, 7, 10, 14, 15, 75, 107, 121, 151, 156, 165, 167, 194, 199, 213, 231, 248, 254, 261, 264, 274, 283, 303, 311, 348, 366, 369, 386
craniotomy, 24
creatinine, 82, 83, 186
critical analysis, 240, 287
criticism, 199
crust, 323
CT, 124, 126, 127, 129, 132, 140, 190, 318, 320, 328, 341, 404
CTA, 141
culture, 13, 203, 235, 323, 325, 326, 351
curriculum, 327
CV, 10, 11, 186
cyclooxygenase, 158
cyst, 123, 124, 125, 139
Cytokines, 152, 208, 237, 248, 353, 367
cytomegalovirus, 361
daily living, 133
data collection, 308
data gathering, 176
database, 157, 162, 249, 273, 329, 336
deficiency, 353, 360, 380
deficiency, 353, 360, 380
dehydration, 132
deposition, 218, 260, 271, 321
depth, 68, 85, 136, 173, 356
derivatives, 158
desensitization, 356
detectable, 297, 300
detection, 90, 94, 98, 99, 101, 102, 105, 107, 110, 111, 113, 131, 133, 134, 140, 142, 143, 146, 182, 244, 303, 318, 319, 328, 369, 376, 380
diabetes, 32, 48, 54, 63, 84, 116, 118, 148, 186, 187, 191, 194, 234, 244, 348
diabetic kidney disease, 82
diabetic nephropathy, 123, 360
diabetic patients, 48, 120, 234, 330, 381
diaphoresis, 190
diaphragm, 316
diarrhea, 324
diastole, 8, 87, 130
diastolic blood pressure, 85
diet, 381
differential diagnosis, 324
diffusion, 268
digestion, 174
dilation, 69, 71, 129, 173, 175, 372, 388
discomfort, 72, 115, 186
diseases, 56, 62, 63, 64, 197, 216, 357, 376, 378, 381, 384
disinfection, 266
distribution, 4, 185, 208, 250, 352
dizziness, 104
docosahexaenoic acid, 168
dogs, 354
donors, 140
doppler, 3, 9, 10, 12, 16, 74
dosage, 161
dose-response relationship, 165
dosing, 263, 325, 337
double blind study, 166
double-blind trial, 159, 272
drainage, 20, 97, 176, 177, 212, 291, 299, 322, 323
drug delivery, 164, 168, 356, 359
drug release, 356
drugs, 157, 158, 160, 165, 168, 283, 351, 371, 381
dyslipidemia, 186
dysplasia, 130, 141
dyspnea, 320
<table>
<thead>
<tr>
<th>E</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>edema, 8, 9, 111, 147, 243, 244, 245, 308, 310, 314, 316, 320, 323</td>
<td></td>
</tr>
<tr>
<td>education, 4, 5, 6, 14, 16, 34, 58, 59, 103, 104, 146, 148, 201, 256, 324</td>
<td></td>
</tr>
<tr>
<td>educational materials, 194</td>
<td></td>
</tr>
<tr>
<td>educational programs, 147</td>
<td></td>
</tr>
<tr>
<td>effluent, 179, 324, 325</td>
<td></td>
</tr>
<tr>
<td>elastase inhibitors, 355</td>
<td></td>
</tr>
<tr>
<td>elastin, 174</td>
<td></td>
</tr>
<tr>
<td>elastomers, 231</td>
<td></td>
</tr>
<tr>
<td>elders, 384</td>
<td></td>
</tr>
<tr>
<td>electromagnetic, 374</td>
<td></td>
</tr>
<tr>
<td>electron, 275</td>
<td></td>
</tr>
<tr>
<td>emboli, 117, 133, 215, 216, 217, 222, 224, 269, 284, 336</td>
<td></td>
</tr>
<tr>
<td>embolism, 334, 340</td>
<td></td>
</tr>
<tr>
<td>embolization, 117, 133, 215, 216, 217, 222, 224, 284</td>
<td></td>
</tr>
<tr>
<td>embolus, 331, 332</td>
<td></td>
</tr>
<tr>
<td>emergency, 8, 90, 331</td>
<td></td>
</tr>
<tr>
<td>EMG, 119</td>
<td></td>
</tr>
<tr>
