Cerebral arteriovenous malformations (AVMs) are vascular abnormalities that consist of direct connections from arteries to veins through an intervening network of low resistance vessels instead of via normal capillary beds, subsequently resulting in disrupted hemodynamics.1 Despite the hemodynamic pathophysiology, current A VM characterization is largely based on anatomic features derived from digital subtraction angiography rather than on flow parameters.2,3 Furthermore, the success of endovascular embolization, a technique approved by the Food and Drug Administration to reduce blood flow in AVMs before definitive treatment with surgery, is primarily assessed by subjective assessment of angiographic findings before and after embolization.4,5 In this study, we aimed to measure cerebral AVM blood flow using quantitative magnetic resonance angiography (QMRA) and to delineate the blood flow changes that occur after embolization.

Background and Purpose—Embolization reduces flow in arteriovenous malformations (AVMs) before surgical resection, but achievement of this goal is determined subjectively from angiograms. Here, we quantify effects of embolization on AVM flow.

Methods—Records of patients who underwent AVM embolization at our institution between 2007 and 2013 and had flow rates obtained pre- and postembolization using quantitative magnetic resonance angiography were retrospectively reviewed. Total flow was estimated as aggregate flow within primary arterial feeders or flow in single draining veins.

Results—Twenty-one patients were included (mean age 35 years, 24% hemorrhagic presentation) with Spetzler–Martin grades 1 to 4. Fifty-four total embolization sessions were performed. The mean AVM flow was 403.4±262.4 mL/min at baseline, 285.3±246.4 mL/min after single session (29% drop, P<0.001), and 102.0±103.3 mL/min after all sessions of embolization (75% drop, P<0.001). Total number of pedicles embolized (P<0.001) and embolization of an intranidal fistula during any session (P=0.002) were significantly associated with total decreased flow postembolization. On multivariate analysis, total pedicles embolized was predictive of total flow drop (P<0.001). However, pedicles embolized per session did not correlate with flow drop related to that session (P=0.44).

Conclusions—AVM flow changes after embolization can be measured using quantitative magnetic resonance angiography. The total number of pedicles embolized after multiple embolization sessions was predictive of final flow, indicating this parameter is the best angiographic marker of a hemodynamically successful intervention. The number of pedicles embolized per session, however, did not correlate with flow drop in that session, likely because of flow redistribution after partial embolization. (Stroke. 2015;46:942-947. DOI: 10.1161/STROKEAHA.114.008569.)

Key Words: arteriovenous malformation ■ cerebral ■ embolization ■ flow ■ hemodynamics ■ magnetic resonance angiography

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Methods

Patient Selection

After institutional review board approval, clinical data for all patients with a cerebral AVM who underwent QMRA at our institution between 2007 and 2013 were collected and reviewed (n=75). Patients who underwent embolization (n=33) and had flow rates obtained both pre- and postembolization using QMRA were included (n=21). Among these 21 patients, 1 patient had an external carotid artery feeder not measurable using QMRA and was therefore excluded from flow analyses. Out of the 21 patients, 17 patients subsequently had surgical resection of their AVM and 11 of these had flow rates measured after surgery. Of the 4 patients who did not have surgery, 1 patient was cured with embolization, another patient underwent radiosurgery, 1 patient refused surgery, and the last patient failed provocative testing with selective Amobarbital injection, and no curative treatment was offered.

Embolization Technique

All sessions of embolization were performed with the liquid embolic agent N-BCA (N-butyl cyanoacrylate; Codman Neurovascular, Inc,
Raynham, MA) at a concentration of 20% to 66% depending on the flow within each pedicle, except 3 sessions performed with Onyx (ethylene-vinyl alcohol copolymer; ev3, Irvine, CA), using standard flow-directed microcatheters, such as the Magic microcatheter (Balt Extrusion, Montmorency, France) and dimethyl sulfoxide-compatible Marathon microcatheter (ev3, Irvine, CA). During each session, pedicles were embolized according to the following algorithm: high-flow intranidal fistulae first, then deep arterial feeders, and superficial arterial feeders last. A fistula was defined as a direct connection between an arterial feeder and draining vein without interposition of the nidus and was demonstrated by the microcatheter traversing directly into the vein. Extent of embolization per session was at the discretion of the neuroendovascular surgeon and was determined primarily by degree of subjective angiographic blood flow reduction. Embolization of feeder vessels derived from >1 principal artery (anterior, middle, and posterior cerebral arteries) was sometimes performed in any given session.

