Large and Deep Brain Arteriovenous Malformations Are Associated With Risk of Future Hemorrhage

Marco A. Stefani, MD; Phillip J. Porter, MD; Karel G. terBrugge, MD; Walter Montanera, MD; Robert A. Willinsky, MD; M. Christopher Wallace, MD, MSc

Background and Purpose—The correlation between features present in brain arteriovenous malformations (AVMs) such as size, location, and angioarchitecture at presentation with subsequent risk of hemorrhage may be valuable in predicting the behavior of AVMs and therefore guiding management.

Methods—We prospectively followed up 390 patients with brain AVMs at the University of Toronto Vascular Malformation Study Group. Location, size, angioarchitecture details, blood supply, and clinical presentation were recorded at baseline. Intracranial hemorrhages during follow-up were recorded. Significant factors from univariate analyses were used to construct a multivariate model relating the above features to the occurrence of hemorrhage.

Results—Thirty-eight patients had bleeding caused by the AVM in a follow-up of 1205 patient-years (mean, 3.1 years per patient). In analyses adjusted for multiple AVM characteristics, large AVMs bled more frequently than small lesions (odds ratio [OR], 2.5; 95% confidence interval [CI], 1.41 to 4.35; P<0.0001), and deep-seated AVMs had more bleeding in follow-up than those located at superficial sites (OR, 5.56; 95% CI, 2.63 to 12.5; P<0.0001).

Conclusions—Deep-seated and large AVMs were significantly more prone to hemorrhage during prospective follow-up. The distinction between factors associated with hemorrhagic presentation and the natural history risk of hemorrhage will be emphasized. (Stroke. 2002;33:1220-1224.)

Key Words: angiography ▪ cerebrovascular disorders ▪ intracerebral hemorrhage ▪ vascular malformations

The search for predictors of the clinical behavior of arteriovenous malformations (AVMs) dates to the first reports on the disease.1–3 Many factors related to the natural history of AVMs have been described, including clinical aspects like systemic high blood pressure4 and dynamic physiological measurements of the AVMs such as intranidal pressure.5,6 Other features based on imaging of the AVMs such as size and location have also been assessed.7 Of special interest are the angioarchitectural aspects of the AVMs, which have been associated with initial hemorrhagic events.8–12 Many reports, including recent series,6,7 stated that the presence of some of these factors at initial presentation can be used as risk predictors for future bleeds.

The most frequently reported example by several authors13–15 and most recently by Langer et al4 is that small AVMs have a higher risk of bleeding. These studies, however, fail to make the critical distinction between factors present at initial bleeding and the prospective risk of hemorrhage seen in AVM patients followed up over time after clinical presentation. The ideal case would be the prospective follow-up of nontreated AVMs, with researchers knowing their angioarchitecture and looking for new events from the time of the first clinical presentation. That is difficult because it is not acceptable to leave curable AVMs without treatment.

In this study of a series of 390 patients enrolled in the vascular malformation study group at the University of Toronto, we investigated the association between angiographic features of brain AVMs and the risk of future hemorrhagic events.

Materials and Methods

The University of Toronto Arteriovenous Malformation Study Group has been assessing patients with brain AVMs since 1989. These patients were prospectively followed up by a multidisciplinary team of neurosurgeons, neuroradiologists, and radiotherapists using diagnostic and therapeutic methodology described elsewhere.16 Patients with cranial dural arteriovenous fistulae and vein of Galen malformations were excluded from this study.

Angiographic characteristics present at the time of the diagnosis such as size, location, arterial feeders, venous drainage pattern, and presence of aneurysms were noted following a standard protocol. The definitions used in the present report are similar to those recently proposed by the Joint Writing Group of the Technology Assessment Committee and intended for use in AVM research protocols.17

Size was initially classified according to the Spetzler-Martin18 criteria as small (≤3 cm), medium (>3 and <6 cm), or large (≥6 cm).
cm). The medium and large groups were brought together to form the “large” group used in the final statistical analyses.

