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Defining Vasospasm After Subarachnoid Hemorrhage

What Is the Most Clinically Relevant Definition?

Jennifer A. Frontera, MD; Andres Fernandez, MD; J. Michael Schmidt, PhD; Jan Claassen, MD; Katja E. Wartenberg, MD; Neeraj Badjatia, MD; E. Sander Connolly, MD; Stephan A. Mayer, MD

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 patients^{3,4} 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,

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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.^{7,9,10} 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.⁶ 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 for accelerated TCD values among patients with good-grade status. All patients underwent standardized serial neurological examinations performed off sedation throughout each day. Head CT was performed on an as-needed basis for clinical purposes only; prearranged routine serial CT scans were not performed. TCD were performed daily by 1 of 2 technicians at the same time each morning.

Patients in whom symptomatic vasospasm or DCI developed were treated with vasopressors (usually phenylephrine or norepinephrine) to maintain a systolic blood pressure between 180 and 220 mm Hg, adjusted to clinical response, or inotropes to maintain a cardiac index >4.0 L/min per meter squared with milrinone or dobutamine as needed. Normal saline and 5% albumin solution was administered to maintain positive fluid balance and central venous pressure >8 mm Hg, and blood transfusions were performed to maintain a target hemoglobin of >10 mg/dL. Angiography was routinely performed on patients in whom symptomatic spasm or DCI devel-

oped. Endovascular treatment of vasospasm entailed either intra-arterial chemical vasodilation with papaverine or verapamil or angioplasty. The decision to perform endovascular intervention was made at the discretion of the interventionalist.

Clinical and Radiographic Assessment

We recorded baseline data as previously described.^{6,11–13} Admission neurological status was evaluated with the Hunt-Hess scale.¹² Hospital complications were recorded including clinically significant arrhythmia (defined as any cardiac arrhythmia other than sinus tachycardia or bradycardia or sinus rhythm with premature atrial or ventricular complexes), pulmonary edema (diagnosed by clinical examination and chest X-ray), myocardial infarction (diagnosed by ECG, troponin values, and echocardiography), cardiac arrest, cerebral edema (diagnosed by CT), fever (>38.3°C), hyperglycemia (>200 mg/dL), pneumonia (defined as a new infiltrate on chest X-ray with either fever, hypoxemia, or purulent secretions), and blood stream infection (defined by ≥ 2 positive blood cultures). Hospital and intensive care unit length of stay were documented.

Outcome Measures

Survival and functional outcome were assessed at 3 months using the modified Rankin scale (0=full recovery; 6=death); poor outcome was defined as death or severe disability (modified Rankin scale score 4–6). High-level instrumental disability (ie, shopping, using a telephone, writing checks) was assessed with the Lawton instrumental activities of daily living scale (score: 8=fully independent, 30=completely dependent),¹⁴ and evaluated as fully independent vs some dependency. Quality of life was assessed with the sickness impact profile total score (score: 0=no dysfunction, 100=maximal dysfunction),¹⁵ and dichotomized at the median value of the SAH study population. Global cognitive function was evaluated with the telephone interview of cognitive status (score: 51=best, 0=worst),¹⁶ with cognitive impairment defined as a score of ≤ 30 .¹⁷ Outcome data were collected via phone interview either with the patient or with a surrogate if the patient was unable to participate via telephone.

Statistical Analysis

We evaluated admission predictors of symptomatic vasospasm, DCI, angiographic vasospasm and TCD vasospasm, associations of each type of vasospasm with hospital complications, and associations of each type of spasm with 3-month clinical outcomes. Continuous variables were dichotomized based on clinical cut-points or median 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.^{6,18} 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. The Lawton score was adjusted for 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 $P \leq 0.05$ for all analyses.

Table 1. Admission Risk Factors for the Development of Symptomatic Vasospasm and Infarct on CT Attributable to Vasospasm or Delayed Cerebral Ischemia

