Blood Flow Velocity and Vasomotor Reactivity in Patients With Arteriovenous Malformations

A Transcranial Doppler Study

Rolf R. Diehl, PhD; Hans Henkes, MD; Hans-Christian Nahser, MD; Dietmar Kühne, MD; Peter Berlit, MD

**Background and Purpose** A large percentage of patients with a cerebral arteriovenous malformation (AVM) show focal neurological signs or have a history of intracranial hemorrhage. The present study used transcranial Doppler sonography to assess the clinical significance of hemodynamic disturbances in the intracranial arteries of patients with an AVM.

**Methods** Eighteen patients with untreated AVMs were examined clinically, angiographically, and with transcranial Doppler sonography (blood flow velocity measurement and vasomotor reactivity in all main intracranial arteries).

**Results** A pathological increase in blood flow velocity (57.6%) and a decrease in vasomotor reactivity (72.7%) were frequently found in AVM feeding arteries. Vasomotor reactivity was also reduced in several nonfeeding arteries both ipsilateral (53.3%) and contralateral (30.8%) to the AVM. AVM size was a poor predictor of pathological transcranial Doppler results. Vasomotor reactivity of arteries ipsilateral to an AVM in patients with a history of hemorrhage was significantly higher (2.10±1.66% per mm Hg; mean±SD) than in patients with no history of bleeding (1.12±1.48% per mm Hg; P<.05). In patients with focal neurological signs but no history of hemorrhage, the percentage of arteries ipsilateral (100%) and contralateral (63.6%) to an AVM showing a pathological vasomotor reactivity was significantly larger than in nonhemorrhagic patients without focal signs (66.7% and 22.2%, respectively; both P<.05).

**Conclusions** Our results suggest two distinct relations between transcranial Doppler results and clinical findings: (1) Normally vasomotor reactivity values in arteries ipsilateral to an AVM indicate a high-pressure AVM with an increased risk of hemorrhage. (2) A strongly pathological vasomotor reactivity in arteries ipsilateral and contralateral to an AVM indicates a low-pressure AVM with a higher prevalence of hemodynamically induced neurological signs.

**Key Words** • angiography • arteriovenous malformations • cerebral arteries • ultrasonics
Subjects and Methods

Patients and Control Subjects
A total of 18 consecutive patients with AVMs in supratentorial regions were studied before embolization. None of the patients previously received radiological or neurosurgical treatment. All patients were examined by computed tomographic (CT) scanning and magnetic resonance imaging. Table 1 shows the demographic data of the patients, the angiographic characteristics of the AVMs, and the clinical features of the patients. Fifteen healthy volunteers served as control subjects.

Clinical Investigations
All patients received a complete neurological examination and a neuropsychological assessment using a test battery including subtests for aphasia, recent and remote memory, ideomotor and constructional apraxia, visual hemineglect, spatial orientation, cognitive speed, and attention.

Angiography and Arteriovenous Malformation Classification
All patients received a complete four-vessel angiographic evaluation of the cerebral circulation. AVMs were classified according to the criteria of Spetzler and Martin11 (Table 1). The Spetzler score is the sum of the size score of the nidus (maximal angiographic diameter of the nidus <3 cm, 1 point; 3 to 6 cm, 2 points; and >6 cm, 3 points), AVM location in eloquent brain regions (1 point), and presence of deep draining veins (1 point). A nonoperable AVM is scored with 6 points.

The main intracerebral arteries were classified as AVM feeders when a filling of the AVM nidus by contrast material could be demonstrated by selective injection of contrast material into the respective arteries (Table 1). AVM filling by large proximal feeders as well as by cortical anastomoses was observed.

Transcranial Doppler and Carbon Dioxide Stimulation
Cerebral blood flow velocities of the main intracerebral arteries (MCA, ACA, and PCA) were recorded by a TCD monitor (Multidop, DWL). Corresponding vessels on both
TABLE 2. Blood Flow Velocity and Vasomotor Reactivity in Arteriovenous Malformation Patients