<td>encapsulation, 321</td>
<td></td>
</tr>
<tr>
<td>encoding, 372</td>
<td></td>
</tr>
<tr>
<td>end stage renal disease, 3, 123, 124, 140, 145, 146, 151, 194, 207, 217, 244</td>
<td></td>
</tr>
<tr>
<td>end stage renal disease (ESRD), 3, 146, 151, 194, 244</td>
<td></td>
</tr>
<tr>
<td>endocarditis, 235, 236</td>
<td></td>
</tr>
<tr>
<td>endothelial cells, 19, 20, 152, 356, 361, 372, 383</td>
<td></td>
</tr>
<tr>
<td>endothelial dysfunction, 352, 367, 368</td>
<td></td>
</tr>
<tr>
<td>endothelium, 152, 153, 232, 237, 282, 333, 352, 353, 355, 359</td>
<td></td>
</tr>
<tr>
<td>end-stage renal disease, 15, 16, 31, 148, 192, 203, 265, 267, 277</td>
<td></td>
</tr>
<tr>
<td>energy, 400</td>
<td></td>
</tr>
<tr>
<td>engineering, 382</td>
<td></td>
</tr>
<tr>
<td>England, 287</td>
<td></td>
</tr>
<tr>
<td>enlargement, 89, 123, 124, 222, 254</td>
<td></td>
</tr>
<tr>
<td>enrollment, 373</td>
<td></td>
</tr>
<tr>
<td>entrapment, 119</td>
<td></td>
</tr>
<tr>
<td>environment, 6, 9, 268, 322</td>
<td></td>
</tr>
<tr>
<td>enzyme, 157, 168, 351, 370, 379</td>
<td></td>
</tr>
<tr>
<td>enzyme inhibitors, 168, 351, 370</td>
<td></td>
</tr>
<tr>
<td>epidemic, 15</td>
<td></td>
</tr>
<tr>
<td>epidemiology, 229, 243, 244, 345, 357, 363, 378</td>
<td></td>
</tr>
<tr>
<td>epidural abscess, 235</td>
<td></td>
</tr>
<tr>
<td>epithelium, 323</td>
<td></td>
</tr>
<tr>
<td>EPS, 320, 321, 322</td>
<td></td>
</tr>
<tr>
<td>equilibrium, 153</td>
<td></td>
</tr>
<tr>
<td>equipment, 102, 278, 331, 334, 335, 336, 369</td>
<td></td>
</tr>
<tr>
<td>erosion, 332</td>
<td></td>
</tr>
<tr>
<td>erythropoietin, 153, 348, 354</td>
<td></td>
</tr>
<tr>
<td>ethanol, 262, 264, 266</td>
<td></td>
</tr>
<tr>
<td>etiology, 118, 237, 328, 374</td>
<td></td>
</tr>
<tr>
<td>Europe, 39, 63, 194, 202, 230, 320, 345</td>
<td></td>
</tr>
<tr>
<td>evolution, 356</td>
<td></td>
</tr>
<tr>
<td>examinations, 112, 176, 246, 321</td>
<td></td>
</tr>
<tr>
<td>exchange rate, 156</td>
<td></td>
</tr>
<tr>
<td>excision, 22, 294</td>
<td></td>
</tr>
<tr>
<td>exclusion, 224, 225, 312</td>
<td></td>
</tr>
<tr>
<td>exercise, 186, 316</td>
<td></td>
</tr>
<tr>
<td>expenditures, 231, 234, 243</td>
<td></td>
</tr>
<tr>
<td>exposure, 13, 14, 38, 67, 75, 82, 90, 152, 153, 164, 262, 326, 330</td>
<td></td>
</tr>
<tr>
<td>external validation, 346</td>
<td></td>
</tr>
<tr>
<td>extracellular matrix, 174, 208, 367</td>
<td></td>
</tr>
<tr>
<td>extravasation, 212, 334</td>
<td></td>
</tr>
<tr>
<td>extrusion, 314, 316</td>
<td></td>
</tr>
<tr>
<td>false negative, 178</td>
<td></td>
</tr>
<tr>
<td>family history, 124</td>
<td></td>
</tr>
<tr>
<td>FAS, 241, 278, 283, 286</td>
<td></td>
</tr>
<tr>
<td>fascia, 20, 21, 22, 24, 26, 47, 70, 121</td>
<td></td>
</tr>
<tr>
<td>fasting, 130, 330</td>
<td></td>
</tr>
<tr>
<td>fat, 121, 123, 124, 126, 322</td>
<td></td>
</tr>
<tr>
<td>fatal arrhythmia, 262</td>
<td></td>
</tr>
<tr>
<td>fatty acids, 162, 167</td>
<td></td>
</tr>
<tr>
