The recent publication of the A Randomized Trial of Unruptured Brain Arteriovenous Malformations (ARUBA)\(^1\) has suggested a benefit of conservative management for non-hemorrhagic brain arteriovenous malformations (bA VMs). The risk of death or neurological disability at 30 months was significantly lower for the medical management arm (15.1%) than for interventional therapy (46.2%) in an as-randomized analysis. Nevertheless, as in earlier natural history studies, in which the hemorrhage risk for bA VMs has been approximated between 2% and 4%,\(^2\) the annualized risk of hemorrhage in the conservatively managed arm of ARUBA was found to be a not negligible (2.2%).\(^1\) To calculate a risk/benefit ratio accurately to inform clinical decision making, a model for determining hemorrhage risk on an individual basis is essential.

A substantial body of research has attempted to address this issue,\(^3\)\(\text{–}21\) and many studies have found statistically significant associations between bAVM characteristics and hemorrhage risk. However, there is no clear rationale as to why many of the bAVM parameters studied might increase risk of rupture. For example, bAVM nidal size,\(^3\),\(^6\),\(^10\),\(^13\),\(^15\),\(^22\)–\(^25\) deep/only deep venous drainage,\(^3\),\(^5\)–\(^7\),\(^11\),\(^13\)–\(^17\),\(^22\),\(^26\) deep location,\(^10\),\(^20\) ventricular/periventricular location,\(^4\) posterior fossa location,\(^5\),\(^27\) and arterial nonborderzone location\(^1\) have all been statistically associated with rupture risk; however, the rationale for causality of these parameters is not entirely clear. In the absence of a clear mechanism to explain why these bAVM characteristics increase rupture risk, one cannot confidently use them to determine prospective hemorrhagic risk.

Four articles have demonstrated an association between bAVMs with a single draining nidal vein and increased hemorrhage risk,\(^4\),\(^7\),\(^23\),\(^24\) however, none has explored the potential physiological implication of this anatomic observation. In this study, we examine detailed bAVM angioarchitectural features and their association with hemorrhagic presentation using a retrospective case series of all bAVMs embolized at our medical center between 1997 and 2006,\(^28\) in much the same way that other studies have done previously. In addition, we attempt to clarify the potential physiological significance of the factors associated with hemorrhagic presentation. Although the retrospective nature of the series precludes prospective hypothesis

**Features Predictive of Brain Arteriovenous Malformation Hemorrhage**

**Extrapolation to a Physiologic Model**

Daniel H. Sahlein, MD; Paloma Mora, MD; Tibor Becske, MD; Paul Huang, MD; Jafar J. Jafar, MD; E. Sander Connolly, MD; Peter K. Nelson, MD

**Background and Purpose**—Although there is generally thought to be a 2% to 4% per annum rupture risk for brain arteriovenous malformations (bAVMs), there is no way to estimate risk for an individual patient.

**Methods**—In this retrospective study, patients were eligible who had nidiform bAVMs and underwent detailed pretreatment diagnostic cerebral angiography at our medical center from 1996 to 2006. All patients had superselective microcatheter angiography, and films were reviewed for the purpose of this project. Patient demographics, clinical presentation, and angioarchitectural characteristics were analyzed. A univariate analysis was performed, and angioarchitectural features with potential physiological significance that showed at least a trend toward significance were added to a multivariate logistic regression model.

**Results**—One hundred twenty-two bAVMs met criteria for study entry. bAVMs with single venous drainage anatomy were more likely to present with hemorrhage. In addition, patients with multiple draining veins and a venous stenosis reverted to a risk similar to those with 1 draining vein, whereas those with multiple draining veins and without stenosis had diminished association with hemorrhage presentation. Those bAVMs with associated aneurysms were more likely to present with hemorrhage. These findings were robust in both univariate and multivariate models.

**Conclusions**—The results of this article lead to the first physiological, internally consistent model of individual bAVM hemorrhage risk, where 1 draining vein, venous stenosis, and associated aneurysms increase risk. (Stroke. 2014;45:1964-1970.)

**Key Words:** arteriovenous malformations ▶ cerebral hemorrhage ▶ hemorrhage ▶ stroke

---

Received February 16, 2014; final revision received May 2, 2014; accepted May 5, 2014.