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Ipsilateral n</th>
<th>Contralateral n</th>
<th>Significance*</th>
<th>Normal Values n</th>
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</thead>
<tbody>
<tr>
<td>BFV, cm/s</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>MCA</td>
<td>110.1±38.8</td>
<td>80.4±19.7</td>
<td>P=.004</td>
<td>72.5±20.5</td>
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<tr>
<td>ACA</td>
<td>84.3±34.4</td>
<td>76.9±30.0</td>
<td>P=.051</td>
<td>56.3±18.0</td>
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<tr>
<td>PCA</td>
<td>69.5±30.2</td>
<td>38.3±12.9</td>
<td>P&lt;.001</td>
<td>43.4±15.0</td>
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<tr>
<td>VMR, %/mm Hg</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>MCA</td>
<td>1.56±1.63</td>
<td>3.26±1.55</td>
<td>P&lt;.001</td>
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<tr>
<td>ACA</td>
<td>1.48±1.95</td>
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<td>5.26±1.61</td>
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<tr>
<td>PCA</td>
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<td>4.65±2.34</td>
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<tr>
<td>AVM feeders only</td>
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<tr>
<td>BFV, cm/s</td>
<td></td>
<td></td>
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<tr>
<td>MCA</td>
<td>118.2±36.6</td>
<td>82.5±21.5</td>
<td>P=.004</td>
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<tr>
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<td>98.1±29.9</td>
<td>P=.098</td>
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<tr>
<td>PCA</td>
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<td>40.9±13.0</td>
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<tr>
<td>VMR, %/mm Hg</td>
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<td></td>
<td></td>
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<tr>
<td>MCA</td>
<td>1.23±0.92</td>
<td>3.04±1.47</td>
<td>P&lt;.001</td>
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<tr>
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<td>PCA</td>
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<td>4.66±2.45</td>
<td>P&lt;.001</td>
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</tbody>
</table>

BFV indicates blood flow velocity; MCA, middle cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery; VMR, vasomotor reactivity; and AVM, arteriovenous malformation.

* Ipsilateral vs contralateral comparison (one-tailed t test).

Results

Control Group

A total of 78 arteries were investigated in 15 control subjects aged 18 to 63 years (mean, 38.3±12.1). In 3 control subjects neither PCA could be insonated, while a single MCA, ACA, or PCA was missing in another 6 subjects. Two-factorial ANOVAs (factor 1, side; factor 2, vessel) were calculated for mean value differences in BFV and VMR, respectively. No left-right difference was found for BFV. BFV of the three arteries differed significantly (MCA>ACA>PCA; P<.001). The interaction between side and vessel was not significant. Data from left- and right-sided vessels were pooled to calculate the normal reference values (Table 2) and the upper normal limits for each vessel (mean±2 SD).

For VMR values, neither the main effects nor the interaction between side and vessel revealed statistical significance. We therefore calculated the mean and SD over all 78 vessels as the normal reference value of VMR (Table 2). The pathological limit was set to VMR=2.04% per mm Hg (mean−2 SD).

AVM Patients

The mean age was 35.0±14.3 years (range, 16 to 68 years). A complete TCD study of all main intracranial arteries was possible in 12 of the 18 patients. In 2 patients no ultrasonic window for either PCA was
found. Three patients showed retrograde flow through the A1 segment of the ACA ipsilateral to the AVM via cross flow from the anterior communicating artery (AcomA). In these patients only the contralateral ACA was investigated. In 1 patient the ipsilateral MCA could not be insonated because of a proximal MCA occlusion.

**Blood Flow Velocity**

BFV was significantly increased against the normal reference values in ipsilateral MCAs, ACAs, and PCAs as well as in contralateral ACAs (all P<.001).

Table 2 compares BFV for all vessels ipsilaterally and contralaterally to the AVM. Significantly higher flow velocities in ipsilateral vessels were revealed by t tests for dependent samples for the MCA (P<.001) and the PCA (P<.001), whereas borderline significance was found for the ACA (P=.051). The differences between ipsilateral and contralateral vessels were more accentuated when AVM feeders only (n=33) were compared with their corresponding contralateral vessels.

Twenty of 48 ipsilateral arteries (41.7%) showed pathological flow values. Only 1 of the 15 nonfeeding vessels (6.7%) was classified as pathological, whereas increased flow velocities were recorded in 19 of the 33 feeders (57.6%, P<.001). The rate of pathological flow velocities in feeding vessels did not differ significantly between middle, anterior, and posterior cerebral arteries. Increased BFV values were found in 7 of 52 arteries (13.5%) contralateral to the AVM. In 5 of these 7 arteries the ACA was the affected vessel. A retrograde flow through the ipsilateral A1 segment was observed in 3 of the 5 patients with an increased contralateral ACA flow velocity. A pathological reduction in BFV (normal mean±2 SD) was never found in either ipsilateral or contralateral arteries.

