Measuring Cerebral Blood Flow in Moyamoya Angiopathy by Quantitative Magnetic Resonance Angiography Noninvasive Optimal Vessel Analysis

BACKGROUND: Moyamoya disease causes progressive occlusion of the supraclinoidal internal carotid artery, and middle, anterior, and less frequently the posterior cerebral arteries, carrying the risk of stroke. Blood flow is often partially reconstituted by compensatory moyamoya collaterals and sometimes the posterior circulation. Cerebral revascularization can further augment blood flow. These changes to blood flow within the cerebral vessels, however, are not well characterized.

OBJECTIVE: To evaluate blood flow changes resulting from the disease process and revascularization surgery using quantitative magnetic resonance angiography with noninvasive optimal vessel analysis (NOVA).

METHOD: We retrospectively analyzed 190 preoperative and postoperative imaging scans in 66 moyamoya patients after revascularization surgery. Images were analyzed for blood flow using NOVA and compared with preoperative angiographic staging and postoperative blood flow. Blood flow rates within superficial temporal artery grafts were compared based on angiographic evidence of patency.

RESULTS: Diseased vessels had lower blood flow, correlating with angiographic staging. Flow in posterior cerebral and basilar arteries increased with disease severity, particularly when both the anterior and middle cerebral arteries were occluded. Basilar artery flow and ipsilateral internal carotid artery flow decreased after surgery. Flow rates were different between angiographically robust and poor direct bypass grafts, as well as between robust and patent grafts.

CONCLUSIONS: Preoperative changes in cerebral vessel flow as measured by NOVA correlated with angiographic disease progression. NOVA demonstrated that preoperative augmentation of the posterior circulation decreased after surgery. This report is the first to quantify the shift in collateral supply from the posterior circulation to the bypass graft.

KEY WORDS: Cerebral blood flow, Moyamoya disease, Noninvasive optimal vessel analysis (NOVA), Quantitative MRI (QMRA)

Moyamoya disease causes stenosis and occlusion of the supraclinoid internal carotid arteries (ICAs) along with the anterior and middle cerebral arteries (ACAs and MCAs) and, in some cases, also the posterior cerebral arteries (PCAs).1,2 Cerebral revascularization in moyamoya has been shown to prevent strokes.3-6 The indication for surgery in ischemic patients is currently based on symptomatology correlating with anatomic and hemodynamic changes on preoperative studies. It is unclear how revascularization surgery affects the compensatory collateral arterial supply that develops during the natural
course of the disease. Acquiring additional information on blood flow patterns within the circle of Willis (COW) and the MCAs may further help choose patients for surgery and understand the effect of direct bypass surgery on flow distribution. Here we provide the first report correlating the pattern of preoperative blood flow observed in moyamoya patients to the angiographic severity of disease, as well as blood flow changes measured after direct cerebral revascularization using noninvasive optimal vessel analysis (NOVA).

METHODS

Patient Selection
We retrospectively reviewed, with Institutional Review Board approval, data from 88 moyamoya patients who underwent cerebral revascularization surgery over a 3-year period from 2008 to 2010. A total of 220 (102 preoperative and 118 postoperative) quantitative magnetic resonance angiography (QMRA) scans were performed with corresponding preoperative cerebral angiograms. The preoperative scan closest to time of surgery was used for the preoperative flow analysis, and the first postoperative scan at 6 months postsurgery was used for the comparison.

We excluded patients with angiographic evidence of posterior circulation disease and those whose posterior circulation was not fully evaluated. As a result, 22 patients with 30 scans were excluded from analyses except for the evaluation of postoperative bypass patency. Statistical analysis was therefore performed on 66 patients for staging comparison. Both preoperative and postoperative scans were available for paired statistics in 56 of the 66 patients.

Blood Flow Quantification Using QMRA
All patients were imaged at 3.0 T (General Electric, Milwaukee, Wisconsin), and the volume flow measurements were calculated using the commercially available Non-Invasive Optimal Vessel Analysis (NOVA) software (VasSol, Inc., Chicago, Illinois) on a separate workstation. The protocol utilized standard 3-dimensional (3-D) time-of-flight (TOF) MRA of the cranial vasculature, as described by Zhao et al. The acquired TOF images were transmitted to a workstation where rotating 3-D surface-rendered vascular images were reconstructed using a marching-cube algorithm. Optimal perpendicular scan plane determination was based on the scan line calculated by a line-fitting algorithm introduced by Zhao et al.. The coordinates obtained specify the Segmentalinvolvement of the ICA with additional magnetic resonance angiography (QMRA) scans were performed with corresponding preoperative cerebral angiograms. The preoperative scan closest to time of surgery was used for the preoperative flow analysis, and the first postoperative scan at 6 months postsurgery was used for the comparison.