Locations were grouped into frontal, temporal, parietal, occipital, corpus callosum, basal ganglia, insular, brainstem, and cerebellum. The location was also grouped into deep (basal ganglia, thalamus, cerebellum, and corpus callosum) and superficial (all other locations). Arterial feeders were classified as deep supply alone, superficial supply alone, or combined deep and superficial blood supply. The superficial group included the cortical branches of the anterior, middle, and posterior cerebral arteries; the deep group included the perforating branches and choroidal and posterior fossa arteries.

Venous drainage was categorized as deep or superficial according to the Spetzler-Martin\textsuperscript{18} classification criteria. The number of draining veins was also noted, and AVMs were divided into 3 groups: presence of 1 vein only, presence of 2 veins, or presence of $\geq 2$ draining veins.

Venous drainage was also described with respect to the presence or absence of ectasias (abnormal dilatations) and outflow obstruction of $\geq 50\%$ of the venous lumen (stenosis).\textsuperscript{10,12,19} The presence of arterial aneurysms was noted, as well as their locations, which included pre nidial, intranidal, or remote aneurysms, by use of the same methodology previously reported.\textsuperscript{20}

Patients were followed up prospectively in the AVM clinic at the Toronto Hospital. All treatment (surgery, embolization, and stereotactic radiosurgery) and new imaging tests were recorded. The primary outcome was interval hemorrhage from the AVM. This was defined as any intracranial bleeding occurring after the initial clinic visit with no easily identifiable alternative source that was more likely than the AVM to be the cause. All hemorrhages were documented by imaging or pathological confirmation at surgery or autopsy. Patients were censored that the time of hemorrhage, death, angiographically documented cure, or last clinic visit.

We used survival analyses techniques to study the natural history of AVM bleeding. Significant factors ($P<0.05$) were chosen from univariate analyses to construct multivariate models by forward stepwise methods with the use of Cox regression.

### Results

The group comprised 390 patients with brain AVMs who were on average 31.4 years of age at disease presentation. We achieved a 97% follow-up with a total of 1205 patient-years and a mean of 3.1 years per patient. Among the patients contributing to follow-up, 82 (21%) had no therapy for their AVM at any time. Of the remainder, 65 had surgery, 76 had embolization, and 69 had stereotactic radiotherapy as single treatment modalities. Thirty-four had embolization combined with surgery, 50 had embolization combined with stereotactic radiotherapy, 9 had surgery and radiotherapy, and 5 had all 3 types of treatment. At the end of the study period, 172 patients (44%) had been cured of the AVM. Of the 218 patients not cured, 136 (35%) had partial therapy (ie, had received therapy but did not yet have documented AVM obliteration).

There were 218 men (55.9%) and 172 women (44.1%). Previous hemorrhagic presentation was present in 146 patients (37.4%) and was not associated with increased risk of subsequent hemorrhage (odds ratio [OR], 0.81; 95% confidence interval [CI], 0.41 to 1.59; $P=0.44$) compared with other forms of initial clinical presentation.

The group of deep-seated AVMs was made up of 44 in the thalamus, 26 in the cerebellum, 12 in the corpus callosum, and 9 in the brainstem. The superficial group was composed of 96 AVMs in the frontal lobe, 78 in the temporal lobe, 75 in the parietal lobe, 37 in the occipital lobe, and 13 in the insula. No particular location was found to be more commonly associated with risk of hemorrhage. Analyzed as a group, deep-seated AVMs carried a higher subsequent risk of bleeding ($P<0.009$), confirmed by multivariate analysis (OR, 5.56; 95% CI, 2.63 to 12.5; $P<0.0001$).

Small ($<3$ cm) AVMs were present in 233 patients, and malformations $>3$ cm were found in 167 patients. In the multivariate analysis, AVMs $>3$ cm were more prone to experience new hemorrhagic events (OR, 2.5; 95% CI, 1.41 to 4.35; $P<0.0001$).

Angiographic analysis revealed 226 patients (58%) with deep venous drainage and 164 (42%) with superficial drainage when the criteria of the Spetzler-Martin\textsuperscript{18} grading system were used. Hemorrhagic events occurred more often in AVMs with deep venous drainage (OR, 2.17; 95% CI, 1.03 to 4.55; $P=0.043$), but this characteristic was not significantly associated with subsequent risk of hemorrhage in the multivariate analyses.

