Changes in Wall Shear Stress of Cerebral Arteriovenous Malformation Feeder Arteries After Embolization and Surgery

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Background and Purpose—Wall shear stress (WSS) has been implicated as an important stimulus for vascular remodeling. The purpose of this study is to measure WSS in AVM arterial feeders using quantitative magnetic resonance angiography pre- and post-embolization/surgery.

Methods—Records of patients who underwent AVM embolization and surgical resection at our institution between 2007 and 2013 were collected and reviewed (n=75). Among these 21 patients, 1 patient had an external carotid artery feeder not measurable using QMRA and was therefore excluded from WSS 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 so no curative treatment was offered.

Results—Twenty-one patients were included (mean age 34 years, 19% hemorrhagic presentation), with Spetzler–Martin grades 1 to 4. WSS, blood flow, and vessel diameter were assessed in a total of 51 feeder arteries. At baseline, mean WSS was significantly higher compared with the contralateral vessel (29.7±12.0 dynes/cm² versus 23.3±11.0 dynes/cm²; P=0.007). After embolization (23.0 dynes/cm² versus 22.5 dynes/cm²; P=0.78) and surgery (17.9 dynes/cm² versus 23.2 dynes/cm²; P=0.09), WSS was not significantly different than in the contralateral vessel. Reduced WSS post-embolization corresponded to significantly decreased flow (338.1 mL/min versus 170.5 mL/min; P<0.001) and smaller vessel diameter (3.7 mm versus 3.5 mm; P=0.01).

Conclusions—Enlargement of cerebral AVM arterial feeders is insufficient to compensate for increased blood flow, creating high WSS. After treatment, flow diminishes and so WSS and vessel diameter concomitantly decrease. Thus, WSS plays a pivotal role in vascular remodeling that may be exploited to monitor AVM response to treatment or understand other high-flow vascular pathologies. (Stroke. 2015;46:1216-1220. DOI: 10.1161/STROKEAHA.115.008836.)

Key Words: arteriovenous malformation ■ cerebral ■ embolization ■ magnetic resonance angiography ■ shear stress

Cerebral arteriovenous malformations (AVMs) are vascular abnormalities consisting of direct connections from arteries to veins through an intervening network of low resistance vessels called the nidus, rather than through normal capillary beds, thereby resulting in altered hemodynamics.1 These disrupted hemodynamics are manifested by dilated feeder arteries, feeder or intranidal aneurysms, venous ectasia, and steal phenomena. Moreover, cerebral AVMs are dynamic lesions with arterial feeders that are known to enlarge over time and to decrease in caliber after AVM resection.2–3 Wall shear stress (WSS) has been implicated as an important biomechanical stimulus for vascular remodeling, but its association with cerebral AVMs is unclear.4 Here, we measure WSS in cerebral AVMs using quantitative magnetic resonance angiography (QMRA) before and after treatment with embolization and surgery.

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 WSS, flow rates, and vessel diameter obtained pre- and post-treatment 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 WSS 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 so no curative treatment was offered.

Embolization Technique
All sessions of embolization were performed with the liquid embolic agent 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 of embolization, selective Amobarbital injection, and so no curative treatment was offered.
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.1 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.

Blood Flow and Vessel Diameter Measurements
All patients in this study underwent quantitative vessel flow and size measurements of the extracranial and intracranial arteries 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 and validated in a canine model.6,7 Specifically, all subjects underwent phase contrast QMRA performed on a 1.5 Tesla or 3.0 Tesla magnetic resonance 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 vessel 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; FOV, 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; NEX, 4; slice thickness, 3 mm for intracranial arteries and 5 mm for neck arteries; FOV, 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. The technique is currently used in the clinical setting with the commercially available NOVA software. Flow and diameter of proximal feeder vessels (anterior cerebral artery, A2 segment; middle cerebral artery, M1 segment; and posterior cerebral artery, P2 segment) and their contralateral counterparts (anterior cerebral artery, A2 segment; middle cerebral artery, M1 segment; and posterior cerebral artery, P2 segment) were obtained.

WSS Calculation
Once blood flow and vessel diameter were measured, WSS was calculated using the Hagen–Poiseuille equation: \[ \text{WSS} = \frac{4 \times Q}{\pi D^2} \]

WSS is in dynes/cm², \( Q \) is the volumetric flow rate in mL/s, and \( D \) is the vessel diameter in cm. \( \mu \) is the blood viscosity in poise and was assumed to be constant (0.035 poise). This method was previously described by Zhao et al.5

Statistical Analysis
Mean WSS, flow, and diameter before and after completion of treatment were compared using the paired 2-tailed Student’s t test. Exponential regression analysis was used to assess the relationship between WSS, blood flow, and vessel diameter before and after treatment. All analyses were performed with SPSS (Version 22; IBM, Inc).