We excluded patients with angiographic evidence of posterior circulation disease and those whose posterior circulation was not fully evaluated. As a result, 22 patients with 30 scans were excluded from analyses except for the evaluation of postoperative bypass patency. Statistical analysis was therefore performed on 66 patients for staging comparison. Both preoperative and postoperative scans were available for paired statistics in 56 of the 66 patients.

Blood Flow Quantification Using QMRA
All patients were imaged at 3.0 T (General Electric, Milwaukee, Wisconsin), and the volume flow measurements were calculated using the commercially available Non-Invasive Optimal Vessel Analysis (NOVA) software (VasSol, Inc., Chicago, Illinois) on a separate workstation. The protocol utilized standard 3-dimensional (3-D) time-of-flight (TOF) MRA of the cranial vasculature, as described by Zhao et al. The acquired TOF images were transmitted to a workstation where rotating 3-D surface-rendered vascular images were reconstructed using a marching-cube algorithm. Optimal perpendicular scan plane determination was based on the scan line calculated by a line-fitting algorithm introduced by Zhao et al.. The coordinates obtained specify the position of an oblique fast 2-dimensional (2-D) phase contrast sequence, which was then performed based on these coordinates, using a retrospectively gated 2-D phase-contrast sequence with the following imaging parameters: Repetition time (TR), 10 to 15 ms; echo time (TE), 4 to 7 ms; flip angle, 15; number of excitations, 4; section thickness, 5 mm for neck vessels and 3 mm for intracranial vessels; field-of-view (FOV), 180 mm for neck vessels and 140 mm for intracranial vessels; and matrix, 256_128 for neck vessels and 256_192 for intracranial vessels. Velocity encoding was automatically adjusted with the NOVA software, if necessary. The acquired phase-contrast images were transferred to the NOVA workstation for flow quantification. Regions of interest (ROI) were placed on the phase-contrast images and also displayed in the 3-D surface-rendered image for vessel verification. The vessel borders over a cardiac cycle were automatically extracted and displayed on the color-coded and magnified ROI image for vessel border verification. The velocities at all of the pixels inside the vessel border were then integrated to calculate the flow in milliliters per minute. The flows were averaged over a cardiac cycle to obtain the mean flow for each vessel.

The ROI were placed on all visible intracranial vessels, including the ICA, ACA, MCA, PCA, and basilar artery (BA), as well as on the proximal superficial temporal artery (STA). For bypass evaluation, the ROI were placed on the distal STA. Quality control of all NOVA scans, including ROI placements, was performed by 2 of the authors (NK and LO).

Preoperative Angiographic Staging of Disease
In order to systematically correlate flow changes in individual vessels on QMRA with angiographic severity of disease, a staging system was applied in which progression of disease is graded (0-4) in a simplified manner according to changes in the ICA, ACA, and MCA (Table 1). Stage 0 or normal represents no disease present in the ICA, ACA, or MCA. In all patients with unilateral disease the “nonaffected” side was considered to be stage 0, ie, normal.

Cerebral Revascularization Procedure
All the patients included in this study underwent a direct STA–MCA bypass, ie, a direct anastomosis was performed between a branch of the STA to a distal M4 branch of the MCA. There was no indirect revascularization performed separately or additionally. However, over time the cuff of vascular tissue surrounding the dissected STA, which is placed in contact with the underlying brain surface, develops additional indirect collaterals to the brain.

Evaluation of Postoperative Angiograms for STA–MCA Graft Patency
Based on angiograms performed 6 months to 1 year postoperatively, bypass grafts were described as poor, patent, or robust. Poor grafts were those where the STA alone could be faintly visualized proximally in its extra- and intracranial course without direct filling of the MCA territories through it. In these cases, distal cortical filling was mainly through the indirect component of the revascularization procedure. A patent graft showed a good distal arterial filling without an increase in size of the STA, whereas a robust graft displayed a clear increase in the size of the donor

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Normal (no stenosis/occlusion of ICA, ACA, MCA)</td>
</tr>
<tr>
<td>Stage 1</td>
<td>Focal intracranial stenosis of the ICA</td>
</tr>
<tr>
<td>Stage 2</td>
<td>Segmental involvement of the ICA with additional stenosis/occlusion of the ACA, MCA with or without MM collateral</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Occlusion of A1 and M1</td>
</tr>
<tr>
<td>Stage 4</td>
<td>Occlusion of the supraclinoid carotid with continued filling to the level of ophthalmic artery</td>
</tr>
</tbody>
</table>

ACA, anterior cerebral artery; ICA, internal carotid artery; MCA, middle cerebral artery; MM, moyamoya.