**Blood Flow Measurements**

All patients in this study underwent quantitative flow measurements of the extracranial and intracranial arteries and veins using QMRA before and 2 days after AVM embolization/surgery. This technique of blood flow quantification by QMRA has been described previously by Zhao et al. Specifically, all subjects underwent phase contrast QMRA performed on a 1.5 Tesla or 3.0 Tesla magnetic resonance imaging (MRI) system (Sigma VH1, GE Medical system, Milwaukee, WI) using a 4-channel neurovascular coil. The volume flow rate measurements were acquired with the noninvasive optimal voxel analysis (NOVA) software (VasSol, Inc, River Forest, IL). A three-dimensional (3D) MRA time-of-flight of the head was obtained with the following parameters: TR/TE, 23/3.3 ms; flip angle, 20; field of view, 220 mm; section thickness, 1 mm; matrix, 512x256. MRA time-of-flight images were received by the NOVA software on a separate workstation to reconstruct a 3D surface-rendering of the vasculature for determining the perpendicular scan plane to vessels of interest. Volume flow measurements based on these positions were performed (TR, 10–15 ms; TE, 4–7 ms; flip angle, 15; number of excitations, 4; slice thickness, 3 mm for intracranial arteries and 5 mm for neck arteries; field of view, 140 mm for intracranial arteries and 180 mm for neck arteries; matrix, 256x192 for intracranial arteries and 256x128 for neck arteries). Velocity encoding was automatically adjusted by the NOVA software. All QMRA flow measurements were performed using an oblique 2D fast phase contrast sequence with retrospective gating. Volumetric flow rate (mL/min) in each artery was processed on the NOVA workstation after phase contrast images had been acquired. This QMRA technique has been validated using in vitro and in vivo models and has demonstrated utility in the hemodynamic evaluation of cerebrovascular pathologies and interventions, including extracranial carotid artery stenosis, intracranial angioplasty/stenting, carotid endarterectomy, and extracranial-intracranial bypass.

Total AVM blood flow was derived based on the aggregate flow within the primary arterial feeders relative to flow in their contralateral counterparts, according to the following equation:

\[
\{ \text{Ipsilateral A2 segment + middle cerebral artery} \} + \text{posterior cerebral artery} \\
\{ \text{Contralateral A2 segment + middle cerebral artery} \} + \text{posterior cerebral artery}
\]

Alternatively, flow was measured from single draining veins where possible.

**Statistical Analysis**

Mean flows before and after embolization/surgery were compared using the paired 2-tailed Student’s t test. Univariate analysis to assess the relationship between number of pedicles embolized and change in flow after embolization was performed with linear regression analysis. Multivariate regression analysis was then used to determine the effect of covariates showing significance of \( P < 0.05 \) on univariate analysis. All analyses were performed with SPSS (Version 22; IBM, Inc).

**Results**

**Patient Characteristics**

The mean age of the cohort (n=21) was 35 years. 24% of patients presented with hemorrhage. 10% of AVMs were Spetzler–Martin grade 1, 43% grade 2, 33% grade 3, and 14% grade 4. The mean volume of these AVMs was 10.2 mL (range 1.4 mL-29.8 mL, median 5.9 mL). There were no complications after any of the embolization sessions. Patient characteristics, AVM features, and blood flows are outlined in Table 1.

**AVM Blood Flow Before and After Embolization**

Mean AVM flow in this study was 403.4±262.4 mL/min before any treatment. Baseline AVM flow was significantly associated with AVM volume (\( R^2=0.30, P=0.01 \)). After a single embolization session, mean AVM flow decreased significantly to 285.3±246.4 mL/min (29% flow drop, \( P<0.001 \), range of 10% increase to 95% decrease). Following completion of all embolization sessions, mean AVM flow (102±103.3 mL/min) was significantly lower than baseline (75% flow drop, \( P<0.001 \); Figure 1). If an intranidal fistula was embolized during any session, mean AVM flow dropped on average by 36% (161.5±149.8 mL/min, n=17).

Eight patients each underwent 4 embolization sessions, and baseline AVM flow among these patients was 624.0±229.9 mL/min. Mean AVM flow dropped to 512.0±188.6 mL/min after the first session, 391.3±163.1 mL/min after the second session, 309.9±154.6 mL/min after the third session, and 131.0±142.1 mL/min after the fourth session (Figure 2).

Changes in AVM flow for all 21 patients after all embolization sessions performed are shown in Figure 3. In one patient (patient number 5), AVM flow did not drop below baseline.