From the Departments of Neurology (D.H.S., T.B.), Radiology (D.H.S., P.M., T.B., P.K.N.), and Neurosurgery (P.H., J.J.J., P.K.N.), NYU Langone Medical Center; Department of Radiology, Hospital Bellvitge, Barcelona, Spain (P.M.); and Department of Neurosurgery, Columbia University Medical Center, New York, NY (E.S.C.).

Correspondence to Peter Kim Nelson, MD, Department of Neurosurgery, NYU Langone Medical Center, 660 First Ave Seventh Floor, New York, NY 10016. E-mail nelsop01@med.nyu.edu

© 2014 American Heart Association, Inc.

**Stroke** is available at http://stroke.ahajournals.org DOI: 10.1161/STROKEHA.114.005170
testing, our goal is to study bAVMs exhibiting specific vascular conditions and to explore the physiological meaning of the studied parameters.

Methods

Patients aged >5 years were eligible for this retrospective, institutional review board–approved study if they were discovered to have a bAVM and underwent full diagnostic angiography with superselective microcatheterization from January 1997 through December 2006. The angiography in the vast majority of bAVMs was performed in anticipation of treatment by embolization and surgery (n=85; 70%), embolization and gamma knife (n=20; 16%), or embolization alone (n=15; 12.3%). Two patients were lost to follow-up (1.6%), 1 in whom the plan was preoperative embolization, and a second for whom the plan was occlusion with embolization only. Patients with vein of Galen malformations, pial or dural arteriovenous fistulas, facial AVMs, or spinal AVMs were excluded. Patients with remote histories of partial treatment were excluded as well (9 patients) because of the possibility of altering natural history in unpredictable ways. Eleven patients undergoing surgery alone for evacuation of a hematoma were excluded because of the absence of confirmatory angiography. During this 10-year interval, 121 patients with 122 bAVMs underwent the required angiographic investigation enabling the detailed angioarchitectural analysis sufficient for inclusion in this study. Patients were entered at the time of angiography into a prospectively maintained database. Additional data were collected by reviewing office and inpatient charts and embolization reports and by directly analyzing all diagnostic and procedural angiograms. All imaging studies were reviewed by 3 neuroradiologists for consensus.

Classification of bAVMs

All angiograms were reviewed for the purpose of this study. Detailed angioarchitectural data on each bAVM were recorded from pre- and postembolization angiographies. Every patient had superselective microcatheterization angiography. bAVMs were characterized based on location (hemisphere, lobe, basal ganglia, thalamus, callosal, intraventricular, cerebellar hemispheric, cerebellar vermis, subarachnoid, brain stem, perimesencephalic), depth (hemispheric supratentorial with subcategories of cortical, cortical/subcortical, periventricular, cortical/subcortical/periventricular, subependymal, as well as callosal, deep nuclei, ventricular, cerebellar, brain stem), nidus size (measured in 3 planes by cross-sectional imaging or angiography with fiducial markers), bAVM flow physiology (nidus-predominant, large fistula–predominant, or mixed), arterial supply (organized by major feeding territory and categorized as cortical or perforator), associated aneurysms (number and location characterized as nidal, flow-related, proximal [circle of Willis], venous), pial collaterals (described by whether the collaterals originated from the same arterial distribution [ie, middle cerebral artery to middle cerebral artery] or different [ie, anterior cerebral artery to middle cerebral artery]), bAVM border morphology (compact versus diffuse), presence of moyamoya-type changes, venous characteristics (number of draining veins, superficial versus deep drainage, presence of venous angiopathy), and bAVM eloquence as defined by Spetzler and Martin.27 See Figures 1 and 2 for examples of bAVM angioarchitectural characteristics and how they were classified. Indisputable intracranial hemorrhage was confirmed by computed tomography scan in all patients.

