Analysis of Mean Transit Time of Contrast Medium in Ruptured and Unruptured Arteriovenous Malformations
A Digital Subtraction Angiographic Study

Tatemi Todaka, MD; Jun-ichiro Hamada, MD; Yutaka Kai, MD; Motohiro Morioka, MD; Yukitaka Ushio, MD

Background and Purpose—To clarify hemodynamic risk factors for hemorrhage in arteriovenous malformations (AVMs), the mean transit time (MTT) of feeding arteries and draining veins in AVMs with and without hemorrhage was measured and analyzed.

Methods—Morphological features such as the number and diameter of draining and feeding vessels and the AVM nidus volume were evaluated in 30 patients with supratentorial AVMs. The MTT of feeding arteries and draining veins was measured with the use of time-density curves obtained by digital subtraction angiography. The correlation between hemorrhage and morphology and hemorrhage and MTT was analyzed statistically.

Results—The nidus volume was not significantly different between hemorrhagic and nonhemorrhagic AVMs. However, between ruptured and unruptured AVMs there was a significant difference in the mean number of draining veins ($1.5\pm0.69$ versus $2.3\pm0.50$; $P=0.006$), the MTT of the feeding artery ($1.10\pm0.24$ versus $1.62\pm0.55$; $P=0.03$), and the ratio of the MTT of the draining to the feeding vessels ($1.71\pm0.43$ versus $1.05\pm0.07$; $P<0.001$).

Conclusions—A high ratio of the MTT of draining veins to feeding arteries suggests disequilibrium between nidal inflow and outflow. The consequent increased pressure in the draining vein may contribute to the development of AVM hemorrhage. (Stroke. 2003;34:2410-2414.)

Key Words: angiography, digital subtraction cerebral arteriovenous malformations hemorrhage time factors

While arteriovenous malformations (AVMs) play a role in a relatively small number of strokes, they typically affect otherwise healthy young adults who most commonly present with headache, seizure, or intracranial hemorrhage (ICH). The risk of hemorrhage for AVMs is approximately 2% to 4% per year. Hemorrhage is the initial manifestation of the disease in 50% to 60% of patients, and each bleeding episode is estimated to be associated with a 10% mortality rate and a 30% to 50% morbidity rate. Hartmann et al reported that morbidity associated with hemorrhage from an AVM is much lower than was reported earlier. They showed that 47% of patients with cerebral AVM did not develop neurological deficits, that another 37% were able to continue living independent lives after the insult, and that only 16% were moderately or severely disabled after suffering hemorrhage.

The main goal of AVM treatment by modern endovascular techniques, microsurgery, and radiosurgery is the prevention of ICH. Newly diagnosed patients are usually advised to undergo treatment of the AVM if the anticipated morbidity rate is low. This management approach assumes that the risk of bleeding over a patient’s lifetime is substantial. However, AVM patients constitute a heterogeneous population with respect to their risk of hemorrhage. Therefore, risk predictors of hemorrhage for untreated AVMs are needed to facilitate better clinical decision making. Furthermore, risk predictors of hemorrhage are considered in the treatment choice. Patients with AVMs of low hemorrhage risk are ideal candidates for radiosurgery, while those at high risk for hemorrhage should undergo removal of the AVM.

Characteristics that may indicate an increased risk of hemorrhage from AVMs include small nidus size, deep-seated location, presence of arterial aneurysms, single draining vein, and impaired venous drainage. Hemodynamic risk factors are also thought to play important roles in hemorrhage associated with AVMs, and high-perfusion arterial pressure may represent an especially high risk factor.

Current advances in the field of electronics have facilitated the development and application of a new technology known as digital imaging. Digital subtraction angiography (DSA) allows not only anatomic imaging of the central nervous system but also evaluation of the hemodynamics by assessing rapidly acquired quantitative data. In the present study...
we measured the mean transit time (MTT) of feeding arteries and draining veins in AVMs using time-density curves acquired by DSA, and we evaluated the correlation between hemorrhage and hemodynamic factors.

**Subjects and Methods**

During 2000–2002, 30 patients (8 male, 22 female; age range, 11 to 49 years) with supratentorial AVMs underwent DSA to study the blood velocity of their AVMs. Of the 30 patients, 22 had hemorrhagic AVMs.

