Defining Vasospasm After Subarachnoid Hemorrhage
What Is the Most Clinically Relevant Definition?

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Background and Purpose—Vasospasm is an important complication of subarachnoid hemorrhage, but is variably defined in the literature.

Methods—We studied 580 patients with subarachnoid hemorrhage and identified those with: (1) symptomatic vasospasm, defined as clinical deterioration deemed secondary to vasospasm after other causes were eliminated; (2) delayed cerebral ischemia (DCI), defined as symptomatic vasospasm, or infarction on CT attributable to vasospasm; (3) angiographic spasm, as seen on digital subtraction angiography; and (4) transcranial Doppler (TCD) spasm, defined as any mean flow velocity >120 cm/sec. Logistic regression analysis was performed to test the association of each definition of vasospasm with various hospital complications, and 3-month quality of life (sickness impact profile), cognitive status (telephone interview of cognitive status), instrumental activities of daily living (Lawton score), and death or severe disability at 3 months (modified Rankin scale score 4–6), after adjustment for covariates.

Results—Symptomatic vasospasm occurred in 16%, DCI in 21%, angiographic vasospasm in 31%, and TCD spasm in 45% of patients. DCI was statistically associated with more hospital complications (N=7; all P<0.05) than symptomatic spasm (N=4), angiographic spasm (N=1), or TCD vasospasm (N=1). Angiographic and TCD vasospasm were not related to any aspect of clinical outcome. Both symptomatic vasospasm and DCI were related to reduced instrumental activities of daily living, cognitive impairment, and poor quality of life (all P<0.05). However, only DCI was associated with death or severe disability at 3 months (adjusted OR, 2.2; 95% CI, 1.2–3.9; P=0.007).

Conclusions—DCI is a more clinically meaningful definition than either symptomatic deterioration alone or the presence of arterial spasm by angiography or TCD. (Stroke. 2009;40:1963-1968.)

Key Words: angiography • delayed cerebral ischemia • outcome • subarachnoid hemorrhage • transcranial Doppler • vasospasm

Cerebral vasospasm is an important cause of morbidity after subarachnoid hemorrhage (SAH).1,2 Throughout the literature, authors have used various means of defining vasospasm using terms including symptomatic vasospasm, delayed cerebral ischemia (DCI), transcranial Doppler vasospasm, and angiographic vasospasm. Each definition has its own strengths and limitations. Symptomatic vasospasm occurs in 20% to 40% of SAH patients3,4 and typically refers to clinical worsening after other possible causes of deterioration have been eliminated. This is a subjective diagnosis and can be limited in poor-grade cases in which variations in the examination may be subtle or imperceptible.5 DCI is defined as symptomatic vasospasm, infarction attributable to vasospasm, or both.6 DCI allows for the diagnosis of clinically relevant vasospasm in poor-grade cases with limited neurological examinations; however, infarcts attributable to spasm must be distinguished from those attributable to surgery, angiography, or other causes. Additionally, DCI is a retrospective diagnosis made once an infarct is detected and, thus, possible interventions to mitigate this outcome are limited. Angiographic vasospasm occurs in up to 70% of patients,3,4,7 but the relationship between angiographic spasm and clinical symptoms can be inconsistent, and just how extensive or severe angiographic spasm must be to become clinically relevant remains unclear.8 Transcranial Doppler ultrasound (TCD) is commonly used to diagnose vasospasm, although its positive and negative predictive values for angiographic spasm of the middle cerebral artery is adequate, its sensitivity for detecting angiographic vasospasm of the anterior cerebral artery and distal cerebral vasculature is poor, and the relationship between TCD abnormalities and clinical worsening is unreliable.9,10

In this study, we aimed to determine the clinical relevance of each definition of vasospasm. We identified demographic,
clinical, and radiographic risk factors for each definition of spasm, examined associations with hospital complications, and determined the strength of association of each form of vasospasm with functional and cognitive outcome at 3 months.

Subjects and Methods

Patient Population

The Columbia University SAH Outcomes Project prospectively enrolled 580 consecutive patients with spontaneous SAH admitted to the Neurological Intensive Care Unit, between July 1, 1996 and May 1, 2002. The study was approved by the hospital Institutional Review Board, and in all cases written informed consent was obtained from the patient or a surrogate. The diagnosis of SAH was established on the basis of admission CT scans or by xanthochromia of the cerebrospinal fluid. Exclusion criteria included secondary SAH from trauma, arteriovenous malformation, or other causes, age younger than 18 years, or admission >14 days after SAH onset.