<td>FDA, 238, 266, 329, 403</td>
<td></td>
</tr>
<tr>
<td>fever, 235, 324</td>
<td></td>
</tr>
<tr>
<td>fiber, 20</td>
<td></td>
</tr>
<tr>
<td>fibrinogen, 223, 246, 255</td>
<td></td>
</tr>
<tr>
<td>fibrinolysis, 164, 341</td>
<td></td>
</tr>
<tr>
<td>fibrinolytic, 161, 234, 246, 247</td>
<td></td>
</tr>
<tr>
<td>fibroblast growth factor, 339, 382</td>
<td></td>
</tr>
<tr>
<td>fibroblasts, 361, 378, 406</td>
<td></td>
</tr>
<tr>
<td>fibrosis, 140, 237, 320, 361, 403</td>
<td></td>
</tr>
<tr>
<td>fibrous tissue, 246, 282, 387, 392</td>
<td></td>
</tr>
<tr>
<td>filtration, 4, 16, 82, 201, 229, 249, 330</td>
<td></td>
</tr>
<tr>
<td>first blood access device, 385</td>
<td></td>
</tr>
<tr>
<td>fish, 157, 158, 162, 163, 165, 167, 168, 213, 218, 349, 351, 358, 370, 371, 381</td>
<td></td>
</tr>
</tbody>
</table>
| fistulas, 4, 10, 16, 17, 20, 29, 33, 34, 39, 40, 48, 51, 52, 53, 54, 55, 56, 58, 61, 62, 63, 64, 76, 77, 84, 85, 86, 87, 92, 93, 95, 98, 100, 105, 114, 119, 133, 136, 142, 143, 149, 158, 160, 164, 166, 167, 168, 174, 177, 180, 181, 182, 183, 195, 196, 202, 203, 204, 217, 256, 264,
<table>
<thead>
<tr>
<th>Index</th>
</tr>
</thead>
</table>
hyperkalemia, 330, 337
hyperparathyroidism, 81, 116, 187
hyperphosphatemia, 187
hypertension, 7, 44, 84, 124, 129, 130, 132, 141, 153, 176, 186, 244, 348
hypertrophy, 129, 174, 353, 368
hypotension, 104, 190, 212, 324, 348, 358
hypoxia, 380
iatrogenic, 221, 225, 332, 339
ideology, 200
idiopathic, 244
image(s), 33, 60, 61, 111, 122, 127, 132, 134, 135, 137, 141, 209, 233, 333, 334, 336
immunocompromised, 235, 266
immunohistochemistry, 353
immunosuppressive agent, 322, 351, 355, 361
implants, 347, 358, 382, 383
impregnation, 406
improvements, 194, 238, 329, 356, 407
in transition, 355
in vitro, 158, 162, 168, 260, 261, 262, 272, 351, 382, 396, 402, 408
in vivo, 168, 260, 355, 408
incarceration, 318
incompatibility, 326
increased access, 8, 96
individuality, 4
individualization, 200
indolent, 321
inducible protein, 353
infarction, 118, 340
inferior vena cava, 28, 174, 229, 244, 288, 392
inflammation, 176, 187, 221, 222, 235, 244, 246, 247, 316, 321, 334, 350, 352, 353, 354, 367, 368, 372
inflammatory cells, 232, 246
inflammatory mediators, 231
inflation, 20, 214, 224, 251, 293, 303, 304, 333, 334
inguinal, 26, 28, 189, 192, 318, 331
inguinal hernia, 318
inhibition, 218, 354, 355, 358, 380, 381, 382, 383
inhibitor, 153, 157, 158, 351, 354, 360, 361, 379
innominate, 8, 22, 24, 232, 244, 248, 281, 282
inoculation, 325
insulin, 330, 355
integrity, 7, 9, 12, 223, 232, 262, 279, 280, 316, 387
interface, 235, 322
intestine, 42
intima, 19, 162, 352, 367, 368, 380, 386
iodinated contrast, 233, 294, 337
iodine, 129
ion implantation, 246, 271
ionizing radiation, 121
ions, 261
ipsilateral, 22, 84, 190, 208, 244, 245, 247, 248, 250, 293, 332
iron, 234
irrigation, 396
ischemia, 12, 48, 89, 90, 115, 116, 117, 118, 119, 120, 143, 165, 207, 222, 293, 383
isolation, 234

