Pattern Not Volume of Bleeding Predicts Angiographic Vasospasm in Nonaneurysmal Subarachnoid Hemorrhage

Amanda Raya, MD; Gregory J. Zipfel, MD; Michael N. Diringer, MD; Ralph G. Dacey Jr, MD; Colin P. Derdeyn, MD; Keith M. Rich, MD; Michael R. Chicoine, MD; Rajat Dhar, MD

Background and Purpose—Spontaneous idiopathic subarachnoid hemorrhage (SAH) with a perimesencephalic bleeding pattern is usually associated with a benign course, whereas a diffuse bleeding pattern has been associated with a higher risk of vasospasm and disability. We evaluated whether volume of bleeding explains this disparity.

Methods—Pattern and amount of bleeding (by Hijdra and intraventricular hemorrhage scores) were assessed in 89 patients with nonaneurysmal SAH. Outcomes included angiographic vasospasm, delayed cerebral ischemia, and functional outcome at 1 year.

Results—Diffuse bleeding was associated with significantly higher Hijdra and intraventricular hemorrhage scores than perimesencephalic SAH, \( P \leq 0.003 \). Angiographic vasospasm was more likely in diffuse versus perimesencephalic SAH (45% versus 27%; odds ratio, 2.9; \( P = 0.08 \)), but adjustment for greater blood burden only partially attenuated this trend (adjusted odds ratio, 2.2; 95% confidence interval, 0.69–7.2; \( P = 0.18 \)); delayed cerebral ischemia was only seen in those with diffuse bleeding. Patients with diffuse bleeding were less likely to be discharged home (68% versus 90%; \( P = 0.01 \)) and tended to have more residual disability (modified Rankin scale, 3–6; 20% versus 6%; \( P = 0.18 \)).

Conclusions—Nonaneurysmal SAH can still result in vasospasm and residual disability, especially in those with diffuse bleeding. This disparity is only partially accounted for by greater cisternal or intraventricular blood, suggesting that the mechanism and distribution of bleeding may be as important as the amount of hemorrhage in patients with idiopathic SAH. (Stroke. 2014;45:265-267.)

Key Words: subarachnoid hemorrhage • vasospasm, intracranial

Angiography does not reveal a source of bleeding in 10% to 15% of patients with spontaneous subarachnoid hemorrhage (SAH). Of these nonaneurysmal (idiopathic) patients, those with a perimesencephalic pattern of bleeding (PM-SAH) have a favorable prognosis, whereas those with diffuse bleeding may have worse outcomes. Although predictors of vascular lesions on subsequent evaluation have been studied, less is known about which patients are at risk for vasospasm and delayed cerebral ischemia (DCI) and may benefit from closer neurological monitoring.

After aneurysmal SAH, vasospasm is strongly related to the volume of ventricular and cisternal blood. Whether blood volume similarly predicts risk of vasospasm in nonaneurysmal SAH is unknown. Greater bleeding may explain why patients with diffuse bleeding have greater neurological morbidity than those with PM-SAH. We determined whether blood volume better accounts for risk of vasospasm than pattern of bleeding after nonaneurysmal SAH.

Methods
Patients with nontraumatic SAH admitted between 2005 and 2012 with negative angiography were prospectively enrolled, and those with an aneurysm found on subsequent computed tomography angiography or repeat 1-week angiography (both performed in all) were then excluded.

Pattern of bleeding was categorized from admission computed tomography as: (1) Perimesencephalic: blood around the brain stem with limited extension into Sylvian and interhemispheric fissures, and only limited extension into Sylvian and interhemispheric fissures, and only limited layering of blood in ventricles and (2) Diffuse: blood extending into the Sylvian, interhemispheric fissures, and ventricles. Volume of cisternal bleeding was quantified using the Hijdra sum score, which assigns a score of 0 to 3 to each of 10 cisterns. Ventricular blood was quantified using the intraventricular hemorrhage (IVH) score. Vasospasm was defined as present if there was 33% or greater narrowing in ≥1 intracranial artery on follow-up angiography, as measured retrospectively by a single investigator, with severe vasospasm being 66% or greater stenosis. DCI was defined as new or worsening neurological deficits, after exclusion of other causes. Outcome was assessed by hospital discharge disposition and modified Rankin scale, assessed at 1 year.

Analysis
Variables were compared using \( \chi^2 \) or Mann–Whitney tests. Correlation coefficients were calculated for the association of blood burden and quantitative degree of vasospasm. Odds ratios for rate of outcomes in those with diffuse versus PM-SAH were calculated using logistic regression modeling, after adjustment for covariates, specifically blood burden and established predictors (ie, age and World Federation of Neurosurgical Societies grade).
Results
Our cohort comprised 29 patients with diffuse bleeding and 60 with PM-SAH (Figure). Characteristics of patients are compared in the Table. Those with diffuse bleeding had higher Hijdra and IVH scores and a trend toward worse clinical severity. They were also more likely to develop angiographic vasospasm (45% versus 27%; odds ratio, 2.9; \( P = 0.08 \)), including more severe vasospasm (17% versus 7%; \( P = 0.12 \)). Neither Hijdra nor IVH scores were higher in subjects developing vasospasm compared with those unaffected, and there was no correlation between Hijdra/IVH scores and degree of stenosis. Despite greater blood volume in those with diffuse bleeding, adjustment for Hijdra/IVH scores only minimally attenuated the association between pattern of bleeding and risk of vasospasm (adjusted odds ratio, 2.2; 95% confidence interval, 0.69–7.2; \( P = 0.18 \)). One-year follow-up (available for 67) indicated a trend to worse functional outcome in those with diffuse bleeding (modified Rankin scale, 3–6 in 20% versus 6% in PM-SAH; \( P = 0.18 \)).