In the study of arterial feeders, 20 cases (7%) had only deep feeders, 141 (43%) had both deep and superficial feeding vessels, and 164 (50%) had exclusively superficial feeders. Follow-up hemorrhagic events were more frequent in the presence of deep feeders (OR, 2.17; 95% CI, 1.2 to 3.85; $P=0.009$), but in the multivariate analyses, this factor failed to be related to subsequent risk of bleeding.

From the group of patients analyzed, 38 (10%) had new hemorrhagic events. Univariate analyses demonstrated a significant relation with new hemorrhagic events in AVMs $>3$ cm, deep-seated AVMs, and those with deep feeders, deep venous drainage, a single draining vein, and aneurysms, as presented in Table 1. A correlational analysis (Pearson’s correlation) was performed between different factors to identify associations between the variables, which may explain the reduction to only a few variables in the final model. For example, there was a significant correlation between size and number of draining veins ($P=0.0001$), deep arterial feeders and deep location ($P=0.04$), and deep location and number of draining veins ($P=0.008$).

Multivariate stepwise analyses demonstrated deep location and large size to be the only independent predictors of future hemorrhage (Table 2). The presence of arterial aneurysms, deep feeders, and a single draining vein no longer was a statistically significant predictor in these analyses.

### Discussion

The risk factors for hemorrhage from AVMs have been a matter of discussion in the neurosurgical literature. When

### Table 1. Univariate Analyses of AVM Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep location</td>
<td>3.04</td>
<td>1.53–6.06</td>
<td>0.002</td>
</tr>
<tr>
<td>Large ($&gt;3$ cm)</td>
<td>2.13</td>
<td>1.23–3.57</td>
<td>0.007</td>
</tr>
<tr>
<td>Deep feeders</td>
<td>2.17</td>
<td>1.2–3.85</td>
<td>0.009</td>
</tr>
<tr>
<td>Deep venous drainage</td>
<td>2.17</td>
<td>1.03–4.55</td>
<td>0.043</td>
</tr>
<tr>
<td>Venous ectasias</td>
<td>1.87</td>
<td>0.61–5.72</td>
<td>0.444</td>
</tr>
<tr>
<td>Presence of aneurysm</td>
<td>1.79</td>
<td>0.58–5.66</td>
<td>0.0005</td>
</tr>
<tr>
<td>Single draining vein</td>
<td>1.61</td>
<td>1.05–2.5</td>
<td>0.029</td>
</tr>
<tr>
<td>Venous stenosis</td>
<td>1.54</td>
<td>0.51–4.76</td>
<td>0.315</td>
</tr>
<tr>
<td>Previous hemorrhage</td>
<td>0.81</td>
<td>0.41–1.59</td>
<td>0.44</td>
</tr>
</tbody>
</table>

Stefani et al AVM Features and Subsequent Risk of Hemorrhage

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TABLE 2. Final Models With Multivariate Analyses With Significant Factors Associated With New Hemorrhagic Events

<table>
<thead>
<tr>
<th>Feature</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep location</td>
<td>5.56</td>
<td>2.63–12.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Large size (&gt;3 cm)</td>
<td>2.5</td>
<td>1.41–4.35</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

analyzed at initial presentation, these factors reflect only features present in one moment of the natural history of the AVM and provide limited information in terms of outcome. Although it seems logical, factors associated with hemorrhagic presentation do not necessarily predict a higher subsequent risk of bleeding.

If one characteristic is more commonly present at initial presentation, it does not mean that in the future patients with that characteristic will be more prone to bleed again. Only analyses of the association of angiographic characteristics with new events during prospective follow-up may answer this question.

We have tested the significance of hemorrhagic presentation in univariate models, and it was not a significant predictor of subsequent bleeding. The literature to date on this topic has been variable, and probably the best natural history study performed by Ondra et al did not find significance. Thus, we did not feel it was warranted to force this variable into the final multivariate model.