K

K⁺, 362
kinetic model, 348
laboratory studies, 331
lack of control, 273
laminar, 322, 352
landscape, 364
laparoscopy, 321
laparotomy, 321
leaks, 316, 318, 319, 320, 327
left ventricle, 42
legionella, 325
leukocytes, 260
liability insurance, 57
life expectancy, 7, 14, 201, 207
life experiences, 13
life strategy, 13
lifetime, 15
ligament, 26, 28, 188, 189, 192, 331
ligand, 355
lipoproteins, 246
liver, 122, 126
local anesthesia, 59, 117, 118, 132, 284, 316, 403
local anesthetic, 189
localization, 98, 369, 382
longevity, 51, 86, 103, 133, 193, 309, 395
low-density lipoprotein, 116
lymphadenopathy, 126
lysis, 287
macrophages, 353, 406
magnetic resonance, 182, 322
malignancy, 124, 140
malnutrition, 176, 192, 234, 235, 244, 247
mandible, 24
manipulation, 234, 246, 268
mapping, 3, 7, 9, 10, 14, 17, 19, 28, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 44, 58, 63, 70, 73, 85, 93, 142, 146, 148, 149, 181, 196, 376, 385
mass, 126, 127, 191, 222, 244, 348
mast cells, 354
mastoid, 24
matrix, 174, 175, 181, 234, 246, 268, 269, 353, 355, 380, 383
matrix metalloproteinase, 181, 353, 355, 380, 383
maturation process, 173, 180, 200, 201
MCP-1, 380
mean arterial pressure, 99
measurement(s), 33, 99, 100, 101, 102, 105, 134, 137, 143, 174, 183, 197, 292, 380, 403, 408
mechanical properties, 266
media, 20, 22, 116, 152, 330, 337, 352, 354, 367, 368, 380
mediastinitis, 244
mediastinum, 23, 279
Medicaid, 4, 16, 102, 103, 194, 202, 230, 243
medical, 5, 6, 7, 13, 42, 57, 82, 107, 122, 139, 194, 201, 216, 234, 244, 287, 328, 330, 337, 387
medication, 130, 159, 163, 164, 168, 355
medicine, 15, 16, 17, 264, 358, 382
medulla, 122
mellitus, 119, 244
membranes, 162, 348
meta-analysis, 102, 103, 213, 218, 261, 266, 338, 348, 409
metabolic acidosis, 330
metabolism, 116
metabolized, 158
methodology, 308
methylation, 264, 266, 320, 406
Mg$^{2+}$, 261
mice, 353, 354
microcirculation, 383
microorganisms, 261, 268
microscopy, 356
models, 164, 211, 237, 246, 321, 351, 352, 353, 355, 356, 368, 371, 372, 373, 374
molecular biology, 165
molecular weight, 161
molecules, 355, 356, 371
morphology, 139, 163, 362, 379
MRI, 124, 126, 129, 181
mRNA, 354, 355
mucosa, 323
multiple factors, 221
multivariate analysis, 247
muscle mass, 82
muscles, 21, 118, 119, 186
mycobacteria, 325
myocardial infarction, 7
myofibroblasts, 208, 353, 355, 360, 367
nanoparticles, 356
National Health and Nutrition Examination Survey (NHANES), 186, 191, 192
National Institutes of Health, 15, 39, 192, 202, 239, 256, 274, 312, 357, 370, 378
nausea, 7, 321, 324
necrosis, 89, 128, 138
neoplasm, 124, 126
neovascularization, 367
nephrectomy, 140
nephrocalcinosis, 127, 128, 140
nephrolithiasis, 127
nephrologist(s), 4, 5, 7, 41, 44, 48, 51, 53, 63, 81, 82, 83, 84, 85, 86, 88, 89, 90, 96, 98, 147, 175, 181, 193, 195, 201, 244, 249, 256, 257, 277, 279, 280, 285, 313, 327, 363, 364, 369, 370, 375
nephropathy, 34, 40, 93, 123, 140, 330, 337
nephrotic syndrome, 132
core, 20, 26, 47, 115, 116, 118, 119
eurologic symptom, 118
neuropathy, 90, 115, 116, 118, 120
nucleotides, 158
nurses, 89, 96, 98, 104, 145, 147, 148, 217, 244, 327, 364
nutrition, 91