Definitions of Vasospasm

Symptomatic vasospasm was defined as the development of new focal neurological signs, deterioration in level of consciousness, or both, when the cause was felt to be ischemia attributable to vasospasm after other possible causes of worsening (for example, hydrocephalus, seizures, metabolic derangement, infection, or over-sedation) had been excluded. The diagnosis of symptomatic vasospasm was adjudicated on a weekly basis by consensus of the study team (authors S.A.M. and E.S.C.). DCI was defined as symptomatic vasospasm or the appearance of new infarction on CT or MR when the cause was felt to be attributable to vasospasm. Imaging studies were reviewed by the study team to differentiate infarction from other causes of hypodensity. Angiographic vasospasm was defined as moderate-to-severe arterial narrowing on digital subtraction angiography not attributable to atherosclerosis, catheter-induced spasm, or vessel hypoplasia, as determined by a neuroradiologist. TCD vasospasm was defined as a mean flow velocity in any vessel >120 cm/sec. We chose this cut-point because it is commonly used in the literature when examining the association with angiographic or symptomatic vasospasm. We constructed a receiver-operating characteristic curve to identify velocities with the greatest sensitivity and specificity for predicting each outcome.

Clinical Management

The management of these patients has been described in detail previously. All patients received nimodipine every 4 hours and phenytoin perioperatively for seizure prophylaxis. All patients received 0.9% normal saline at a rate of 1 mL/kg per hour and supplemental 5% albumin solution was administered to maintain central venous pressure >5 mm Hg. All patients underwent digital subtraction angiography on admission, and then between SAH days 4 and 8 in patients with poor-grade status (Hunt-Hess grade 3–5), or as needed to evaluate neurological deterioration or new infarction on CT, or as accelerated TCD values. Candidate demographic and clinical variables were assessed in a univariate analysis and then used to create a multivariable model for independent associations with each vasospasm type using binary logistic regression. Candidate variables were entered in a forward stepwise fashion. Among similar clinical variables that were inter-correlated, only the variable with the highest OR and smallest P value were used as candidate values in the final multivariate model. The association of each type of vasospasm with hospital complications was adjusted for intensive care unit length of stay.

Established independent admission predictors of the outcome measures that we evaluated (modified Rankin scale, Lawton instrumental activities of daily living, telephone interview of cognitive status, and sickness impact profile total score) were used to construct multiple logistic regression models. The modified Rankin outcome was adjusted for age, Hunt-Hess grade, and aneurysm size. The sickness impact profile was adjusted for Hunt-Hess grade, race, and education level. The telephone interview of cognitive status was adjusted for age, Hunt-Hess grade, race, and education level. Each vasospasm type was then added individually to these models to calculate adjusted OR for the strength of association of each type of vasospasm with each aspect of outcome. Tests for interactions were performed for all significant variables in the multivariable models. Significance was set at P≤0.05 for all analyses.
Of 580 SAH patients, the mean age was 53 years (16–89), 68% were female, 64% (N = 310) underwent aneurysm clipping, and 20% (N = 95) underwent aneurysm coiling (data on aneurysm repair was missing in 93 patients and 12% of patients did not have an identifiable aneurysm). Symptomatic vasospasm occurred in 16% of patients, delayed cerebral ischemia in 21%, angiographic vasospasm in 31%, and TCD spasm was associated only with intracerebral hemorrhage. TCD spasm was predicted by younger age, female gender, and thick SAH clot on CT (Table 1).

After adjusting for intensive care unit length of stay, DCI was associated with 7 hospital complications, including clinically significant arrhythmia, pulmonary edema, myocardial infarction, cerebral edema, fever (>38.3°C), pneumonia, and blood stream infection. Symptomatic vasospasm was associated with 4 hospital complications (pulmonary edema, myocardial infarction, fever, and blood stream infection), angiographic vasospasm was associated only with intracerebral hemorrhage, and TCD spasm was associated only with blood stream infection (Table 2). When examining 3-month outcome measures, only DCI was independently associated with severe disability or death (modified Rankin score 4–6) after adjusting for established baseline predictors. Both DCI and symptomatic vasospasm was also associated with worse instrumental activities of daily living (Lawton instrumental activities of daily living scale ≥9), cognitive impairment (telephone interview of cognitive status ≤30), and worse quality of life (sickness

**Results**

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impact profile (≥15.5). Angiographic and TCD vasospasm were not associated with any outcome measures (Table 3). An ROC curve analysis was not helpful in identifying a cut-point that was superior to a mean flow velocity of 140 cm/sec for predicting 3-month outcomes. We performed a secondary analysis using the cut-point of 140 cm/sec, but we did not find any significant relationship with any outcome measure on univariate analysis.