TABLE 1. Stage 0 to Stage 4 Disease Progression Angiographic Staging of Disease for the Anterior Circulation. Changes and Progression of Disease From Stenosis to Occlusion in the ICA, ACA, and MCA are Graded From 0 to 4.
STA with more MCA territory filling distally on postoperative external carotid injections.

Statistical Analyses

All statistical analyses were performed using SPSS Version 20.0 (IBM, Armonk, New York) with the a priori significance level $\alpha = 0.05$. Blood flow within the intracranial vessels was compared across categories of disease stage, while flow within bypass grafts was compared across levels of angiographic patency (ie, poor, patent, or robust), each using the Kruskal–Wallis test for independent samples with pairwise comparisons.

RESULTS

A total of 220 QMRA scans were performed on 88 moyamoya patients (74 females and 14 males). Median age was 37.5 (range 17-68) years. There were 45 patients with bilateral disease and 43 with unilateral disease (22 left-sided, 21 right-sided). Disease severity was categorized by the angiographic staging system as shown in Table 1. The postoperative scans from this cohort were used for analysis of bypass patency. For all other tests, 190 scans in 66 patients were included in the analysis after exclusion of patients with posterior circulation disease.

Preoperative Blood Flow and Correlation to Stage of Disease

Figure 1 shows an example of 3-D MRA images of the intracranial vessels with blood flow measurements. Blood flow was stratified by the angiographic disease stage in 66 patients as shown in Table 2.

More severe angiographic disease—defined as stage 1 to stage 4—was associated with significantly decreased flow in the ICA, MCA, and ACA, and a trend toward increased flow in the BA. This inverse change in blood flow between the anterior and

| TABLE 2. Preoperative Median Arterial Blood Flow (mL/min) Values in the ICA, ACA, MCA, PCA, and BA in Relation to Angiographic Staging of Disease (Stages 0-4) |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Stage 0 (Normal) | Stage 1 | Stage 2 | Stage 3 | Stage 4 | $P$-value |
| ICA | 352 | 213 | 188 | 155 | 26 | <.001 |
| MCA | 132 | 138 | 74 | 0 | 89 | .007 |
| ACA | 129 | 155 | 38 | 0 | 0 | .007 |
| PCA | 76 | 104 | 131 | 194 | 67 | <.001 |
| BA | 233 | 208 | 239 | 278 | 347 | .291 |

ACA, anterior cerebral artery; ICA, internal carotid artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; BA, basilar artery.
posterior circulation was more notable between stages 2 and 3, when the ICA terminus as well as the MCA and ACA become occluded. In some cases, blood flow was reversed in the A1 segment after ipsilateral M1 occlusion.

**Postoperative Blood Flow Evaluation**

Figure 2 shows an example of a postoperative 3-D MRA image and the blood flow within the intracranial vessels and the bypass (distal STA).

Figure 3 summarizes the effect of a bilateral STA–MCA bypass on the flow in the ICAs, MCAs, and BAs. Preoperative and postoperative ICA median values were 173 (range 11-626 mL/min with interquartile range 100-233 mL/min, n = 78) and 142 (range 8-393 mL/min with interquartile range 83-213 mL/min, n = 73), respectively. Preoperative and postoperative ACA median values were 30 (range 16-57 mL/min with interquartile range 20-54 mL/min, n = 5) and 212 (range 80-289 mL/min with interquartile range 85-261 mL/min, n = 5), respectively. Preoperative and postoperative MCA median values were 60 (range 26-218 mL/min with interquartile range 42-129 mL/min, n = 16) and 164 (range 82-240 mL/min with interquartile range 89-235 mL/min, n = 4), respectively. Preoperative and postoperative BA median values were 242 (range 57-517 mL/min with interquartile range 199-334 mL/min, n = 54) and 200 (range 78-443 mL/min with interquartile range 170-297 mL/min, n = 55), respectively. Blood flow was significantly different between preoperative and postoperative measurements of the ICA and BA (P < .05).