Index

nanoparticles, 356
National Health and Nutrition Examination Survey (NHANES), 186, 191, 192
National Institutes of Health, 15, 39, 192, 202, 239, 256, 274, 312, 357, 370, 378
nausea, 7, 321, 324
necrosis, 89, 128, 138
neoplasm, 124, 126
neovascularization, 367
nephrectomy, 140
nephrocalcinosis, 127, 128, 140
nephrolithiasis, 127
nephrologist(s), 4, 5, 7, 41, 44, 48, 51, 53, 63, 81, 82, 83, 84, 85, 86, 88, 89, 90, 96, 98, 147, 175, 181, 193, 195, 201, 244, 249, 256, 257, 277, 279, 280, 285, 313, 327, 363, 364, 369, 370, 375
nephropathy, 34, 40, 93, 123, 140, 330, 337
nephrotic syndrome, 132
core, 20, 26, 47, 115, 116, 118, 119
eurologic symptom, 118
neuropathy, 90, 115, 116, 118, 120
nucleotides, 158
nurses, 89, 96, 98, 104, 145, 147, 148, 217, 244, 327, 364
nutrition, 91

oil, 157, 162, 163, 167, 213, 349, 371
omega-3, 162
open heart surgery, 335
optical microscopy, 356, 361
optimal dialysis, 3, 6, 9, 55, 173, 347
organism, 235, 236, 262, 324, 325
organs, 62, 166, 382
osteomyelitis, 235, 236
ostium, 130
ototoxicity, 263
outpatient, 9, 51, 52, 57, 58, 59, 61, 65, 118, 147, 279, 294, 340, 370, 376, 385, 403
oxidative stress, 116, 187, 353, 354, 367, 368
oxygen, 186, 212

paclitaxel, 157, 164, 353, 356, 372, 373, 382
pain, 7, 90, 115, 117, 118, 127, 138, 190, 191, 243, 244, 294, 303, 309, 315, 316, 321, 324, 407
palindrome, 275
palmar arch, 16, 24, 26, 84, 115, 116, 117
tpall, 9, 87, 97, 109, 110, 212
paralysis, 90, 118
parenchyma, 122, 124, 125, 127
parotid gland, 24
pathogenesis, 116, 153, 162, 235, 243, 259, 367, 368, 370
pathogens, 234, 323
pathology, 8, 96, 175, 176, 315, 325, 352, 363, 367, 370
pathophysiology, 152, 217, 232, 244, 269, 352, 360, 363, 367, 371, 379
pathways, 162, 350, 351
patient care, 3, 145, 147, 148
pattern recognition, 141
pelvis, 28, 127, 128
penicillin, 324
peptide(s), 181, 352
perforation, 277, 282, 286, 314, 332, 333
perfusion, 117, 340
peri-anastomotic region, 363
peripheral blood, 235
peripheral vascular disease, 7, 27, 118, 185, 190, 191, 192, 346, 348, 371
peritoneal cavity, 81, 190, 317, 322
peritoneum, 6, 8, 315, 320, 321, 325
peritonitis, 321, 322, 323, 324, 325, 326, 328