Statistical Analysis

Means, percentages, and proportions were used to summarize the data. Categorical variables were compared using χ² or Fisher exact test where appropriate. Continuous variables were compared using Student t test, 1-way ANOVA, and Wilcoxon rank-sum where appropriate. A univariate model was constructed using all demographic and angioarchitectural characteristics. Categorical variables were assessed for dependence using 2×2 contingency tables to calculate a percentage agreement. Percentage agreement >70% was considered significant. A multivariate logistic regression model was then constructed using the physiological parameters of the univariate analysis, which showed at least a trend toward significance, with a cut-off of P=0.1. The multivariate logistic regression model was built using the forced-entry method.
Results

One hundred twenty-two bAVMs were analyzed. Mean maximum diameter (mean±SD) was 34.4±11.5 mm. There were 11 (9.0%) Spetzler–Martin grade 1, 30 (24.6%) grade 2, 55 (45.1%) grade 3, 24 (19.7%) grade 4, and 2 (1.6%) grade 5 bAVMs. Of the 122 bAVMs, 54 (44%) had hemorrhaged. Patient demographic and presentation data are listed in Table 1 for the entire cohort and organized by hemorrhage presentation. The average age was 33.8±16.3, and 64 (53%) of the cohort were women. The hemorrhage group was statistically significantly older than the nonhemorrhage group (P=0.045). There was a significant association between history of hypertension and presentation with hemorrhage (P=0.04; odds ratio [OR], 3.1; 95% confidence interval [CI], 1.1–8.8), and patients with hemorrhage tended to present with a chief complaint of headache (P=0.012; OR, 2.6; 95% CI, 1.2–5.8) and not with seizure (P=0.005; OR, 0.3; 95% CI, 0.15–0.70). On physical examination, patients with hemorrhage were significantly more likely to have a focal deficit (P<0.001; OR, 4.0; 95% CI, 1.9–8.7).

The angioarchitectural characteristics that were significantly associated with hemorrhage are listed in Table 2. Deep supratentorial location was associated with hemorrhage (P=0.04; odds ratio [OR], 3.1; 95% confidence interval [CI], 1.1–8.8), and patients with hemorrhage tended to present with a chief complaint of headache (P=0.012; OR, 2.6; 95% CI, 1.2–5.8) and not with seizure (P=0.005; OR, 0.3; 95% CI, 0.15–0.70). On physical examination, patients with hemorrhage were significantly more likely to have a focal deficit (P<0.001; OR, 4.0; 95% CI, 1.9–8.7).

After review of the initial data analyses, we proposed that the association between bAVMs with single draining vein and hemorrhagic presentation, seen in our study and elsewhere, might be related to outflow ideology. In this hypothesis, bAVMs with higher numbers of draining nidal veins would be protected from hemorrhage by lower outflow impedance, whereas those with 1 draining vein would be at risk because of their relatively constrained, higher outflow impedance. Variability in the dispositions of venous drainage among the bAVMs in our cohort provided an opportunity to test this hypothesis and develop a physiological model for hemorrhagic risk of bAVMs, related to constrained outflow. bAVMs with multiple primary draining veins, some of which were constrained by outflow stenosis, provided a group mimicking single venous drainage physiology and were used to test this hypothesis.

For this purpose, a second univariate analysis was performed to explore the effect of venous stenosis on bAVM hemorrhage in patients with multiple draining veins (Table 3). Patients with ≥2 draining veins were much more likely to present with hemorrhage (P=0.08; OR, 1.9; 95% CI, 0.9–4.1).

bAVMs with 1 draining vein were more likely to hemorrhage than those with ≥2 draining veins (P=0.004; OR, 4.4; 95% CI, 1.6–12.1), the same association demonstrated by 4 previous papers.4,7,23,24 In addition, bAVMs with venous outflow stenosis showed a trend toward significance with respect to hemorrhage presentation (P=0.08; OR, 1.8; 95% CI, 0.9–3.7).

After review of the initial data analyses, we proposed that the association between bAVMs with single draining vein and hemorrhagic presentation, seen in our study and elsewhere, might be related to outflow ideology. In this hypothesis, bAVMs with higher numbers of draining nidal veins would be protected from hemorrhage by lower outflow impedance, whereas those with 1 draining vein would be at risk because of their relatively constrained, higher outflow impedance. Variability in the dispositions of venous drainage among the bAVMs in our cohort provided an opportunity to test this hypothesis and develop a physiological model for hemorrhagic risk of bAVMs, related to constrained outflow. bAVMs with multiple primary draining veins, some of which were constrained by outflow stenosis, provided a group mimicking single venous drainage physiology and were used to test this hypothesis.