In the 33 AVM feeders, BFV was not significantly related to the size of the AVM, as classified according to Spetzler and Martin. In addition, the proportion of arteries with pathological BFV values did not differ significantly between the three size classes (Table 3).

BFV of AVM feeding vessels was compared between patients with a history of intracerebral hemorrhage (ICH+; n=13 vessels in 8 patients) and without (ICH−; n=20 vessels in 10 patients). Arteries in the ICH+ group showed significantly lower BFV values (85.8±39.3 cm/s) than in the ICH− group (109.0±36.7 cm/s) (P<.05). However, the percentage of vessels with a pathological BFV did not differ significantly between the ICH+ (46.2%) and the ICH− group (65.0%) (Table 4). No significant differences between two groups were found with respect to mean BFV and percentage of pathological values of nonfeeding arteries ipsilateral and contralateral to the AVM, respectively.

Nine of the 18 patients showed focal clinical signs (Table 1). To study the relation between TCD findings and the presence of symptoms, we excluded all patients with a history of ICH (in these patients, symptoms were clearly related to the bleeding). From a total of 25 arteries ipsilateral to the AVM in 10 patients without ICH, 15 belonged to neurologically asymptomatic patients, and 10 belonged to patients with clinical signs (seizures were not counted as signs). Neither the grouped mean BFV nor the percentage of pathological BFV differed significantly when feeders or ipsilateral and contralateral nonfeeders, respectively, were compared between groups.

**Vasomotor Reactivity**

VMR in the MCA, ACA, and PCA ipsilateral to the AVM was strongly reduced against normal values (all P<.001). Contralateral to the AVM, a decreased VMR was found only in the ACA (P<.001) and the MCA (P<.001), whereas for the PCA, VMR was close to the normal value (P>.05).

Table 2 shows the comparison between ipsilateral and contralateral vessels. Ipsilaterally, VMR values were significantly lower in the MCA (P<.001), the ACA (P<.05), and the PCA (P<.001). Largely similar results were found when comparison was restricted to feeding arteries and their contralateral counterparts. However, the difference in VMR between the ipsilateral and contralateral ACA did not, in this case, reach statistical significance.

Ipsilaterally to the AVM, 32 of 48 arteries (66.7%) showed pathological VMR values. The difference between the percentage of pathological VMR values in AVM feeders (72.7%) and in nonfeeders (53.3%) was not significant. In the hemisphere contralateral to the
AVM, a pathological VMR was found in 16 of 52 arteries (30.8%). The contralateral ACA was affected most frequently (8 of 18 ACAs).

There was a tendency for a higher incidence of pathological VMR in arteries ipsilateral to larger AVMs with a size score of 3 (71.4%) or 2 (80.0%) than in those arteries associated with small AVMs (size score, 1; 43.8%) (Table 3, \( P = .054 \)).

In the ICH+ group, the grouped mean VMR from all ipsilateral vessels (VMR=2.10±1.66%/mm Hg; \( n = 23 \)) was significantly higher than in the ICH− group (VMR=1.12±1.48 mm Hg; \( n = 25 \)) (\( P < .05 \)). The percentage of vessels ipsilateral to the AVM showing pathological VMR was significantly lower in the ICH+ group (52.1%) than in the ICH− group (80.0%) (Table 4). The ICH+ and ICH− groups showed no significant difference in the incidence of pathological VMR values in contralateral vessels.

VMR was significantly lower in arteries of symptomatic patients without ICH (0.45±0.68%/mm Hg) than in those of asymptomatic patients without ICH (1.57±1.71%/mm Hg) (\( P < .05 \)). Each of the 10 ipsilateral arteries of symptomatic patients showed VMR values below the pathological limit, whereas only 10 of 15 (66.7%) arteries in asymptomatic patients reached the pathological limit (\( P < .05 \), Table 5). Differences in VMR between symptomatic and asymptomatic patients were even stronger in contralateral vessels. The mean VMR was 1.90±1.63%/mm Hg in 11 arteries contralateral to asymptomatic AVMs compared with 4.05±2.46%/mm Hg in 18 contralateral vessels of asymptomatic patients (\( P < .01 \)).