Both hospital and intensive care unit length of stay were significantly prolonged in each vasospasm cohort (Mann–Whitney U; P<0.001), although the effect was most pronounced in those with DCI or symptomatic vasospasm (Figure.).

**Discussion**

The medical literature has used a variety of terms to describe delayed ischemic complications related to SAH. Vasospasm may be defined on a clinical, radiographic, Doppler, or angiographic basis. As of August 2008, a search of PubMed revealed 561 articles using the term “symptomatic vasospasm,” 181 articles using “angiographic vasospasm,” 504 articles using “transcranial Doppler and cerebral vasospasm” and 134 using “delayed cerebral ischemia.” Mixed terminology can lead to confusion in the interpretation of the relevance of vasospasm as an outcome. In this study, we demonstrated that DCI, a definition that incorporates both symptomatic worsening or cerebral infarction, is the most clinically relevant definition of vasospasm, because it has the strongest associations with overall poor outcome, cognitive impairment, and reduced quality of life. In addition, we found that DCI corresponds in general with a more complicated hospital course than the other definitions of vasospasm.

DCI encompasses not only symptomatic deterioration in the neurological examination but also radiographic evidence of ischemia or infarction in patients with marginal exams in whom ischemia may go undetected. In a recent study, we found that ≈20% of SAH patients who meet the definition of DCI experience new infarction from spasm in the absence of concurrent deterioration, that this phenomenon occurs most commonly in comatose patients, and that these clinically

### Table 2. Hospital Complications in Patients With Symptomatic Vasospasm, Delayed Cerebral Ischemia, Angiographic Vasospasm, and TCD-Defined Vasospasm, Adjusted for Intensive Care Unit Length of Stay

<table>
<thead>
<tr>
<th>Complication</th>
<th>Symptomatic Vasospasm</th>
<th>Delayed Cerebral Ischemia</th>
<th>Angiographic Vasospasm</th>
<th>TCD Vasospasm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>aOR (95% CI)</td>
<td>P</td>
<td>N (%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>13 (14)</td>
<td>1.9 (0.9–3.8)</td>
<td>0.080</td>
<td>17 (14)</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>26 (27)</td>
<td>2.1 (1.2–3.6)</td>
<td>0.008</td>
<td>31 (26)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>11 (12)</td>
<td>2.3 (1.0–4.9)</td>
<td>0.038</td>
<td>13 (11)</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>10 (11)</td>
<td>1.1 (0.5–2.3)</td>
<td>0.827</td>
<td>17 (14)</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>50 (53)</td>
<td>1.4 (0.9–2.2)</td>
<td>0.151</td>
<td>68 (56)</td>
</tr>
<tr>
<td>Intracerebral edema</td>
<td>16 (17)</td>
<td>0.8 (0.4–1.5)</td>
<td>0.486</td>
<td>27 (22)</td>
</tr>
<tr>
<td>Fever (≥38.3°C)</td>
<td>73 (77)</td>
<td>2.5 (1.5–4.3)</td>
<td>0.001</td>
<td>95 (78)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>34 (36)</td>
<td>1.2 (0.8–2.0)</td>
<td>0.361</td>
<td>44 (36)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>24 (25)</td>
<td>1.0 (0.6–1.7)</td>
<td>0.973</td>
<td>38 (31)</td>
</tr>
<tr>
<td>Blood stream infection</td>
<td>16 (17)</td>
<td>2.5 (1.3–4.9)</td>
<td>0.006</td>
<td>19 (16)</td>
</tr>
</tbody>
</table>

aOR indicates adjusted odds ratio.

### Table 3. Effect of Symptomatic Vasospasm, Delayed Cerebral Ischemia, Angiographic Vasospasm, and TCD-Defined Vasospasm on Outcome

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Symptomatic Vasospasm</th>
<th>Delayed Cerebral Ischemia</th>
<th>Angiographic Vasospasm</th>
<th>TCD Vasospasm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>aOR (95% CI)</td>
<td>P</td>
<td>N (%)</td>
</tr>
<tr>
<td>mRS 6</td>
<td>19 (20)</td>
<td>1.1 (0.6–2.2)</td>
<td>0.751</td>
<td>31 (26)</td>
</tr>
<tr>
<td>mRS 4–6</td>
<td>27 (28)</td>
<td>1.3 (0.7–2.5)</td>
<td>0.360</td>
<td>44 (36)</td>
</tr>
<tr>
<td>Lawton IADL Scale ≥9</td>
<td>48 (51)</td>
<td>1.9 (1.1–3.6)</td>
<td>0.031</td>
<td>56 (46)</td>
</tr>
<tr>
<td>TICS ≥30</td>
<td>23 (24)</td>
<td>2.5 (1.1–5.6)</td>
<td>0.027</td>
<td>26 (22)</td>
</tr>
<tr>
<td>SIP total ≥15.5</td>
<td>42 (44)</td>
<td>1.9 (1.0–3.6)</td>
<td>0.048</td>
<td>51 (42)</td>
</tr>
</tbody>
</table>