The morphological features we evaluated were the number of draining veins and the nidus volume (volume=$\pi x y z/6$, where $x$, $y$, and $z$ represent the diameter of each axis on MRI).25 All patients with hemorrhage underwent MRI ≥1 month after the event. This interval was thought to be sufficient to minimize possible confounding contributions from hemorrhage and edema to measurements of AVM nidus volume. Patients with severe stenosis of the draining vein and those with AVM-associated aneurysms (defined as flow-related and/or flow-unrelated feeding artery aneurysms and/or intranidal aneurysms) were excluded from this study.

DSA was performed on an AHD 150G unit (SHIMADZU Medical Systems) with a pixel matrix of 512×512. All patients with hemorrhage underwent repeated angiography ≥1 month after the event to measure the MTT of the feeding artery and draining vein. This interval was considered to be sufficient to minimize the possible confounding contributions from hemorrhage and hematoma on the intracerebral hemodynamics. The catheter tip was advanced into the internal carotid artery or vertebral artery, 4 to 6 mL of contrast medium was delivered at 1.2 to 2.0 mL/s via an automatic pressure injector, and 30 frames per second were acquired for 10 seconds. We calculated the time-density curve on the lateral plane to compensate for the large amount of fluctuation in background density. The values obtained were fitted to a gamma variate function by the least-squares method (Figure, panels B and C), with $C(t)=K(1-AT)\alpha x \exp\left(-\frac{t-AT}{\beta}\right)$, where $C(t)$ is the density increment, $t$ is the time after the start of contrast medium injection, $K$ is a constant scale factor, $\alpha$ and $\beta$ are fit coefficients, and $AT$ is the time of arrival of the contrast medium. $\alpha$ and $\beta$ were determined by the least-squares method to best fit the change in the time-density curve for each region of interest (ROI). Each ROI had a diameter of 2 pixels. ROIs were drawn on the feeding artery and on the draining vein as close as possible to the nidus without superimposition of adjacent arteries and veins (Figure, panel A). For each ROI, the value of the hemodynamic parameter was calculated with the use of these 2 coefficients. The calculated hemodynamic parameters included the MTT, defined as the difference between the time of arrival of contrast medium and the center of gravity of the area under the time-density curve (Figure, panels B and C). In each case, the MTT of the feeding and draining vessels was measured, and the ratio of the MTT of the draining vein to the feeding artery was calculated. If the AVM had multiple feeding and/or draining vessels, ROIs were drawn on each vessel, and MTTs were measured individually. The average MTT of multiple feeding arteries was obtained and defined as the MTT of the feeding arteries. In patients whose AVM had multiple draining veins, the longest MTT of the drainers was defined as the MTT of the draining veins because we posited that the longest MTT of the drainers reflects impaired venous drainage for AVMs with multiple draining vessels.

The diameter of the feeding and draining vessels was measured on the DSA image. The occipitofrontal diameter was determined on the CT and on the lateral plane of the DSA image, and the reduction rate was calculated (reduction rate=$A/B$, where $A$ is the occipitofrontal diameter on the lateral plane of the DSA and $B$ is the occipitofrontal diameter on the CT). The diameter of feeding and draining vessels at the ROIs was measured on the DSA images. To obtain the actual diameter of these vessels, the diameter on the DSA image was divided by the reduction rate.

The study population ($n$=30) was grouped into patients with ($n$=22) and without hemorrhage ($n$=8), patients with single ($n$=12) and multiple draining veins ($n$=18), and patients with small (<3 cm)
(n=14) and medium or large (≥3 cm) AVMs (n=16). The groups were compared with respect to the MTT of the feeding and draining vessels, and the ratio of the MTT of drainers to feeders was recorded.

All analyses were performed by a clinician blinded to the patients’ history, mode of presentation, and clinical course. The statistical methods employed were Student’s t test and Welch’s t test for unpaired data. If the distribution of 2 mother groups was the same, Student’s t test was used. If it was different, Welch’s t test was applied. Differences in the distribution of the 2 mother groups were examined by the F test. A probability value of <0.05 was considered significant.