Results
Patient Characteristics
The mean age of the cohort (n=21) was 34 years. 19% 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 11.2 mL (median 6.4 mL, range 1.4–29.8 mL). WSS, blood flow, and vessel diameter were assessed in a total of 51 feeder arteries, including 31 embolized feeders. There were no complications after any of the embolization sessions (n=54). Patient characteristics, AVM features, and feeder artery WSS are outlined in Table.

Baseline AVM WSS
Mean WSS assessed in 48 feeder arteries in this study was 29.7±12.0 dynes/cm² (median 29.9 dynes/cm², range 7.7–58.9 dynes/cm²) before any treatment, which was significantly higher (\( P=0.007 \)) compared with the mean WSS in the contralateral vessel 23.3±11.0 dynes/cm² (median 22.1 dynes/cm², range 2.1–67.4 dynes/cm²). Mean baseline flow in the feeder arteries was 301.4±241.2 mL/min (median 245.0 mL/min, range 45–1175 mL/min) versus 151.8±67.7 mL/min (median 152.0 mL/min, range 46–315 mL/min) in the contralateral vessel (\( P<0.001 \)). Mean diameter of these feeder vessels was 3.7±0.7 mm (median 3.7 mm, range 2.5–6 mm) compared with 3.1±0.6 mm (median 3.1 mm, range 1.9–4.8 mm) in their contralateral counterparts (\( P<0.001 \)). Using exponential regression analysis, we found that larger feeder arteries had significantly higher flow rates (\( R^2=0.68, P<0.001 \)).

WSS, Blood Flow, and Vessel Diameter Before and After Embolization
Before embolization, mean WSS analyzed in 31 feeder arteries was significantly higher than in the contralateral vessel

| Table. Summary of Patient Characteristics, AVM Features, and WSS |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Patients (n=21) | Male, % | 67 | Male, % | 67 |
| Mean age, years (range) | 34 (16–60) | 19 | Mean age, years (range) | 34 (16–60) |
| Hemorrhagic presentation, % | 19 | Hemorrhagic presentation, % | 19 |
| AVM characteristics | Spetzler–Martin grade (% of cohort) | 1 (10) | Spetzler–Martin grade (% of cohort) | 1 (10) |
| | Volume, mL (range) | 11.2 (1.4–29.8) | Volume, mL (range) | 11.2 (1.4–29.8) |
| | Feeder artery type, % | A2 (26) | Feeder artery type, % | A2 (26) |
| | P2 (30) | P2 (30) |
| | Feeder aneurysm present (% of feeder arteries) | 4 | Feeder aneurysm present (% of feeder arteries) | 4 |
| Wall shear stress | Baseline mean WSS, dynes/cm² (range) | 29.7 (7.7–58.9) | Baseline mean WSS, dynes/cm² (range) | 29.7 (7.7–58.9) |
| | Mean WSS after embolization, dynes/cm² (range) | 23.0 (2.7–42.4) | Mean WSS after embolization, dynes/cm² (range) | 23.0 (2.7–42.4) |
| | Mean WSS after surgery, dynes/cm² (range) | 17.9 (4.8–52.4) | Mean WSS after surgery, dynes/cm² (range) | 17.9 (4.8–52.4) |

AVM indicates arteriovenous malformations; and WSS, wall shear stress.
(32.6±12.0 dynes/cm² versus 22.7±12.6 dynes/cm²; P=0.003). After all embolization sessions were performed (total of 54 sessions, mean 2.6 sessions per patient, range 1–6 sessions), WSS in the feeder artery was significantly lower than in pre-embolization (23.0±9.4 dynes/cm² versus 32.6±12.0 dynes/cm², P<0.001) and decreased to nearly match the WSS of the contralateral vessel (23.0±9.4 dynes/cm² versus 22.5±9.6 dynes/cm², P=0.78; Figure 1).

Exponential regression analysis showed that higher flows were significantly associated with larger vessel diameter before (R²=0.73, P<0.001) and after embolization (R²=0.43, P<0.001), as well as demonstrated the drop in WSS after embolization (Figure 2). Decreased WSS post-embolization corresponded to the significant decrease in mean flow (338.1±219.1 mL/min versus 170.3±94.8 mL/min; P<0.001) and mean diameter (3.7±0.6 mm versus 3.5±0.5 mm; P=0.01) of the feeder vessels. Additionally, exponential regression revealed that a greater decrease in flow post-embolization corresponded to shrinking of AVM arterial feeders (R²=0.40, P=0.002; Figure 3).