Risk Factor	Symptomatic Vasospasm			Delayed Cerebral Ischemia			Angiographic Vasospasm			TCD Vasospasm		
	N (%)	OR (95% CI)	P	N (%)	OR (95% CI)	P	N (%)	OR (95% CI)	P	N (%)	OR (95% CI)	P
Demographic												
Age >53	45 (47)	1.2 (0.8–1.9)	0.411	67 (55)	1.4 (0.9–2.1)	0.097	76 (42)	0.6 (0.4–0.9)	0.018	89 (34)	0.3 (0.2–0.5)	<0.001
Gender (female)	72 (76)	1.6 (1.0–2.6)	0.075	90 (74)	1.5 (1.0–2.4)	0.076	126 (70)	1.0 (0.6–1.6)	0.941	188 (72)	1.5 (1.0–2.2)	0.030
Nonwhite race	39 (41)	0.7 (0.4–1.1)	0.093	50 (41)	0.7 (0.5–1.0)	0.063	84 (46)	1.0 (0.7–1.6)	0.864	132 (51)	1.2 (0.8–1.6)	0.435
Medical history												
Tobacco use in 6 mon	42 (44)	1.2 (0.8–2.0)	0.373	55 (46)	1.4 (0.9–2.2)	0.109	87 (48)	1.9 (1.2–3.1)	0.006	123 (47)	1.4 (1.0–2.1)	0.060
Hypertension	47 (49)	1.2 (0.7–1.8)	0.519	62 (51)	1.3 (0.9–2.0)	0.172	86 (48)	0.8 (0.5–1.3)	0.450	112 (43)	0.7 (0.5–1.0)	0.087
Admission clinical features												
MAP >112	60 (63)	2.1 (1.4–3.4)	0.001	75 (62)	2.1 (1.4–3.2)	<0.001	99 (55)	1.4 (0.9–2.2)	0.116	124 (48)	1.0 (0.7–1.5)	0.899
APACHE II subscore ≥5	57 (60)	1.4 (0.9–2.2)	0.146	75 (62)	1.6 (1.1–2.5)	0.020	104 (58)	1.4 (0.9–2.3)	0.103	147 (56)	1.4 (1.0–2.0)	0.060
Hunt–Hess grade ≥3	68 (72)	2.0 (1.3–3.3)	0.004	90 (74)	2.6 (1.6–4.0)	<0.001	106 (59)	1.7 (1.1–2.6)	0.027	155 (59)	1.2 (0.8–1.7)	0.369
Admission radiographic features												
IVH present	22 (23)	1.1 (0.6–1.8)	0.840	33 (27)	1.5 (0.9–2.3)	0.107	36 (20)	0.9 (0.5–1.6)	0.852	58 (22)	1.2 (0.8–1.8)	0.493
ICH present	17 (18)	1.2 (0.7–2.1)	0.546	25 (21)	1.6 (0.9–2.7)	0.084	32 (18)	2.9 (1.4–6.2)	0.005	40 (15)	1.0 (0.6–1.6)	1.000
Aneurysm size ≥10 mm	24 (25)	1.3 (0.8–2.2)	0.351	33 (27)	1.6 (1.0–2.5)	0.060	39 (22)	1.1 (0.6–1.8)	0.806	59 (23)	1.1 (0.7–1.7)	0.751
SAH sum score	62 (65)	1.0 (0.1–1.1)	0.007	73 (60)	1.0 (0.0–1.1)	0.034	105 (58)	1.0 (1.0–1.1)	0.079	162 (62)	1.0 (1.0–1.1)	0.001

*As assessed by the Hijdra sum score.¹¹

APACHE indicates Acute Physiology and Chronic Health Evaluation; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; MAP, mean arterial pressure.

Results

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 in 45%. Both symptomatic vasospasm and DCI were highly correlated with angiographic and TCD spasm. Of those with symptomatic vasospasm, 85% also had angiographic spasm and 81% had TCD spasm. Of those with DCI, 84% had angiographic spasm and 76% had TCD spasm. Conversely, angiographic and TCD spasm were less well-correlated with symptomatic spasm or DCI. Of those with angiographic vasospasm, only 34% had symptomatic spasm, 41% had DCI, and 72% had TCD spasm. Similarly, of those with TCD spasm, only 28% had symptomatic spasm, and 34% had DCI. Stratification by Hunt-Hess grade (1–2 vs 3–5) did not remarkably change these correlations.

Significant univariate admission risk factors for symptomatic vasospasm and delayed cerebral ischemia were similar and included elevated mean arterial pressure at admission (>112 mm Hg), poor Hunt-Hess grade (≥3), thick SAH clot

on CT, and poor APACHE II subscore (for DCI only). Admission risk factors for angiographic spasm were more diverse, including younger age, tobacco use in the past 6 months, poor Hunt-Hess grade (≥3), and 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