Results

The mean±SD age at the time of the initial hemorrhage was 34.3±15.5 years in patients with hemorrhagic AVMs. The mean age at which patients with nonhemorrhagic AVMs presented was 28.0±9.9 years; there was no significant difference between these 2 groups. In addition, there was no significant difference in the nidal volume between patients with and without hemorrhage. However, the number of draining veins was significantly lower in hemorrhagic than in nonhemorrhagic AVMs (Table 1). The 22 patients with hemorrhage had a total of 68 feeding arteries; the mean diameter of these 68 arteries was not significantly different from that of the 28 feeding arteries counted in the 8 patients free of hemorrhage. Similarly, there was no significant difference with respect to the mean diameter of the draining veins, irrespective of the presence or absence of hemorrhage (Table 1). Of the 30 patients evaluated, 14 had small AVMs (<3 cm); the MTT of both their feeding and draining vessels was significantly lower than in the 16 patients with medium or larger AVMs (Table 2), although the 2 groups did not significantly differ with respect to the MTT ratio of drainers to feeders. Single draining veins were present in 12 patients, and multiple drainers were present in 18 (Table 3). The MTT of their feeding and draining vessels was not significantly different. However, the MTT ratio of drainers to feeders was significantly higher in patients with single draining veins (P=0.05; Table 3). As shown in Table 4, in hemorrhagic AVMs, the MTT of the feeding artery was significantly shorter than in nonhemorrhagic AVMs (P=0.03); there was no significant difference in the MTT of the draining vessels. The MTT ratio of drainers to feeders was significantly higher in hemorrhagic AVMs (P<0.001).

Discussion

Factors that contribute to venous hypertension are also thought to increase the risk of ICH. In AVM patients with deep venous drainage there is a high incidence of ICH.10,14,17,21 Impaired venous drainage due to severe stenosis or occlusion of draining veins, as well as the presence of a single drainer, has been shown to be a statistically significant for predicting the risk of hemorrhage.8,11,16 Studies of intravascular pressure revealed that it was higher in the feeding arteries of ruptured than unruptured AVMs.9,11–13,21

There is currently no consensus on the relationship between draining vein pressure (DVP) and the risk for hemorrhage. Nornes and Grip28 reported that average DVP tended to be higher in AVM patients with hemorrhage than in those without hemorrhage; however, their sample was small, and their results were inconclusive. Kader et al9 found no difference in DVP between ruptured and unruptured AVMs. More recently, Miyasaka et al12 demonstrated that the pressure in draining veins as well as feeding vessels was significantly higher in AVMs with than without hemorrhage. Furthermore, in their study population, DVP was inversely related to the number of draining veins and the size of the AVMs. DVP elevation may be attributable to the presence of a central venous drainage pattern, stenotic or occlusive involvement of the venous drainage system, or a low number of draining veins.10,11,15,16

### Table 1. Correlation Between AVM Hemorrhage and Morphological Features

<table>
<thead>
<tr>
<th>Hemorrhage</th>
<th>Mean AVM Size, cm³</th>
<th>No. of Draining Veins</th>
<th>Mean Diameter of FA</th>
<th>Mean Diameter of DV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes (n=22)</td>
<td>7.0 (±4.6)</td>
<td>1.5 (±0.69)</td>
<td>1.8 (±0.6)</td>
<td>4.3 (±1.6)</td>
</tr>
<tr>
<td>No (n=8)</td>
<td>13.5 (±11.0)</td>
<td>2.3 (±0.50)</td>
<td>1.6 (±0.6)</td>
<td>3.9 (±1.8)</td>
</tr>
<tr>
<td>Significance</td>
<td>NS</td>
<td>P=0.006</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

AVM, arteriovenous malformation; FA, feeding arteries; DV, draining veins; n*, total number of vessels in each group; SD, standard deviation; NS, not significant.

### Table 2. Correlation Between AVM Size and MTT

<table>
<thead>
<tr>
<th>AVM Size</th>
<th>No. of Draining Veins</th>
<th>Mean Diameter of Feeders, mm</th>
<th>FA MTT</th>
<th>Mean Diameter of Drainers, mm</th>
<th>DV MTT</th>
<th>DV MTT/FA MTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small (&lt;3 cm)</td>
<td>1.57 (±0.53)</td>
<td>1.64 (±0.50)</td>
<td>0.98 (±0.17)</td>
<td>3.96 (±1.33)</td>
<td>1.51 (±0.30)</td>
<td>1.62 (±0.56)</td>
</tr>
<tr>
<td>(4.0±3.1 cm³, n=14)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Medium, large</td>
<td>1.88 (±0.83)</td>
<td>1.94 (±0.67)</td>
<td>1.46 (±0.42)</td>
<td>4.19 (±1.90)</td>
<td>2.07 (±0.56)</td>
<td>1.46 (±0.41)</td>
</tr>
<tr>
<td>(12.8±7.1 cm³, n=16)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Significance</td>
<td>NS</td>
<td>NS</td>
<td>P&lt;0.001</td>
<td>NS</td>
<td>P=0.002</td>
<td>NS (mean±1 SD)</td>
</tr>
</tbody>
</table>