<table>
<thead>
<tr>
<th>Table 1. Summary of Patient Characteristics, AVM Features, and Blood Flow</th>
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<tbody>
<tr>
<td>Patients (n=21)</td>
</tr>
<tr>
<td>Male, %</td>
</tr>
<tr>
<td>Mean age, years (range)</td>
</tr>
<tr>
<td>Hemorrhagic presentation, %</td>
</tr>
<tr>
<td>AVM characteristics</td>
</tr>
<tr>
<td>Spetzler–Martin grade (% of cohort)</td>
</tr>
<tr>
<td>2 (43)</td>
</tr>
<tr>
<td>3 (33)</td>
</tr>
<tr>
<td>4 (14)</td>
</tr>
<tr>
<td>Deep venous drainage, %</td>
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<tr>
<td>Volume, mL (range)</td>
</tr>
<tr>
<td>Blood flow</td>
</tr>
<tr>
<td>Baseline mean flow, mL/min</td>
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<tr>
<td>Mean flow after single session, mL/min</td>
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<tr>
<td>Mean flow after all sessions, mL/min</td>
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</tbody>
</table>

AVM indicates arteriovenous malformations.
flow over 4 embolization sessions but was redistributed. Review of this patient’s angiogram at the completion of all embolization sessions demonstrated a small amount of Onyx mainly within feeder arteries rather than in the nidus. Thus, the flow was redistributed into the nidus through collateral pial feeders with maintenance of the same flow within the AVM nidus. Another patient (patient number 9) with an AVM (feeders from the internal and external carotid arteries) had erroneously increased measured flow (within the internal carotid artery feeders) after embolization of an external carotid artery feeder because flow in the external feeder was not measured at baseline using QMRA. Consequently, embolization of the external feeder resulted in redistribution within the nidus and increase measured flow from the internal carotid artery feeders. The data from this patient was not used for the rest of the statistical analysis.

**Predictors of Decreased AVM Blood Flow After Embolization**

A total of 54 sessions of embolization were performed (mean 2.6 sessions per patient, range 1–6). The mean number of pedicles embolized per session was 3 (range 1–8) and the mean total number of pedicles embolized was 8 (range 1–17). The total number of pedicles embolized was related to AVM size ($\rho=+0.60, P=0.004$). Linear regression analysis showed that neither the number of pedicles embolized per session ($R^2=0.03, P=0.44$) nor embolization of an intranidal fistula ($R^2=0.03, P=0.45$) is significantly correlated with decreased AVM flow per session (Table 2). However, the total number of pedicles embolized ($R^2=0.64, P<0.001$) and embolization of an intranidal fistula ($R^2=0.40, P=0.002$) are each significantly associated with total decreased AVM flow after completion of all sessions of embolization. Multivariate analysis demonstrated that total number of pedicles embolized ($P<0.001$), but not occlusion of an intranidal fistula ($P=0.06$), remains predictive of the total AVM blood flow drop after all sessions of embolization.

**AVM Blood Flow Before and After Surgery**

Of the 21 patients who underwent AVM embolization, 17 patients subsequently underwent surgical resection of their AVM. Eleven patients had flow rates obtained before and after surgery. Among these patients, mean AVM flow was $102.7\pm126.4$ mL/min before surgery. After surgery, mean ipsilateral hemisphere flow was on average $51.2$ mL/min less than the contralateral hemisphere ($P=0.004$). All patients underwent immediate postoperative digital subtraction angiography that demonstrated complete AVM resection without a nidus remnant or early draining vein.
Discussion

The characterization of cerebral AVM hemodynamics is of significant interest in the evaluation and management of AVMs. In their seminal work, Lindegaard et al used transcranial Doppler ultrasound to demonstrate high flow velocities within AVM feeder arteries and concomitant low perfusion pressure in areas of brain adjacent to the AVM responsible for steal phenomena. More recently, Kaspera et al used transcranial color-coded Doppler to examine AVM flow after staged embolization. They found that although flow velocity decreased significantly (P<0.01) within embolized vessels, this flow drop did not correlate with the extent of AVM volume reduction after a single embolization session, which they attributed to redistribution of AVM blood flow through newly recruited feeders. Ultrasound, however, remains a highly operator-dependent imaging modality with poor anatomic resolution, allowing only a rudimentary ability to correlate AVM flow with angioarchitecture.

Cerebral AVM hemodynamics has also been assessed with 4-dimensional (4D) flow magnetic resonance imaging and time-resolved spin-labeled MRA. In the largest of these studies, Ansari et al evaluated flows in 20 patients, 4 of whom underwent staged embolization with the liquid embolic material Onyx. They showed that higher Spetzler–Martin grade corresponded to increased venous rather than arterial velocities. Additionally, in the postembolization subgroup, 4D flow magnetic resonance imaging revealed successively more compact AVMs with flows redistributed within the feeder arteries. Further analysis of the determinants of changes in AVM flow after embolization, though, was lacking in their study.