obesity, 6, 32, 377
obstruction, 8, 129, 139, 176, 177, 243, 244, 252, 257, 282, 292, 318, 332, 339
<table>
<thead>
<tr>
<th>Index</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>permeability, 261</td>
<td>prognosis, 187, 241</td>
</tr>
<tr>
<td>phenotypes, 378, 379</td>
<td>propagation, 223, 273</td>
</tr>
<tr>
<td>phosphate, 116</td>
<td>prophylactic, 105, 106, 142, 213, 234, 261, 311, 323, 356, 381</td>
</tr>
<tr>
<td>photographs, 59, 60</td>
<td>propylene, 319</td>
</tr>
<tr>
<td>platelet aggregation, 153, 158, 162, 165, 237</td>
<td>proteins, 153, 174, 175</td>
</tr>
<tr>
<td>platelet(s), 132, 152, 153, 159, 212, 247, 260, 331, 341, 386</td>
<td>proteinuria, 4, 16, 82</td>
</tr>
<tr>
<td>platelet aggregation, 153, 158, 162, 165, 237</td>
<td>Pseudomonas aeruginosa, 323</td>
</tr>
<tr>
<td>platelet(s), 132, 152, 153, 159, 212, 247, 260, 331, 341, 386</td>
<td>prophylactic, 105, 106, 142, 213, 234, 261, 311, 323, 356, 381</td>
</tr>
<tr>
<td>pleural effusion, 320</td>
<td>prophylaxis, 161, 266, 270, 274, 294, 322, 323, 330, 339</td>
</tr>
<tr>
<td>pleurodesis, 320</td>
<td>pulmonary circulation, 212, 215, 216</td>
</tr>
<tr>
<td>plexus, 20, 22</td>
<td>pulmonary embolism, 219, 270</td>
</tr>
<tr>
<td>pneumothorax, 133, 331, 332, 338</td>
<td>pulmonary hypertension, 216</td>
</tr>
<tr>
<td>point mutation, 360</td>
<td>quality assurance, 112</td>
</tr>
<tr>
<td>policy, 142, 200, 249, 376</td>
<td>quality improvement, 82, 194, 195, 249, 266</td>
</tr>
<tr>
<td>polycystic kidney disease, 124, 125, 320, 328</td>
<td>quality of life, 4, 14, 67, 186, 195, 259, 347</td>
</tr>
<tr>
<td>polymer(s), 164, 246, 382</td>
<td>Q</td>
</tr>
<tr>
<td>polymorphisms, 153, 353, 354, 360, 379</td>
<td>quality assurance, 112</td>
</tr>
<tr>
<td>polysaccharide, 234, 272</td>
<td>quality improvement, 82, 194, 195, 249, 266</td>
</tr>
<tr>
<td>polysaccharides, 261</td>
<td>quality of life, 4, 14, 67, 186, 195, 259, 347</td>
</tr>
<tr>
<td>propylene, 319</td>
<td>quality of life, 4, 14, 67, 186, 195, 259, 347</td>
</tr>
<tr>
<td>radiation, 8, 38, 129, 165, 169, 211, 218, 244, 351, 373, 374, 383</td>
<td>quality of life, 4, 14, 67, 186, 195, 259, 347</td>
</tr>
<tr>
<td>radiation therapy, 218, 244, 351, 373, 383</td>
<td>quality of life, 4, 14, 67, 186, 195, 259, 347</td>
</tr>
<tr>
<td>real estate, 83, 188, 250</td>
<td>quality of life, 4, 14, 67, 186, 195, 259, 347</td>
</tr>
<tr>
<td>rebound tenderness, 324</td>
<td>Q</td>
</tr>
<tr>
<td>receptors, 159, 356</td>
<td>quality assurance, 112</td>
</tr>
<tr>
<td>recognition, 64, 191, 318, 323, 333, 337</td>
<td>quality improvement, 82, 194, 195, 249, 266</td>
</tr>
<tr>
<td>recovery, 84, 224</td>
<td>quality of life, 4, 14, 67, 186, 195, 259, 347</td>
</tr>
<tr>
<td>recurrence, 298, 299, 300, 302, 303, 338</td>
<td>quality of life, 4, 14, 67, 186, 195, 259, 347</td>
</tr>
<tr>
<td>regeneration, 406</td>
<td>Q</td>
</tr>
<tr>
<td>regression, 346, 352, 353, 359</td>
<td>quality of life, 4, 14, 67, 186, 195, 259, 347</td>
</tr>
<tr>
<td>rehabilitation, 119</td>
<td>Q</td>
</tr>
<tr>
<td>reliability, 51, 52</td>
<td>quality of life, 4, 14, 67, 186, 195, 259, 347</td>
</tr>
<tr>
<td>relief, 89, 254</td>
<td>quality of life, 4, 14, 67, 186, 195, 259, 347</td>
</tr>
<tr>
<td>religious beliefs, 13</td>
<td>quality of life, 4, 14, 67, 186, 195, 259, 347</td>
</tr>
<tr>
<td>renal artery stenosis, 123, 130, 141</td>
<td>quality of life, 4, 14, 67, 186, 195, 259, 347</td>
</tr>
</tbody>
</table>
Index