Patients with PM-SAH were more likely discharged home (90% versus 68%; \( P = 0.01 \)). One-year follow-up (available for 67) indicated a trend to worse functional outcome in those with diffuse bleeding (modified Rankin scale, 3–6 in 20% versus 6% in PM-SAH; \( P = 0.18 \)).

Discussion
Pattern of bleeding seems to be the primary determinant of the risk for neurological injury after idiopathic SAH. Those with PM-SAH had a lower rate of vasospasm, similar to that reported in prior studies.\(^5\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^11\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\) The higher risk seen in those with diffuse bleeding was still somewhat lower than that seen in aneurysmal SAH and was not associated with infarction.\(^2\) This could be accounted for by the fact that none of even the diffuse nonaneurysmal patients had Hijdra sum scores \( \geq \)23, a threshold above which vasospasm was especially frequent in a recent study of aneurysmal SAH.\(^7\)

Most prior studies have assumed that the higher risk of vasospasm in those with diffuse bleeding was mediated by differences in blood burden.\(^4\) We are the first to measure Hijdra scores in a large cohort with diffuse versus PM-SAH, confirming that although diffuse bleeding is associated with more intracranial blood, this disparity does not seem to explain the vasospasm risk. In fact, we did not find an association between blood burden and vasospasm (whether quantified or categorized) in contradistinction to studies in aneurysmal SAH which correlate Hijdra score with risk of vasospasm/DCI.\(^7\)\(^,\)\(^,\)\(^13\) This unexpected novel finding echoes that demonstrated in an earlier study showing that those with PM-SAH had a lower risk of vasospasm than a matched cohort with aneurysmal SAH despite similar Hijdra scores.\(^14\)

There may be pathophysiologic distinctions between diffuse and PM-SAH that contribute to their differential course. The bleeding may be arterial in diffuse cases, compared with a venous origin postulated for PM-SAH; venous blood may lack factors that trigger the vasospasm cascade. Arterial rupture may also precipitate increases in intracranial pressure and early brain injury, as implicated in the pathogenesis of DCI. The diffuse distribution of blood, around the entire circle of Willis, may also be more likely to induce vasospasm than focal PM-SAH which does not envelop the entirety of the proximal intracranial arteries.

Despite a differential risk of vasospasm, the majority of patients with idiopathic SAH still do well. Prior studies have shown similar high rates achieving functional recovery, especially among those with PM-SAH.\(^1\)\(^,\)\(^,\)\(^11\) Those with diffuse bleeding seemed to do somewhat worse, although we had too few patients with long-term follow-up to confirm significant differences in functional outcome.

Limitations
Despite prospectively studying a large, well-defined cohort of patients with idiopathic SAH, we still had too few patients with poor clinical status and follow-up data to relate initial severity and functional outcome. Although our use of the validated Hijdra score allowed us to analyze the relationship

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**Table. Demographic, Clinical, and Radiographic Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Perimesencephalic (n=60)</th>
<th>Diffuse (n=29)</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>54±12</td>
<td>55±11</td>
<td>NS</td>
</tr>
<tr>
<td>Male</td>
<td>25 (42%)</td>
<td>8 (28%)</td>
<td>NS</td>
</tr>
<tr>
<td>Race, white</td>
<td>51 (85%)</td>
<td>22 (76%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>30 (50%)</td>
<td>16 (55%)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>12 (20%)</td>
<td>3 (10%)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking</td>
<td>13 (22%)</td>
<td>8 (29%)</td>
<td>NS</td>
</tr>
<tr>
<td>WFNS IV–V</td>
<td>3 (5%)</td>
<td>5 (17%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Hijdra score, median (IQR)</td>
<td>5 (3–8)</td>
<td>12 (7–17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IVH score, median (IQR)</td>
<td>0 (0–2)</td>
<td>2 (0–7)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

IQR indicates interquartile range; IVH, intraventricular hemorrhage; NS, not significant; and WFNS, World Federation of Neurosurgical Societies grading.

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**Figure.** Flow of patients with subarachnoid hemorrhage (SAH) into this cohort. CTA indicates computed tomography angiography; and LP, lumbar puncture.
between blood burden and vasospasm for the first time, a quantitative volumetric approach may have uncovered subtle but important differences in volume and location of bleeding. Finally, although we did not detect DCI-related infarcts in this cohort, it is possible that some patients had asymptomatic and therefore undetected infarction. However, the incidence of asymptomatic infarction is likely even lower in those with idiopathic SAH than that seen in those with aneurysmal SAH, especially given that the majority had normal functional recovery. A multicenter study with prospective imaging could address some of these limitations.

Acknowledgments
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Disclosures
None.

References
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