For this purpose, a second univariate analysis was performed to explore the effect of venous stenosis on bAVM hemorrhage in patients with multiple draining veins (Table 3). Patients with ≥2 draining veins were much more likely to present with hemorrhage (P=0.08; OR, 1.9; 95% CI, 0.9–4.1).
hemorrhage if they had an outflow stenosis (48%) versus if they did not (24%; \( P = 0.022 \) by 2-sided Fisher exact test), with an estimated risk (OR, 2.8; 95% CI, 1.2–6.7) similar to the OR calculated for bAVMs with single draining vein anatomy (OR, 4.4; 95% CI, 1.6–12.1).

Table 4 shows the results of the multivariate logistic regression model. The following variables met the criteria for entry into the logistic regression analysis: Venous Number, Venous Stenosis, and Presence of Any Associated Aneurysm. All variables were statistically significant. Adjusted ORs were highest for 1 draining vein (adjusted OR, 6.6), followed by presence of venous stenosis (adjusted OR, 2.6), and finally presence of any aneurysm (adjusted OR, 2.4). Note that venous stenosis...
and presence of any aneurysm went from demonstrating trends toward significance in the univariate model ($P=0.08$ for both) to statistically significant ($P=0.023$ and $0.049$, respectively) in the multivariate analysis with the other physiological parameters.

**Discussion**

The results presented here provide empirical evidence supporting the physiological hypothesis that bAVMs with single draining veins are at increased risk of rupture because of increased outflow impedance. Specifically, the physiological implication of single venous drainage was explored and validated by examining separate subsets of bAVMs with multivenous drainage: those in which drainage was constrained by a stenosis versus those in which outflow was not affected. Among our bAVM cohort, we identified a marked increase in likelihood of hemorrhagic presentation among bAVMs with single venous outflow as well as in those bAVMs with multivenous drainage compromised by outflow stenosis, suggesting an elevated hemorrhagic risk associated with conditions of increased nidal outflow impedance. Given the physiological understanding of these variables gleaned from the univariate analysis, it was not surprising that all 3 parameters (number of draining veins, presence of venous stenosis, and presence of any aneurysm) became statistically significant when included in a multivariate model with one another.

This hemorrhage risk model focuses on bAVM venous outflow rather than arterial inflow, which is concordant with both the body of literature as a whole$^{4,7,22,23}$ as well as with an hypothesized cause of postembolization hemorrhages, some of which are related to unintentional venous occlusion or obstruction by embolic agent.$^{28}$

As noted above, this is not the first article to find that bAVMs with 1 draining vein are more likely to present with hemorrhage.$^{4,7,23,24}$ However, it is the first to test the physiological meaning of single venous drainage using different groups of bAVMs defined by unique sets of outflow conditions. In fact, 3 of the articles that demonstrated an association between single venous drainage anatomy and hemorrhage failed to consider venous outflow stenosis as a bAVM characteristic.$^{7,23,24}$ Refining the understanding of why single venous drainage is associated with increased hemorrhage risk (increased outflow impedance) enabled the identification of confounders such as small nidal size, exclusively deep drainage, and deep location, characteristics that other studies have embraced as risk factors themselves.$^{3–7,9–11,13,15–17,20,22–25}$ Agreement analysis confirms that the statistically significant relationship of each of these bAVM characteristics with hemorrhage can be explained by significant association with parameters that play a plausible role in bAVM outflow impedance (number of draining veins, outflow stenosis), thus identifying these characteristics as confounders. This insight serves to clarify