WSS, Blood Flow, and Vessel Diameter Before and After Surgery

Among the 17 patients who underwent surgical resection of their AVM after embolization, mean WSS in the feeder artery after surgery was significantly lower than that before surgery (17.9±10.3 dynes/cm² versus 24.4±10.4 dynes/cm²; P=0.02) and not significantly different than the WSS in the contralateral vessel (17.9±10.3 dynes/cm² versus 23.2±7.3 dynes/cm²; P=0.09; Figure 4). Decreased WSS after surgery was accompanied by lower feeder vessel mean flow (222.7±253.1 mL/min versus 116.3±77.2 mL/min; P=0.06) and mean diameter (3.5±0.8 mm versus 3.3±0.6 mm, P=0.29) compared with before surgery.

Shear stress is a physical principle that describes the force that a fluid exerts on the cylindrical tube that it flows through and is defined by the Hagen–Poiseuille equation \( \frac{\mu Q}{\pi D^2} \), where \( Q \) is the volumetric flow rate in mL/s, \( D \) is the vessel diameter in cm, and \( \mu \) is the blood viscosity in poise.8 WSS represents the force of blood against the vessel wall, which is applied mainly to the innermost layer of the vessel wall—the endothelium. This hemodynamic force has been identified as a critical determinant of vessel diameter and vascular remodeling.4,9,10 Specifically,
vessel remodeling in response to sustained increased blood flow may result in vessel dilation and, conversely, diminished caliber in the setting of long-term decreased flow. The molecular mechanism that mediates vascular remodeling by coupling endothelial cell response to WSS is thought to include vasoactive agents, such as nitric oxide synthase, and growth factors, such as platelet-derived growth factor and transforming growth factor β. More recently, Notch signaling was positively correlated with increased WSS and AVM formation in a rat model.11

The first and only other study to measure WSS in patients with cerebral AVMs was published by Rossitti and Svendsen in 1995.12 They calculated WSS in a total of 17 feeder arteries in 15 patients (27% with hemorrhagic presentation) by obtaining blood flow velocity within the principal feeder arteries (anterior, middle, and posterior cerebral arteries) and their normal contralateral counterparts (also anterior, middle, and posterior cerebral arteries) using transcranial Doppler ultrasound (TCD) and assessing vessel size from digital subtraction angiography. They found that mean vessel caliber was significantly larger within the AVM feeder arteries compared with the corresponding arteries in the contralateral hemisphere (0.14 cm versus 0.12 cm; P=0.0008). Additionally, mean blood flow velocity (98.0 cm/s versus 76.7 cm/s; P=0.0017) and mean blood flow rate (3.37 mL/s versus 1.78 mL/s; P=0.001) were significantly higher than WSS in the contralateral vessel (17.9 dynes/cm² versus 23.2 dynes/cm²; P=0.09). CI indicates confidence interval.

Figure 4. Wall shear stress (WSS) before and after surgery. Mean WSS in the feeder artery after surgery was significantly lower than before surgery (17.9 dynes/cm² vs 24.4 dynes/cm²; P=0.02) and not significantly different than WSS in the contralateral vessel (17.9 dynes/cm² vs 23.2 dynes/cm²; P=0.09). CI indicates confidence interval.

After completion of all embolization sessions, WSS in the feeder artery was significantly lower than pre-embolization (23.0 dynes/cm² versus 32.6 dynes/cm²; P=0.001) and dropped to almost match the WSS of the contralateral vessel (23.0 dynes/cm² versus 23.5 dynes/cm²; P=0.78). This decrease in WSS post-embolization corresponded to a significant decrease in mean flow (338.1 mL/min versus 170.3 mL/min; P<0.001) and mean vessel diameter (3.7 mm versus 3.5 mm; P=0.01), thus suggesting a possible mechanism for vessel remodeling that is observed after AVM treatment.21 Most patients in our cohort underwent subtotal embolization the day before surgical resection, and so mean WSS still dropped further from 24.4 dynes/cm² before surgery to 17.9 dynes/cm² (P=0.02) after resection of the AVM. Mean ipsilateral WSS after surgery was not significantly different compared with the contralateral side (17.9±10.3 dynes/cm² versus 23.2±7.3 dynes/cm²; P=0.09), but was somewhat lower perhaps because of the discrepancy between the large flow drop and small change in feeder diameter after surgery. In other words, mean vessel diameter had not yet normalized 2 days after surgery when WSS was measured to match the contralateral side (3.3 mm versus 3.1 mm), despite a substantial drop in ipsilateral mean flow. This possibly lower WSS may be a driving force for long-term remodeling.