AVM, arteriovenous malformation; MTT, mean transit time; FA, feeding artery; DV, draining vein; DV MTT/FA MTT, the MTT ratio of drainers to feeders; NS, not significant; SD, standard deviation.
Excess blood may be redistributed into the fragile plexiform vessels around the nidus, and drainage pressure elevation and blood flow redistribution may result in hemodynamic overload and increase the risk for rupture. However, in our study the MTT ratio of draining to feeding vessels was not significantly different between small and larger AVMs. While excess nidal inflow may lead to hemorrhage, this is not consistent with findings that small AVMs have a higher rate of hemorrhage. The MTT ratio of drainers to feeders in our small and larger AVMs was 1.62 and 1.46, respectively, and the absence of a significant difference may be attributable to the small size of our study population. Because there was no significant difference with respect to the number of draining veins we observed in small and larger AVMs, we posit that the increased risk for hemorrhage in smaller AVMs may not be merely a reflection of the number of drainers. Although there was no statistical difference in the number of venous draining vessels in large and small AVMs in this study, this sample size was small, and the trend we observed was toward more draining veins in larger AVMs.

Our results suggest that fast nidal inflow and a high MTT ratio of drainers to feeders are risk factors for hemorrhage in patients with AVMs. As shown in Table 4, fast nidal inflow, evidenced by the significantly shorter feeding artery MTT in 22 hemorrhagic AVMs, resulted in a trend toward increased venous drainage times, manifested by the longer MTT in single than multiple drainers (Table 3). Of the 2 risk factors for hemorrhage, we posit that a high MTT ratio of drainers to feeders is the most reliable. The MTT obtained from time-density curves tends to be affected by the contrast medium injection site, injection rate, and injection volume. In addition, the degree of atherosclerosis, patient’s cardiopulmonary functions, total blood volume, and blood viscosity are factors that must be considered. Therefore, the MTTs of feeders and drainers are relative parameters that vary among patients. On the other hand, because the ratio of drainers to feeders is not strongly affected by patient characteristics, we suggest that comparative assessments are possible. The feeder-to-drainer ratio is an independent risk factor but a numerical expression of the degree of mismatch between nidal inflow and outflow, which are affected by nidus size, number and stenotic status of drainers, and drainage pathway.

The increased availability and use of diagnostic tools have raised the number of incidentally detected AVMs and the dilemma of whether and how to treat them. While in many cases these decisions are made empirically, there is a need for objective criteria to guide the patient and the physician. Although the Spetzler-Martin grading system has already proved its usefulness, it does not take into account angioarchitectonic features that may put individual patients at disproportionate risk.

### Table 3. Correlation Between Number of Draining Veins and MTT

<table>
<thead>
<tr>
<th>No. of Draining Veins</th>
<th>FA MTT</th>
<th>DV MTT</th>
<th>DV MTT/FA MTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single (n=12)</td>
<td>1.16 (±0.30)</td>
<td>1.98 (±0.66)</td>
<td>1.74 (±0.52)</td>
</tr>
<tr>
<td>Multiple (n=18)</td>
<td>1.28 (±0.48)</td>
<td>1.70 (±0.42)</td>
<td>1.39 (±0.41)</td>
</tr>
<tr>
<td>Significance</td>
<td>NS</td>
<td>NS</td>
<td>P&lt;0.05 (mean±1 SD)</td>
</tr>
</tbody>
</table>

MTT, mean transit time; FA, feeding artery; DV, draining vein; DV MTT/FA MTT, the MTT ratio of drainers to feeders; NS, not significant; SD, standard deviation.