**BLEEDING RISK AND ARTERIOVENOUS MALFORMATION SIZE**

Four of 6 (66.7%) patients with small AVMs and 4 of 12 (33.3%) patients with medium and large AVMs had a history of hemorrhage. This difference was, however, not significant.

**Discussion**

In confirmation of other TCD studies, the present results demonstrate that AVM feeders are characterized by increased BFV and reduced VMR. Moreover, it is shown that pathological VMRs also can be found in many nonfeeding arteries ipsilateral and contralateral to the AVM.

The present findings can be explained in the context of pathophysiological considerations. An AVM is a region of very low cerebrovascular resistance producing abnormally decreased pressure values in proximal segments of the feeders. From this it can be assumed that pressure is also reduced at the level of the circle of Willis. Despite the low pressure level, blood flow in AVM feeders is high because of the low peripheral resistance. The situation in nonfeeders is equivalent to a drop in systemic blood pressure: to compensate for the pressure-related reduction in blood flow, vasodilation of small arteries is initiated by autoregulatory mechanisms. As a consequence, BFV in nonfeeders remains normal. However, VMR may sometimes be decreased in nonfeeders if the capacity for a further decline in cerebrovascular resistance is limited.

The frequent observation of pathological BFV and VMR in the contralateral ACA can also be explained by the pressure conditions at the circle of Willis. Blood pressure is decreased in the circle of Willis ipsilateral to the AVM with normal pressure on the contralateral side. This pressure difference between the two entries of the AcomA evokes a blood flow through the AcomA from the contralateral to the ipsilateral ACA with an increased BFV in the contralateral A1 segment. Be-
cause a large part of the flow through the contralateral A1 segment supplies the AVM and/or that part of the territory of the ipsilateral ACA with an exhausted autoregulatory reserve, VMR measured at the contralateral A1 segment is frequently pathological.

Although the ipsilateral PCA acted as an AVM feeder in most of our patients, the contralateral PCA showed normal VMR values in general (Table 2). This is remarkable because in all but one of the patients both PCAs were supplied exclusively by the basilar artery. The hemodynamic far-field effect of AVMs to nonfeeding arteries in the posterior circulation is obviously not as strong as in the anterior circle of Willis.

The size of the AVM was a poor predictor of hemodynamic disturbances in the different arteries. BFVs were similar for feeding arteries of AVMs of different sizes, and a tendency toward a higher percentage of pathological VMRs in feeders of large AVMs only reached borderline significance.

Several epidemiological studies in AVM patients have demonstrated a correlation between AVM size and risk of hemorrhage: small AVMs bear a higher risk of hemorrhage than larger ones. In the present study, there was also a higher but nonsignificant tendency for bleeding in patients with small AVMs compared with those with medium and large AVMs. However, the strong relation between VMR and history of hemorrhage in the present series could not be explained by the slight association between VMR and AVM size.

The hemodynamic far-field effect of AVMs to nonfeeding arteries in the anterior circulation is remarkable because in all but one of the patients both AVMs were supplied exclusively by the basilar artery. Therefore, the pressure-hemorrhage relation because in small AVMs had significantly higher pressures (6.5 mm Hg below systemic blood pressure) than feeders of nonruptured AVMs (40 mm Hg below systemic blood pressure). Moreover, feeder arteries of small AVMs had significantly higher pressures than feeders of large AVMs. Thus, it seems probable that high pressure within an AVM nidus is a major risk factor for rupture. Presumably, the association between AVM size and hemorrhage is only a secondary effect of the pressure-hemorrhage relation because in small AVMs the total reduction of cerebrovascular resistance below the normal range. The pressure drop reduction in feeders and in nonfeeders is not as strong as in large AVMs, and the pressure within the nidus of a small AVM is probably higher than in a large AVM nidus, leading to an increased risk of bleeding.

The current finding of an association between less pathological VMR and history of hemorrhage can also be explained with respect to the assumed pressure differences between ruptured and unruptured AVMs. Because the pressure gradient proximal to feeders of high-pressure AVMs is not as steep as in low-pressure AVMs, a relatively high pressure level is also present at the circle of Willis and in arterial branches supplying normal brain tissue. The need for autoregulatory compensation of the relatively low-damped flow reduction is therefore less than in the case of a low-pressure AVM. Hence the capacity for a further dilation of resistance vessels is larger, and carbon dioxide stimulation leads to higher VMR values.