**Bypass Patency**

A significant difference in flow was seen between angiographically characterized poor (median 58 mL/min, range 19-68) and robust (114 mL/min, range 52-198) grafts (P = .036), as well as between angiographically patent (58 mL/min, range 10-186) and robust (114 mL/min, range 52-198) grafts (P = .007; Figure 4). Blood flow in the STA increased 3-fold after a well-functioning direct bypass.

**DISCUSSION**

QMRA has been used previously to define blood flow changes in intracranial arterial occlusive disease, to measure the success of neurointerventional procedures, and to assess extracranial–intracranial bypass function. One recent publication evaluated the relative contributions of direct vs indirect revascularization after combined STA–MCA and encephalo-duroarteriosynangiosis revascularization in 13 moyamoya patients (16 hemispheres), comparing angiography with QMRA and showing a change from more direct supply from the STA to an M4 branch, to more indirect supply via small collaterals arising from the STA or middle meningeal arteries to the pial brain arteries. Our study reports the first use of QMRA to evaluate quantitative blood flow and direction of blood flow within the COW in moyamoya patients.
Cerebral blood flow can be evaluated at each angiographic stage of the disease, from stenosis to occlusion, within the ICA, ACA, and MCA. While there was good correlation between the angiographic staging and QMRA data, it is important to emphasize that angiography demonstrates structural status and direction of flow or no flow, as seen during injection of the contrast within an arterial territory, ie, either anterior circulation or posterior circulation independent of each other. Collateral flow is appreciated when it is substantial and its visualization is dependent on the neuroradiologist’s technique of injection (volume of contrast injected and the force of injection).

The NOVA method provides additional physiological information through the placement of precise, 2-D scan planes oriented perpendicular to the vessel at the ROI locations selected by the radiologist or MR technologist on a rotating 3-D model of the vasculature rendered from the TOF MRA.

As the QMRA principle is not based on the diffusion of contrast, the technique can measure both the quantity and the direction of flow in the posterior communicating arteries or flow in the distal MCA where there is a proximal MCA occlusion observed on the angiogram.

A reversal of flow (negative blood flow values) can also be quantitatively measured, for example, in the ACA when the anterior communicating arteries supplied blood from the contralateral side, or in the MCA, where the vessel was reconstituted postoperatively through blood flow via the STA–MCA bypass.

This information may be complementary to assessing the cerebrovascular reserve status (obtained from cerebral blood flow studies such as single photon emission tomography (SPECT), positron emission tomography (PET), Xenon computed tomography (CT), CT perfusion, or MR perfusion) in the surgical decision-making process as well as in follow-up planning, not only in symptomatic patients with clear-cut hemodynamic compromise, but also in asymptomatic patients and/or patients with unclear symptoms and normal hemodynamic reserves.

As preoperative total blood flow in the anterior circulation decreased with more severe disease, preoperative blood flow in the

![Figure 3. Comparison of pre- and postoperative (6 months postbypass) median blood flow in the ICA, ACA, MCA, and BA using QMRA. *Significant at P < .05.](image)

![Figure 4. A, Preoperative and B, 6 months postoperative angiograms showing a robust STA–MCA graft with an increase in the postoperative size of the STA and good distal arterial filling of the MCA via the direct bypass. C, Box plots presenting flow in the postbypass STA. Solid bar in box plot is median value. Flow differences measured using QMRA were significant between the angiographically poor and patent (P = .036), as well as between the patent and robust grafts (P = .007).](image)
posterior circulation showed a trend toward increasing, consistent with previous reports in which angiography demonstrated an increase in blood supply from the posterior circulation at the time of ICA bifurcation stenosis/occlusion along with proliferation of basal moyamoya vessels fed by the PCA.\(^\text{17,18}\) It is not clear why the preoperative blood flow in the MCA increases from stage 3 (0 mL/min median flow) to stage 4 (89 mL/min median flow). However, this may be related to complete occlusion of the M1 in stage 3 in contrast to an occluded supraclinoid ICA but patent reconstituted M1 being supplied by ophthalmic and pial collaterals in stage 4.

After successful bilateral direct STA–MCA bypass, BA cerebral blood flow was decreased, likely reflecting the efficacy of direct extracranial–intracranial bypass in reducing demand on native collaterals. Similarly, ipsilateral ICA flow was decreased after bypass surgery, as the graft was now supplying the anterior circulation.