renal failure, 83, 123, 124, 139, 193, 246, 255, 331, 379
renal replacement therapy, 3, 13, 16, 29, 31, 140, 145, 146, 229, 267, 313, 327
renin, 322
repair, 40, 61, 101, 102, 106, 142, 187, 191, 218, 223, 224, 225, 311, 312, 319, 320, 327, 335, 339, 381, 382
researchers, 34, 269, 273
resolution, 117, 269, 298, 301, 302
resources, 82, 90, 194, 196, 201, 376
respiratory acidosis, 330
responsiveness, 353
restoration, 167, 240, 279, 283
retinoblastoma, 165, 352
rheology, 162, 352
rhythm, 248, 250, 256, 338
right atrium, 22, 23, 232, 237, 247, 282, 387, 388, 392, 399, 405, 406
right ventricle, 42
risk factors, 17, 93, 140, 141, 186, 187, 192, 231, 234, 247, 256, 268, 316, 318, 335, 338, 346, 348, 357, 376
risks, 14, 17, 59, 100, 132, 133, 263, 335, 349, 352
sanctuaries, 260, 261
science, 143, 262, 345, 356, 357
sclerosis, 83, 126, 314, 327, 328
scope, 214, 319, 330, 332
scrotal, 314, 316
secondary prophylaxis, 161
secretion, 162, 380
sedatives, 214
sediment, 325
seeding, 231, 352, 359, 386, 397
sensitivity, 98, 111, 112, 127, 179, 180, 326, 369
sepsis, 14, 83, 146, 222, 236, 377
septic arthritis, 235
serum, 174, 187, 325, 330, 381
sex, 139, 318
shape, 20, 334, 388, 396, 397
shear, 21, 152, 174, 175, 238, 352, 356, 367, 368, 379, 382, 393, 396, 397
shortness of breath, 320, 332
side effects, 102, 260, 261, 356
signs, 73, 74, 75, 96, 97, 104, 112, 118, 124, 175, 190, 222, 235, 250, 293, 316, 318, 321, 324, 335, 405
silver, 238, 242, 271, 272, 276, 349
simulation, 382
skin, 8, 9, 10, 26, 32, 42, 48, 60, 61, 68, 86, 89, 104, 134, 136, 173, 189, 190, 223, 234, 259, 268, 282, 316, 322, 324, 330, 335, 337, 340, 374, 383, 387, 388, 392, 407
small intestine, 321
smoking, 186, 348
smooth muscle, 20, 126, 151, 152, 158, 162, 163, 166, 168, 174, 175, 208, 232, 246, 269, 272, 350, 352, 359, 367, 368, 370, 380, 381, 383
sodium, 156, 160, 161, 232, 315, 406
spastic, 294
specialists, 51, 56
species, 261, 262
spine, 26, 188, 189
spleen, 122
sponge, 128
Sprague-Dawley rats, 162, 381
standardization, 173
staphylococci, 275
stasis, 246, 269
statin, 157, 164
statistics, 308, 332
sterile, 132, 316, 322, 324, 325, 331, 334, 405
sternoclidomastoid, 24
sternum, 22, 23
stimulation, 362
stimulus, 174, 353, 355, 406
stratification, 16, 181
streptokinase, 283
stress, 21, 152, 174, 175, 182, 238, 351, 352, 356, 359, 367, 368, 378, 379, 382, 394
strictures, 302
stroke, 174, 348
structural changes, 246
structure, 19, 42, 261
subacute, 231
subcutaneous tissue, 48, 281, 316, 387
success rate, 34, 85, 86, 175, 216, 224, 251, 283, 308
superior vena cava, 8, 22, 23, 29, 70, 84, 244, 247, 286, 338, 339, 388, 392
supplementation, 168
suppression, 351
surface area, 190
surface treatment, 238, 272, 274, 276
surgical intervention, 58, 117, 118, 157, 181, 336
surgical removal, 335
surgical technique, 44, 53, 211, 253, 314, 318, 349, 367
survival rate, 395
suture, 61, 215, 277
swelling, 10, 22, 84, 89, 100, 103, 108, 111, 135, 208, 244, 250, 292, 301, 318, 332
symbiosis, 242, 247
syndrome, 7, 12, 55, 58, 59, 116, 119, 120, 128, 235, 243, 244, 247, 285, 294, 296, 303, 332
synovitis, 90
synthesis, 161, 162
systolic blood pressure, 348
systolic pressure, 84
tamoxifen, 322
team members, 13
team, 96
technetium, 320
technical support, 6
technician, 146, 147, 148
technology, 41, 98, 193, 238, 292, 356, 372, 373, 406
teflon, 52, 62
temperature, 10, 315
tension, 316, 319
testing, 16, 84, 87, 104, 190, 236, 262
TGF, 153, 353, 354, 355, 360, 367
therapeutic agents, 356
thoracentesis, 318, 320
thoracotomy, 320
thrombin, 191, 223, 224, 225, 272, 310, 311
thrombocytopenia, 260, 265
thrombolytic therapy, 213, 283
thrombophlebitis, 236
thyroid, 22
TNF, 362
tobacco, 186
topical antibiotics, 234
tourniquet, 9, 10, 32, 33, 73, 74, 85, 134, 143, 173, 177
toxicity, 90, 121, 262, 263, 272, 372
TPA, 156
tracks, 323
training, 6, 51, 53, 54, 56, 57, 61, 64, 86, 98, 107, 130, 147, 195, 201, 204, 316, 369
training programs, 107
transcatheter, 117, 240, 286
transcription factors, 165, 352
transducer, 134
index