The issue of size has been analyzed by several authors. Guidetti et al found that small AVMs present more frequently with bleeding, but when they followed up 24 small AVMs, only 3 cases had repeated bleedings. Graf et al, in a follow-up analysis of 71 unruptured AVMs, had 14 patients readmitted with episodes of bleeding. The occurrence of hemorrhage in large malformations was 0% at 1 year, 10% at 5 years, and 34% after 10 years; in small AVMs, it was 10% at the first year and 52% at the fifth year. In this population of unruptured AVMs, however, there were only 12 small and 33 large AVMs, and the size of 26 malformations was unknown. In the same report, 134 patients with previously ruptured AVMs were followed up, and there were 8 hemorrhages (15%) in 51 small malformations, 11 (33%) in 33 large AVMs, and 13 (40%) in the group of 50 AVMs of unknown size. No significant association linking size and risk for hemorrhage was found in this group of patients with previous hemorrhage.

Several previous studies, however, could not demonstrate any association of size and subsequent risk of bleeding. Fults and Kelly found no risk of hemorrhage related to size, but they examined initial bleeding together with follow-up events. Crawford et al followed up 216 unruptured AVMs and found no relation between size and risk of hemorrhagic events. In this study, bleeding rates were 21% at 5 years for small AVMs and 18% at 5 years for large AVMs. As discussed by Pollock et al, much controversy exists about the role of AVM size in the natural history of the disease. Those authors presented some evidence that small AVMs do not increase the risk of bleeding. That study, however, was composed mainly of small AVMs referred for stereotactic radiosurgery, with only 41 cases >3 cm. This fact made it difficult to compare bleeding rates between different sizes. In another recent report by Mast et al on a group of 281 patients, no relation between size and hemorrhage was found in a multivariate model. Unfortunately, hemorrhage at presentation was analyzed together with subsequent hemorrhagic episodes.

In the present series, AVMs >3 cm determined a higher risk of hemorrhage in the follow-up. This finding goes against the beliefs that the small AVMs are the more hemorrhage-prone group and that the group of large AVMS would have a more “benign” behavior. It also serves to emphasize the distinction that although small AVMs may tend to present with hemorrhage simply because they are less likely to cause other symptoms (such as bruist or seizures) than large AVMs, they do not necessarily subsequently behave in a more dangerous manner.

In our center and probably almost every center treating AVMs, there is a higher rate of successful AVM obliteration for small lesions than large ones. This will, by necessity, affect the patients who end up contributing “natural history” data for studies like ours. In other words, if patients with small AVMs arrive at curative treatment more frequently and rapidly than patients with large AVMs, they will contribute less follow-up information. This introduces a potential bias for which there is no easy solution. Purely observational, population-based studies on an unselected group of untreated AVMs, which would address this problem, are not ethical or feasible. In our study, deep lesions were more prone to hemorrhagic episodes. This has also been supported by others. Mast et al found deep-seated AVMs to bleed more, but as mentioned, presentation hemorrhages were included in the analyses with follow-up events. In a retrospective analysis of a series of 32 patients with AVMS in the brainstem and cerebellum at the University of Texas Health Science Center at Dallas, 23 (72%) presented with hemorrhage. It is interesting in that study that the recurrent hemorrhage in 11 cases (34%) was separated by intrahemorrhage intervals of 3 months to >6 years, which supports the high risk of subsequent hemorrhage of these deep lesions.

Temporal locations of an AVM were concluded to be a risk factor for bleeding by Crawford et al in a large series of 216 nontreated cases. The depth of the malformation was not a significant factor in the same study, but deep-seated AVMs made up only 7% of the total group. In addition, by analyzing the natural history for subsequent risk of hemorrhage, other studies could not demonstrate a relationship between location and increased tendency to bleed. Brown et al found no specific location to be at risk for follow-up bleeding. They reported 31 hemorrhages in 168 patients who were followed up, but only 18 malformations would have been considered deep by our criteria.