Our study is the first to measure WSS in cerebral AVM arterial feeders before and after embolization and surgery 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, including extracranial carotid artery stenosis, intracranial angioplasty/stenting, carotid endarterectomy, and extracranial–intracranial bypass.6–8,13–17 Before any treatment, mean WSS among 48 feeder arteries in our study was significantly higher compared with the mean WSS in the contralateral vessel (29.7±12.0 dynes/cm² versus 23.3±11.0 dynes/cm²; P=0.007). This result reveals that cerebral AVMs are a high WSS pathology, which disputes Rossitti and Svendsen’s hypothesis that WSS in arteries supplying AVMs is the same as in arteries within normal brain parenchyma.12 This difference may be attributed to varying methods of blood flow measurement—Rossitti and Svendsen used TCD, whereas we used QMRA. Indeed, TCD is considered to be highly operator-dependent and inferior to QMRA that provides better resolution and 3D localization capability.6–8 Interestingly, WSS in middle and posterior cerebral artery feeders assessed using TCD in the Rossitti and Svendsen study was higher than on the normal contralateral side, which actually supports our results. Furthermore, their mean WSS in arteries of the AVM was likely skewed by the fact that nearly half of the feeders were anterior cerebral arteries that reportedly had slightly lower WSS compared with the anterior cerebral artery on the side without the AVM. This erroneous result was probably a manifestation of the inaccuracy of TCD measurements of the anterior cerebral artery caused by more variable angles of insolation.14 The absolute values of WSS reported by Rossitti and Svendsen are also out of the normal range for intracranial arteries (7–23 dynes/cm²), perhaps reflecting differences in WSS calculation.8 Our results confirm the prevailing notion of AVMs as lesions that are dynamic, instead of balanced in a steady state, and suggest that WSS may play a part in this process.
insufficient compensation with feeder enlargement. After embolization and surgery, WSS decreases because of lower flows, and this change in WSS is accompanied by decreased vessel diameter. Additionally, as seen in Figure 2, there is a greater drop in flow post-embolization as compared with diameter, which is expected because vessel remodeling is unlikely to occur within 2 days. More specifically, we measured vessel diameter 2 days post-embolization and found that mean vessel diameter decreases from 3.7 mm to 3.5 mm, but does not normalize to match the mean contralateral vessel diameter of 3.1 mm. Of note, our study does not pinpoint whether this change in vessel diameter is caused by lower flows or decreased WSS, but rather it identifies WSS as a possible biomechanical factor that may be important in AVM remodeling over time and in feeder aneurysm regression after AVM treatment.\textsuperscript{23,19}

QMRA is not only an invaluable research tool that shed light on WSS in AVMs, but it may also be clinically useful in monitoring changes in WSS after treatment. Furthermore, better insight into the molecular pathways underlying endothelial cell response to WSS could reveal the possible mechanism for flow-related aneurysm formation and other high-flow vascular lesions.

Possible limitations of this study include its retrospective design and small sample size. However, our cohort is the largest to date to measure WSS in patients with cerebral AVMs, and this study is the only one to assess WSS before and after treatment. Potential variability in the data reflects the fact that blood flow is a physiological parameter. AVM WSS calculated from blood flow and vessel diameter measurements was examined relative to WSS in the contralateral vessel to control for confounders, such as age, heart rate, and blood pressure. Although QMRA measurements may have lower accuracy in the presence of arterial stenosis and turbulent flow, there were no such cases in the present study; and in fact, QMRA measurements have higher accuracy at higher flow rates, as is the case in AVMs.\textsuperscript{7} QMRA also has important advantages over phase contrast techniques alone by providing 3D vessel localization capability and, therefore, more exact flow measurements. Another plausible shortcoming of this study is its generalizability. All 54 embolization sessions were performed with N-butyl cyanoacrylate, except 3 with Onyx, and so it remains unclear if the use of Onyx, which varies in its thrombogenicity and penetration compared with N-butyl cyanoacrylate, would result in different changes in flow and WSS.

Conclusions

Our results indicate that enlargement of cerebral AVM arterial feeders is insufficient to compensate for increased blood flow, resulting in high WSS. After treatment with embolization and surgery, flow diminishes and so WSS and vessel diameter concomitantly decrease.

Disclosures

Dr Alaraj received a research grant from National Institute of Health (NIH) and was a consultant at Cordis-Codman. Dr Aletich received a research grant from Micrus and was a consultant at Cordis-Codman. Dr Amin-Hanjani received a research grant from NIH and research support (no direct funds) from GE Healthcare, VasSol Inc. Dr Charbel received ownership interest from VasSol Inc and was a consultant at Transonic. The other authors report no conflicts.

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