Consistent with this point of view is the observation of lower BFVs in feeders of ruptured AVMs than of unruptured ones. Because flow velocity does not depend on the absolute blood pressure but rather on the steepness of the pressure gradient, BFV should be lower in feeders of high-pressure AVMs when the pressure gradient is relatively flat. The present results are also in accordance with the observation that an impaired venous drainage (venous stenosis or occlusion) may increase the risk of hemorrhage. In this case it can be assumed that the major pressure drop takes place at the venous site because of increased resistance while leaving a higher pressure level more proximally.

Fleischer et al have recently used TCD to compare feeder artery pressure with BFV and obtained a significant inverse correlation. However, these authors found no correlation between either ICH and BFV or between ICH and feeder artery pressure. The authors conceded that their results may have been influenced by their highly selective sample of patients, who had predominantly medium- and large-sized AVMs.

Another interesting finding of the present study was the high prevalence of pathological VMRs in patients with focal symptoms not attributable to bleeding. This was true for both ipsilateral and contralateral vessels (Table 5). At first sight, these results seem to confirm the hemodynamic "steal" theory (ie, symptoms are produced by ischemia of normal brain tissue because blood is "stolen" by the AVM). Several factors argue against such an interpretation of the present results.

Although many nonfeeder arteries in the patient group showed pathological VMRs, BFV was almost always in the normal range. This indicates that autoregulatory mechanisms in the patients sufficiently compensated for low-pressure–induced ischemia at remote brain regions. Moreover, the focal symptoms of the 4 symptomatic patients without ICH (patients 6, 8, 12, and 15; Table 1) could be related to the locations of AVMs. In particular, no symptoms due to dysfunction of the contralateral hemisphere were seen.

These arguments do not, however, preclude the possibility that the symptoms in these patients were due to ischemia of brain areas close to the nidus that were supplied by distal branches of the feeders. BFV and VMR of these vessels cannot be measured selectively by TCD. Accordingly, pathological VMRs of nonfeeders can be interpreted merely as indicators for a high-flow/low-pressure AVM, perhaps with an increased risk for the development of clinical signs in other vascular territories.

More direct evidence for "hemodynamic steal" as a mechanism of "clinical steal" stems from observation of patients whose symptoms improve after embolization or resection of their AVM. Sugita et al recently published the case of a patient with a large right-sided AVM who presented with seizures and a left upper quadrantanopia. Single-photon emission computed tomography disclosed a large ischemic lesion in the right temporoparietal region. After nearly complete embolization of the AVM, clinical symptoms and cerebral blood flow in the previously ischemic region improved significantly. In most patients with hemodynamic steal before treatment, however, clinical symptoms remained unchanged after treatment even when the hemodynamic steal disappeared. The underlying mechanism for persistent neurological deficits in many AVM patients may be the development of tissue damage in chronically hyperperfused brain regions. Using positron emission tomogra-
phy, Fink\textsuperscript{20} was able to demonstrate that cerebral blood flow and metabolic activity were proportionally decreased in some regions around AVMs, indicating permanent lesions rather than persistent hemodynamic steal as the cause of cortical dysfunction in these patients. In these cases, AVM resection or embolization would be unlikely to yield an improvement in clinical symptoms.

Regardless of the exact cause of the clinical symptoms, the present study shows that hemodynamic steal, as defined by pathological VMRs in cerebral arteries, is associated significantly with the presence of cortical dysfunction. Using a different approach, Manchola et al\textsuperscript{21} assessed AVM hemodynamics by calculating the flow volume through AVM feeders from TCD flow velocities and angiographically determined feeder diameters. Patients with progressive neurological deficits showed significantly higher flow volumes, again indicating that AVM hemodynamics are correlated with the presence of clinical symptoms.

In conclusion, the present findings show, in agreement with other TCD studies, that AVM feeders are characterized by pathological BFV and VMR values. While pathological increased flow velocities were found almost exclusively in feeders, pathological reduced VMRs were frequently also present in nonfeeders ipsilateral and contralateral to the AVM. From a pathological point of view, abnormal VMRs in arteries remote from an AVM can be interpreted as the consequence of a blood pressure drop at the level of the circle of Willis. In addition to the established angiographic criteria, VMR measurements in AVM patients may help to distinguish between low-flow/high-pressure AVMs (slightly reduced VMRs) with an increased risk of hemorrhage and high-flow/low-pressure AVMs (strongly reduced VMRs) with a risk for the development of progressive neurological deficits.

References


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