transforming growth factor, 153, 360
transfusion, 334, 337
transmission, 123, 124
transplant, 13, 14, 128, 146
transplantation, 4, 18, 62, 63, 64, 322, 378, 379
trauma, 132, 221, 222, 232, 237, 246, 268, 293, 356, 367, 386, 387
tumor, 132, 162, 165, 380

U

UK, 86, 156, 161, 373
ultrasonography, 3, 9, 28, 31, 32, 33, 34, 35, 38, 92, 180, 247
tumor, 132, 162, 165, 380

V

valve, 20, 232, 245, 278, 298
vancomycin, 235, 263, 325, 326
variables, 10, 38, 40, 153, 377, 378
vascular diseases, 185
vascular surgeon, 58, 96, 212, 299
vascular surgery, 64, 168, 181, 358
vascular system, 310
vascular wall, 221
vasculature, 32, 33, 34, 38, 121, 243, 251, 268, 269, 374
vasoconstriction, 9, 20
vasodilation, 355, 374
venipuncture, 52, 62, 202, 249
venography, 32, 40, 93, 248, 249, 251
vertebrae, 23
vessels, 6, 7, 9, 10, 11, 14, 19, 31, 34, 38, 68, 93, 99, 122, 127, 129, 130, 134, 146, 164, 204, 237, 307, 334, 335
viscera, 320
viscosity, 175
vitamin D, 116
vitamin K, 161

W

water, 8, 9, 104, 108, 109, 369
weakness, 118, 222, 316, 318
weight gain, 316
weight loss, 316
withdrawal, 9, 100, 103, 161, 233
wound healing, 57, 75
wound infection, 224

Y

yin-yang, 138
young adults, 130