Our study is the first to directly measure cerebral AVM blood flow before and after embolization using QMRA, a technique that has been validated using in vitro and in vivo models and has demonstrated utility in the hemodynamic evaluation of cerebrovascular pathologies and interventions. We found that mean flow dropped on average by 29% after a single embolization session and by 75% at the end of all embolization sessions. Interestingly, the drop in flow per session did not correspond to occlusion of an intranidal fistula or the number of pedicles embolized in that single session, suggesting redistribution of flow through remaining

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Univariate Analysis P Value</th>
<th>Multivariate Analysis P Value</th>
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<tbody>
<tr>
<td>Pedicles embolized, per session</td>
<td>0.44</td>
<td></td>
</tr>
<tr>
<td>Intranidal fistula occluded, per session</td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td>Pedicles embolized, total</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intranidal fistula occluded, total</td>
<td>0.002</td>
<td>0.06</td>
</tr>
</tbody>
</table>

AVM indicates arteriovenous malformations.

Table 2. Predictors of Decreased AVM Blood Flow After Embolization

Figure 4. Illustrative case. A, Baseline and sequential angiograms after partial embolization of occipital arteriovenous malformations (AVM) with N-butyl cyanoacrylate (N-BCA). B, Corresponding quantitative magnetic resonance angiography (QMRA) flow maps at baseline and postembolization showing sequential drop in flow within the left PCA AVM feeder artery.
compartments of the nidus in the setting of partial embolization, as posited by Kaspera et al. On the other hand, mean flow after completion of all embolization sessions correlated with both the total number of pedicles embolized and embolization of a high-flow fistula, with total pedicles embolized remaining predictive in the multivariate analysis.

Overall, our findings further clarify the hemodynamics of cerebral AVMs and quantify the effect of AVM embolization. We showed that AVM flow decreases substantially after embolization, and this flow drop is most closely related to the total number of pedicles embolized. The total number of pedicles embolized, then, may be the best angiographic correlate of decreased AVM flow after completion of embolization, rather than number of pedicles embolized per session or occlusion of an intranidal fistula during a single session. Nonetheless, the ability to directly measure AVM flow with QMRA can help establish flow parameters to guide AVM therapeutic decision-making and enhance the precision of endovascular embolization.

Our aim with preoperative AVM embolization was to achieve AVM blood flow reduction to minimize perioperative surgical risk because reduced operative time and intraoperative blood loss have been previously correlated with preoperative embolization of AVMs. Moreover, the staged management of AVMs is thought to elicit step-wise changes in cerebral hemodynamics that circumvent the risk of normal perfusion pressure breakthrough associated with abrupt AVM obliteration and resection. More recently published case series on pressure breakthrough associated with abrupt A VM obliteration have been previously correlated with preoperative embolization with Onyx, though, have shown its safety and efficacy even when more aggressive embolization strategies are used. Although the extent of embolization in our patients was not determined by flow reduction measured on QMRA, our results showed a progressive decrease in AVM flow after multiple embolization sessions without any increased attendant risks of embolization (Figures 2-4). In fact, the hemorrhagic and overall complication rates associated with embolization in our patient cohort was zero. These insights may further guide future approaches to the degree of preoperative embolization, indicating when sufficient flow reduction has been achieved and embolization should be stopped or suggesting continued embolization until flow is adequately reduced.

The main potential shortcoming of this study is its generalizability. Specifically, all 54 embolization sessions were performed with N-BCA, except 3 with Onyx, and so it remains unclear if the use of Onyx, which varies in its thrombogenicity and penetration compared with N-BCA, would result in different changes in AVM flow. Interpretation of our data may also be limited by its small sample size, although it is the first publication on AVM flow before and after embolization assessed using QMRA. Potential variability in the data reflects the fact that blood flow is a physiological parameter. Relative flow (ipsilateral minus contralateral hemisphere flow) was used in an attempt to control for confounders, such as age, heart rate, and blood pressure.

Conclusions
After a single session of embolization, AVM flow decreased by 29% on average, and after all sessions were completed, flow dropped by 75%. Total number of pedicles embolized was the factor most significantly associated with final decreased flow, indicating that this parameter is the best angiographic marker of a hemodynamically successful intervention. However, the number of pedicles embolized per session did not correlate with drop in flow per session, which is likely because of rechanneling of flow through residual parts of the nidus after the initial sessions of partial embolization. AVM flow alterations induced by embolization can be quantified with QMRA and may provide a more robust strategy to determine the number and efficacy of embolization sessions.

Disclosures
Dr Alaraj received research grant from National Institute of Health (NIH) and he was consultant at Cordis-Codman. Dr Aletich received research grant from Micrus and was consultant at Cordis-Codman. Dr Amin-Hanjani received research grant from NIH. She also received research support (no direct funds) from GE Healthcare, VasSol Inc. Dr Charbel had ownership interest from VasSol Inc and was consultant at Transonic.

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Quantitative Assessment of Changes in Cerebral Arteriovenous Malformation
Hemodynamics After Embolization
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