QMRA was also helpful in evaluating blood flow through the STA–MCA bypass. Observed differences even if subjective (visual assessment without actual objective measurement of the STA before and after surgery) were found in flow between poor direct bypasses, seen on angiography as either a visible STA without distal filling or distal filling supplied by the indirect component of the graft, ie, the cuff of tissue surrounding the dissected STA. There were no indirect procedures performed separately or additionally in the studied patients. In angiographically robust direct grafts, there was a subjective increase in the size of the donor STA with more MCA territory filling distally. Additionally, STA bypass flows were significantly higher in robust direct grafts (good distal arterial filling with an increase in size of the STA) compared to patent direct grafts (good distal arterial filling without an increase in size of the STA). The postoperative bypass flow values observed in our patients are much higher than previously described for non-moyamoya patients,\(^\text{14}\) likely suggesting that in moyamoya patients, where a chronically low perfusion state exists, there is a high demand for additional blood flow as compared to other arterial steno-occlusive diseases. This supports our premise that the STA can provide adequate blood flow augmentation without the necessity of a high-flow bypass.

**Limitations**

This study is limited by its retrospective nature and subjectivity of angiographic descriptions of the STA grafts, which were used for categorical comparisons. Because of the sample size, nonparametric statistical analyses were used and median values were reported. Thus, a break in the trend toward decreasing flow with worse angiographic staging in MCA vessels appears, as the median will be increased by measurement of flow in a single vessel, which could be backfilling from anterior or posterior communicating arteries.

**CONCLUSION**

Preoperative flow changes in the COW measured with NOVA correlated with angiographic severity of disease. NOVA demonstrated that preoperative augmentation of the posterior circulation was decreased by surgery. This report is the first to quantify the shift in collateral supply from the posterior circulation to the bypass graft. Whereas QMRA data contribute to our understanding of preoperative and postoperative changes in flow patterns in moyamoya patients, more clinical experience is required to determine the utility of NOVA in clinical decision making, and QMRA should not replace standard 6-vessel cerebral angiograms for the diagnosis and follow-up of moyamoya disease. However, NOVA may complement data from both angiography and hemodynamic studies, such as SPECT, PET, Xe-CT, CT perfusion, and MR perfusion to help decide which patients should undergo surgery and which patients with residual or recurrent symptoms may benefit from additional revascularization surgery.

**Disclosures**

This work was supported in part by Russell and Elizabeth Siegelman, Bernard and Ronni Lacroute, the William Randolph Hearst Foundation, Stanley and Alexis Shin, the Reddy Lee Moyamoya Fund, and the Josef Huber Family Moyamoya Fund. Dr. Ostergren is an employee of and holds financial interest in VasSol, Inc. The other authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article. Dr. Steinberg is a consultant for Peter Lazic US, Inc., Qool Therapeutics and NeuroSave.

**REFERENCES**


Acknowledgments
We thank Cindy H. Samos for manuscript and figure editing and Beth Hoyte for assistance with the figures.

COMMENTS

The authors utilized QMRA and NOVA to evaluate changes in blood flow patterns before and after bilateral STA-MCA bypasses in patients with moyamoya disease. They demonstrated a shift in blood flow from the posterior circulation to the bypass graft. This will serve as a useful armamentarium in the evaluation of patients with moyamoya disease, pre- and post-treatment. A future study examining the correlation between the amount of blood flow and stroke/hemorrhage risk will be needed to demonstrate the clinical utility of this technique.

Rose Du
Boston, Massachusetts

The authors present a retrospective study of patients with symptomatic moyamoya disease studied pre- and postoperatively using qMRA. Sixty-six patients were included in the study with pre- and postoperative evaluation compared in 56 of these patients. The authors findings show 1) Progressive diminution of flow in the affected arteries of the circle of Willis (COW) correlating with severity of disease, 2) Decreased basilar collateral flow to the anterior circulation following revascularization, and 3) Apparent correlation of bypass flow to subjective assessment of the quality of the bypass grafts. This paper is a valuable observational review with conclusions regarding flow assessment and quantitative findings that support rearrangement of intracranial flow during the various stages of moyamoya disease as well as after flow augmentation by direct STA-MCA bypass. Their observational approach using qMRA NOVA once again validates the value of NOVA studies while quantifying the changes that are subjectively seen angiographically following moyamoya revascularization. The authors should be commended for their observations and encouraged to continue to investigate ways that pre- and postoperative flow assessment might help to impact patient selection and outcome.

Erez Nossek
David J. Langer
New York, New York