IADL indicates independent activities of daily living; mRS, modified Rankin scale; SIP, sickness impact profile; TICS, telephone interview of cognitive status.
mRS adjusted for age, Hunt-Hess, and aneurysm size.
SIP adjusted for Hunt-Hess, race, and education.
TICS adjusted for Hunt-Hess, race, age, and education.
Lawton adjusted for Hunt-Hess, race, and education.
“silent” infarcts independently contribute to poor outcome. The diagnosis of DCI is limited, however, because it is made retrospectively once an infarct is found radiographically. This may have caused a delay in diagnosis allowing for under-treatment of ongoing ischemia. We did not perform serial MRI or CT on a scheduled basis, but rather on an as-needed basis. Performing serial radiographic examinations looking for ischemia using perfusion/diffusion mismatch modeling might allow for intervention to prevent the progression to infarction. Similarly, serial MRI or CT perfusion imaging that detects infarction may allow for medical or endovascular treatment that would prevent further infarction from occurring.

Symptomatic vasospasm was also independently associated with reduced instrumental activities of daily living, cognitive impairment, and poor quality of life in our study, but not with death or severe disability. The development of arterial spasm as diagnosed by angiography or TCD had no consistent relationship with 3-month outcome. Hence, DCI appears to be both the most inclusive and clinically meaningful definition for capturing the adverse effects of vasospasm after SAH. Although past studies have shown delayed complications or “vasospasm” to be associated with mortality after SAH, DCI, symptomatic vasospasm, angiographic, and TCD vasospasm were not associated with death in our study. This may be attributable to more aggressive medical and endovascular therapies for vasospasm and modern neuro-intensive care.

Not all patients who experience DCI have angiographic vasospasm, and not all patients with angiographic spasm have DCI. Cerebral infarction correlates with the territory of angiographic vasospasm in only 25% to 81% of SAH patients. In our study, only 84% of patients with DCI had angiographic evidence of vasospasm. Studies demonstrating the presence of prolonged cerebral circulation times on angiography in the absence of proximal arterial spasm suggest that circulatory impairment at the microvascular level may sometimes play a role in the development of DCI. Nimodipine has been shown to reduce the incidence of DCI and poor outcome after SAH, yet has no clear effect on angiographic vasospasm. Conversely, clazosentan, an endothelin receptor antagonist, has been shown to significantly reduce moderate to severe angiographic vasospasm; however, in a phase II study, it had no significant effect on DCI, symptomatic vasospasm, morbidity, mortality, or new cerebral infarct from any cause. These observations indicate that the diagnosis of large vessel spasm by angiography or TCD alone does not capture the full pathophysiological spectrum of delayed ischemia after SAH.

We found similar admission risk factors for symptomatic vasospasm and DCI (poor clinical grade, admission hypertension, and thick cisternal clot) as other authors. By contrast, angiographic vasospasm was predicted by younger age, poor clinical grade, cigarette smoking, and intracerebral hemorrhage (Table 1). Although DCI and symptomatic vasospasm were associated with the most hospital complications, it is possible that the medical treatment for these conditions, including induced hypertension and hypervolemia, may have led to other complications such as cardiac arrhythmia, pulmonary edema, myocardial infarction, or cerebroedema. Our data were not coded temporally to allow us to parse apart causality. In regard to the association of TCD vasospasm and blood stream infection, it is possible that some of the elevated velocities recorded were related to hyperemia rather than true vessel spasm. Lindegaard ratios, which would have allowed for such differentiation, were not recorded.

There are several other limitations of our study that are important to point out. First, this is a single center study, which may limit generalizability to different institutions. Although we constructed receiver-operating characteristic curves to identify velocities with the greatest sensitivity and specificity for predicting each outcome, the curves were nearly linear and not useful at identifying an appropriate cut-point, further demonstrating the poor sensitivity and specificity of TCD for predicting outcome. We chose the cut-point of 120 cm/sec because this is a frequently used threshold in the literature. Similarly, we defined angiographic vasospasm in a qualitative fashion, rather than by specifying a percentage of stenosis, because we felt this was more generalizable, although more specific quantification may have improved the predictive value of angiographic spasm.

In conclusion, of the variously used definitions of “vasospasm” that occur in the literature, only DCI was independently associated with poor outcome across the full spectrum of recovery, from death or severe disability to poor quality of life.

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Disclosures

None.

References


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