We found that in hemorrhagic AVMs the MTT of feeding arteries was significantly shorter than in nonhemorrhagic AVMs, while the MTT of draining vessels was not significantly different (Table 4). Our findings support the hypothesis that high pressure in the feeding arteries may lead to AVM rupture because vascular pressure is directly proportional to flow velocity, which, in turn, is inversely proportional to MTT. However, many factors, including the vessel diameter, viscoelastic properties of the vessel wall, and downstream resistance, affect the relationship between pressure and velocity. Further studies are needed to provide direct experimental confirmation of this relationship. Norris et al suggested that AVMs in which feeding vessels were more likely to rupture. On the other hand, Matsumoto et al reported that the MTT of feeders tended to be shorter in hemorrhagic than in nonhemorrhagic AVMs. Likewise, we found that the MTT of feeders was significantly shorter in hemorrhagic than in nonhemorrhagic AVMs (Table 4). Spetzler et al demonstrated that the feeding artery MTT ratio was higher in small AVMs and that they had a high incidence of rupture. Similarly, in our study the ruptured AVMs tended to be small; however, we found no significant correlation between nidus size and the incidence of hemorrhage. In small AVMs, the MTT of feeders and drainers was significantly shorter than in the larger AVMs (Table 2), and the vessel diameter tended to be narrower; the difference was not significant, however. Nonetheless, the narrower vessel diameters may have exerted an influence on MTT. If vascular pressure is indeed directly proportional to flow velocity, pressure in the feeding and draining vessels is higher in small than in large AVMs.

In our unruptured AVMs, the MTT ratio of drainers to feeders was close to 1 (Table 4), suggesting equivalent nidal inflow and outflow. In hemorrhagic AVMs, on the other hand, nidal inflow may exceed outflow because of impediments in the draining system. While the relationship between DVP and the MTT ratio of drainers to feeders remains unclear, disequilibrium in nidal inflow and outflow may lead to drainage pressure elevation.

### Table 4. Correlation Between AVM Hemorrhage and MTT

<table>
<thead>
<tr>
<th>Hemorrhage</th>
<th>No. of Single Drainer Cases, %</th>
<th>FA MTT</th>
<th>DV MTT</th>
<th>DV MTT/FA MTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes (n=22)</td>
<td>12 (54.5)</td>
<td>1.10 (±0.24)</td>
<td>1.85 (±0.54)</td>
<td>1.71 (±0.43)</td>
</tr>
<tr>
<td>No (n=8)</td>
<td>0 (0)</td>
<td>1.62 (±0.55)</td>
<td>1.70 (±0.55)</td>
<td>1.05 (±0.07)</td>
</tr>
<tr>
<td>Significance</td>
<td>P=0.007</td>
<td>P=0.03 NS</td>
<td>P&lt;0.001 (mean±1 SD)</td>
<td></td>
</tr>
</tbody>
</table>

AVM, arteriovenous malformation; MTT, mean transit time; FA, feeding artery; DV, draining vein; DV MTT/FA MTT, the MTT ratio of drainers to feeders; NS, not significant.
for neurological deficits from a hemorrhage. We suggest that objective MTT measurements may be of significant benefit in deciding the appropriate management of unruptured AVMs. Given the dynamic nature of AVMs, serial angiograms are needed to ensure that the transit time characteristics of the particular AVM remain stable.

The results of our study are subject to certain limitations. First, because the study population was small, we cannot draw strong conclusions regarding risk factors for hemorrhage in patients with AVM. Second, because AVMs are compartmentalized structures, the mismatch between arterial and venous flow and the consequent pressure changes determine hemorrhage risk on a case-by-case basis. Studies of the MTT performed in combination with superselective angiography are under way. In subsequent investigations, we will measure feeding artery pressure with an intracranial microcatheter and will analyze the correlation between feeding artery MTT and pressure. Furthermore, AVMs with drainage exclusively into the deep venous system or into severely stenotic vessels are known to have a high incidence of rupture.8,10,17,18,20 We are performing studies to clarify the relationship between flow velocity in deep or stenotic draining vessels and the risk of AVM rupture. Lastly, because MTT tends to be reflective of the aforementioned individual clinical characteristics, care must be exercised when conclusions are drawn on groups of patients with AVM.

Conclusion
We used DSA time-density curves to measure the MTT of feeders and drainers in patients with AVM. Our finding that the MTT ratio of draining to feeding vessels was significantly increased for AVM rupture.

References
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