The association of deep venous drainage with hemorrhagic risk has also been stressed in the previously mentioned series. Marks et al retrospectively studied 65 patients and in a multivariate discriminative analysis found deep venous drainage, intramural aneurysm, and periventricular or ventricular location to be positive predictors of hemorrhage and angiomatous changes to be negative predictors. One must exercise caution in interpreting these data; the figures presented as subsequent risk could be overestimated...
because hemorrhages at presentation were added into the analysis.

Miyasaka et al,9 in a retrospective analyses of 108 patients, found a single draining vein, impaired venous drainage, and deep venous drainage to be associated with increased risk of bleeding, but further multivariate analyses are necessary to discriminate these factors. When Brown et al10 looked at the risk of subsequent hemorrhage, they found no association with deep or superficial venous drainage.

Some studies10,12,19 analyzing venous ectasia did not demonstrate any association with hemorrhage, but those were descriptive reports that did not have follow-up analyses. In the follow-up group, we failed to demonstrate that this characteristic is an important factor to be considered in determining the risk of new hemorrhagic events.

Studies of brain AVM clinical behavior, such as the report by Brown et al,22 could not demonstrate a relationship between arterial feeders and increased risk of bleeding, as also determined in the present report.

The relation between venous stenosis and bleeding as a result of AVM rupture was theoretically studied by Hademenos et al29 with special attention given to high-flow draining veins. As previously mentioned, Miyasaka et al8 stated the importance of the venous impairment in the risk of bleeding. However, careful interpretation is necessary, considering the other dependent angioarchitectural factors present at the initial manifestation of the AVM. In a crude analysis, venous stenosis was reported to be a significant factor for initial AVM bleeding in a small subset of young women in the third decade.19 The report of Turjman et al10 used selective investigation in all 100 patients and found no association between venous stenosis and initial bleeding. With the statistical model of multivariate analysis, venous stenosis was not considered a factor for hemorrhage in the present study. Intranidal aneurysms were reported to be significantly associated with hemorrhage at presentation.10,12,30 The role of this characteristic in the natural history of bleeding, however, is still questioned.23 Pollock et al23 could not find this relation in a series of 313 patients who underwent diagnostic angiography for stereotactic radiosurgery planning. As they stated, the identification of aneurysms in nonsuperselective angiography is difficult, which has also been mentioned by other authors.10,31 These aneurysms are not common findings in reported series, and the practical use of such indicators in the whole population of AVM patients is questionable, especially considering that not all patients undergo superselective angiography. In the same set of patients as in the present study, Redekop et al20 found a 9.8% annual incidence of bleeding in nontreated patients with intranidal aneurysms. Only 13 patients with this feature were followed up, so definitive conclusions of the relation between this feature and new bleeds cannot be drawn.

In other series, the risk of intracranial hemorrhage among patients with a coexisting saccular aneurysm and unruptured AVM was reported to be 7% per year at 5 years after diagnosis compared with 1.7% per year for the group of patients with AVM alone.32 In the same study, aneurysms typically were located on the feeding vessel of AVMs, a finding also reported by others.33 We did not find a sufficient number of cases to state that the presence of aneurysms in any location was statistically significantly associated with subsequent risk of hemorrhage, but this feature was a common finding in the population of patients in this study, as described by Redekop et al.20

Although there were no patient-years of follow-up contributed after curative treatment, patients with partially treated AVMs did contribute to this study after their treatment. Thus, patients who had surgery (after which angiography is routinely done at our center to document cure), curative embolization, or stereotactic radiosurgery leading to obliteration were censured at the time of cure. We agree that this could potentially introduce a bias, eg, if partial treatment selectively and differentially affected one of the variables being tested, such as aneurysms. However, we consider it reasonable to include posttreatment but precure time to increase the total follow-up because to date there is no compelling evidence in the literature that partial therapy affects the rate of hemorrhage from an AVM.

Conclusions

In this prospective cohort of patients with AVMs, large size and deep location in the brain were the most important and significant factors associated with higher risk of future hemorrhagic events. These are different factors than those found to be associated with initial hemorrhagic presentation in the same patient population. This finding stresses the importance of distinguishing between presentation and natural history when making therapeutic decisions, because the two do not necessarily coincide.

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