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

Complication	Symptomatic Vasospasm			Delayed Cerebral Ischemia			Angiographic Vasospasm			TCD Vasospasm		
	N (%)	aOR (95% CI)	P	N (%)	aOR (95% CI)	P	N (%)	aOR (95% CI)	P	N (%)	aOR (95% CI)	P
Arrhythmia	13 (14)	1.9 (0.9–3.8)	0.080	17 (14)	2.2 (1.1–4.3)	0.020	15 (8)	0.8 (0.4–1.9)	0.639	24 (9)	1.2 (0.6–2.2)	0.674
Pulmonary edema	26 (27)	2.1 (1.2–3.6)	0.008	31 (26)	2.0 (1.2–3.4)	0.009	29 (16)	0.7 (0.4–1.3)	0.277	48 (18)	1.3 (0.8–2.1)	0.357
Myocardial infarction	11 (12)	2.3 (1.0–4.9)	0.038	13 (11)	2.2 (1.1–4.7)	0.036	10 (6)	0.7 (0.3–1.7)	0.428	13 (5)	0.6 (0.3–1.4)	0.253
Cardiac arrest	10 (11)	1.1 (0.5–2.3)	0.827	17 (14)	1.8 (1.0–3.4)	0.066	17 (9)	1.1 (0.5–2.3)	0.905	20 (8)	0.9 (0.4–1.7)	0.669
Cerebral edema	50 (53)	1.4 (0.9–2.2)	0.151	68 (56)	1.8 (1.2–2.7)	0.006	93 (51)	1.4 (0.9–2.3)	0.125	119 (46)	1.1 (0.8–1.6)	0.609
Intracerebral hemorrhage	16 (17)	0.8 (0.4–1.5)	0.486	27 (22)	1.3 (0.8–2.2)	0.268	35 (19)	2.2 (1.1–4.6)	0.036	51 (20)	1.3 (0.8–2.1)	0.288
Fever (>38.3°)	73 (77)	2.5 (1.5–4.3)	0.001	95 (78)	3.2 (1.9–5.2)	<0.001	111 (61)	1.1 (0.7–1.7)	0.814	167 (64)	1.4 (1.0–2.1)	0.070
Hyperglycemia	34 (36)	1.2 (0.8–2.0)	0.361	44 (36)	1.4 (0.9–2.1)	0.150	65 (36)	1.1 (0.7–1.8)	0.670	75 (29)	0.9 (0.6–1.3)	0.596
Pneumonia	24 (25)	1.0 (0.6–1.7)	0.973	38 (31)	1.7 (1.0–2.7)	0.038	46 (25)	1.4 (0.8–2.4)	0.299	60 (23)	1.0 (0.6–1.5)	0.876
Blood stream infection	16 (17)	2.5 (1.3–4.9)	0.006	19 (16)	2.5 (1.3–4.7)	0.005	17 (9)	0.9 (0.4–2.1)	0.870	31 (12)	2.1 (1.1–4.0)	0.034

aOR indicates adjusted odds ratio.

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 120 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 361 articles using the term “symptomatic vaso-

spasm,” 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,⁵ we found that $\approx 20\%$ 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 3. Effect of Symptomatic Vasospasm, Delayed Cerebral Ischemia, Angiographic Vasospasm, and TCD-Defined Vasospasm on Outcome

Outcome	Symptomatic Vasospasm			Delayed Cerebral Ischemia			Angiographic Vasospasm			TCD Vasospasm		
	N (%)	aOR (95% CI)	P	N (%)	aOR (95% CI)	P	N (%)	aOR (95% CI)	P	N (%)	aOR (95% CI)	P
mRS 6	19 (20)	1.1 (0.6–2.2)	0.751	31 (26)	1.6 (0.9–3.0)	0.124	25 (14)	0.9 (0.4–2.0)	0.892	36 (14)	1.3 (0.7–2.4)	0.451
mRS 4–6	27 (28)	1.3 (0.7–2.5)	0.360	44 (36)	2.2 (1.2–3.9)	0.007	36 (20)	1.0 (0.5–2.1)	0.910	53 (20)	1.4 (0.8–2.5)	0.232
Lawton IADL Scale ≥ 9	48 (51)	1.9 (1.1–3.6)	0.031	56 (46)	1.8 (0.1–3.2)	0.032	70 (39)	1.2 (0.7–2.2)	0.451	102 (39)	1.0 (0.7–1.7)	0.849
TICS ≤ 30	23 (24)	2.5 (1.1–5.6)	0.027	26 (22)	2.7 (1.3–5.9)	0.011	35 (19)	1.8 (0.8–3.9)	0.155	47 (18)	1.2 (0.6–2.2)	0.653
SIP total ≥ 15.5	42 (44)	1.9 (1.0–3.6)	0.048	51 (42)	2.3 (1.3–4.2)	0.006	67 (37)	1.6 (0.9–2.9)	0.136	95 (36)	1.1 (0.7–1.8)	0.639

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

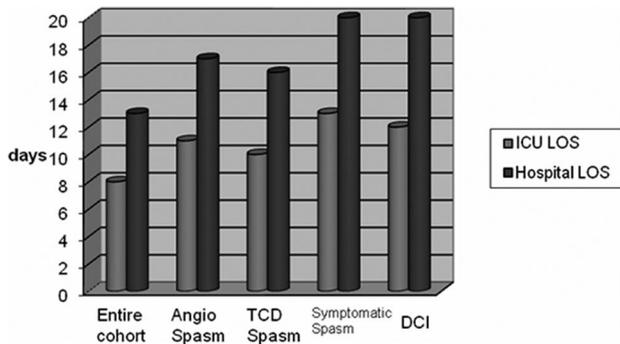


Figure. Intensive care unit and hospital length of stay for all SAH patients and patients with angiographic vasospasm, TCD vasospasm, symptomatic vasospasm, and DCI.

“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 undertreatment 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/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,^{1,2} 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 neurointensive care.

Not all patients who experience DCI have angiographic vasospasm, and not all patients with angiographic spasm have DCI.^{3,4,7} Cerebral infarction correlates with the territory of angiographic vasospasm in only 25% to 81% of SAH patients.^{19–21} 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.^{22,23} Nimodipine has been shown to reduce the incidence of DCI and poor outcome after SAH, yet has no clear effect on angiographic vasospasm.^{24,25} 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.²⁶ 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.^{6,27,28} 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 cerebral edema. 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.^{7,10,29} Similarly, we defined angiographic spasm 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.

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