**Table 2. Brain Arteriovenous Malformation (bAVM) Angioarchitectural Characteristics**

<table>
<thead>
<tr>
<th>Presence of Venous Stenosis</th>
<th>Hemorrhage Groups</th>
<th>Nonhemorrhage Groups</th>
<th>$P$ Value*</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Hemorrhage (N=54; Percentage of Total Group)</td>
<td>Nonhemorrhage (N=68; Percentage of Total Group)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>bAVM &lt;3 cm</td>
<td>35 (29%)</td>
<td>24 (44%)</td>
<td>11 (16%)</td>
<td>0.001</td>
<td>4.2</td>
</tr>
<tr>
<td>Deep supratentorial location (basal ganglia, thalamic, callosal, or intraventricular)</td>
<td>18 (15%)</td>
<td>14 (26%)</td>
<td>4 (6%)</td>
<td>0.004</td>
<td>5.6</td>
</tr>
<tr>
<td>Exclusively deep venous drainage</td>
<td>14 (12%)</td>
<td>11 (20%)</td>
<td>3 (4%)</td>
<td>0.009</td>
<td>5.5</td>
</tr>
<tr>
<td>Venous number</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>22 (18%)</td>
<td>16 (30%)</td>
<td>6 (9%)</td>
<td>0.003†</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>44 (36%)</td>
<td>21 (39%)</td>
<td>23 (34%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>56 (46%)</td>
<td>17 (32%)</td>
<td>39 (57%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 draining vein</td>
<td>22 (18%)</td>
<td>16 (30%)</td>
<td>6 (9%)</td>
<td>0.004</td>
<td>4.4</td>
</tr>
<tr>
<td>Venous outflow stenosis</td>
<td>67 (55%)</td>
<td>34 (63%)</td>
<td>33 (49%)</td>
<td>0.08‡</td>
<td>1.8</td>
</tr>
<tr>
<td>Presence of any aneurysms</td>
<td>81 (66%)</td>
<td>40 (74%)</td>
<td>41 (60%)</td>
<td>0.08‡</td>
<td>1.9</td>
</tr>
<tr>
<td>Absence of pial to pial collaterals between major territories</td>
<td>58 (48%)</td>
<td>33 (61%)</td>
<td>25 (37%)</td>
<td>0.01</td>
<td>2.7</td>
</tr>
</tbody>
</table>

* $P$ value for 2-sided Fisher exact test.
† $P$ value for $\chi^2$ test.
‡ $P$ value for 1-sided Fisher exact test.

**Table 3. Effect of Venous Outflow Stenosis on Brain Arteriovenous Malformation With ≥2 Draining Veins**

<table>
<thead>
<tr>
<th>Presence of Venous Stenosis</th>
<th>Hemorrhage Groups</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hemorrhage</td>
<td>No Hemorrhage</td>
</tr>
<tr>
<td>With stenosis</td>
<td>28</td>
<td>31</td>
</tr>
<tr>
<td>Without stenosis</td>
<td>10</td>
<td>31</td>
</tr>
<tr>
<td>Total*</td>
<td>38</td>
<td>62</td>
</tr>
</tbody>
</table>

* $P=0.022$ by 2-sided Fisher exact test (odds ratio, 2.8 [1.2–6.7]).

**Table 4. Results of the Multivariate Logistic Regression Analysis**

<table>
<thead>
<tr>
<th>Included Variable</th>
<th>Adjusted Odds Ratios</th>
<th>Significance ($P$ Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 draining vein versus ≥2 veins</td>
<td>6.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Presence of stenosis</td>
<td>2.6</td>
<td>0.023</td>
</tr>
<tr>
<td>Presence of any aneurysms</td>
<td>2.4</td>
<td>0.049</td>
</tr>
</tbody>
</table>
Features Predictive of Brain AVM Hemorrhage

Conclusions

We present a cogent physiological hypothesis that bAVMs with single venous drainage are at higher risk of rupture because of increased outflow impedance. We tested this hypothesis by looking at subsets of multivenous bAVMs with distinct venous outflow conditions, looking at bAVMs with multiple draining veins and a venous stenosis to approximate the physiology of 1 draining vein versus those without outflow stenosis. We add to this model the potential angioarchitectural weakness that results from associated aneurysms. The multivariate model includes number of draining veins (1 versus $\geq 2$), presence of any aneurysm, and venous stenosis. We demonstrate that many of the characteristics with less plausible physiological relevance are likely dependent on parameters in the physiological model and, therefore, represent confounders. Further validation of this model will need to come from a large prospective trial.

Disclosures

None.

References


Features Predictive of Brain Arteriovenous Malformation Hemorrhage: Extrapolation to a Physiologic Model
Daniel H. Sahlein, Paloma Mora, Tibor Becske, Paul Huang, Jafar J. Jafar, E. Sander Connolly and Peter K. Nelson

Stroke. 2014;45:1964-1970; originally published online June 12, 2014; doi: 10.1161/STROKEAHA.114.005170
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/45/7/1964

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/