Hemodynamically significant cerebral vasospasm and outcome after head injury: a prospective study

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The authors prospectively investigated cerebral hemodynamic changes in 152 patients with head injuries to clarify
the relationship between cerebral vasospasm and outcome. They also sought to determine the most clinically mean-
ingful criteria for diagnosing cerebral vasospasm. Patients with varying degrees of moderate-to-severe head injury
were monitored using transcranial Doppler (TCD) ultrasonography and intravenous $^{133}$Xe–cerebral blood flow (CBF)
measurements. Outcome was determined at 6 months. Using TCD ultrasonography, mean flow velocities were deter-
mimed for the middle cerebral artery ($V_{mca}$, 149 patients) and basilar artery ($V_{ba}$, 126 patients). Recordings of the mean
extracranial internal carotid artery velocity ($V_{ec-ica}$) were also performed to determine the hemispheric ratio ($V_{mca}/V_{ec-ica}$,
147 patients). Cerebral blood flow measurements were obtained in 91 patients. Concurrent TCD and CBF data from
85 patients were used to calculate a “spasm index” (the $V_{mca}$ or $V_{ba}$, respectively, divided by the hemispheric or glob-
al CBF). The authors investigated the clinical significance of elevated flow velocity, hemispheric ratio, and spasm
index. Patients diagnosed as having MCA or BA vasospasm on the basis of TCD-derived criteria alone had a significa-
antly worse outcome than patients without vasospasm. When CBF was considered, hemodynamically significant
vasospasm, as defined by an elevated spasm index, was even more strongly associated with poor outcome. Stepwise
logistic regression analysis confirmed that hemodynamically significant vasospasm was a significant predictor of poor
outcome, independent of the effects of admission Glasgow Coma Scale score and age. On the basis of the results of
this study, the authors suggest that the important factor impacting on outcome is not vasospasm per se, but hemody-
namically significant vasospasm with low CBF. These findings show that vasospasm is a pathophysiologically impor-
tant posttraumatic secondary insult, which is best diagnosed by the combined use of TCD and CBF measurements.

KEY WORDS • cerebral vasospasm • outcome • head injury • ultrasound •
cerebral blood flow • secondary injury

Cerebral arterial spasm (vasospasm) was first dem-


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stronstrated using cerebral angiography and has long
been known to occur after head injury.30,48,52 The
findings of early angiographic studies indicated an im-
portant role for posttraumatic vasospasm in determining
outcome by reporting an association between angiograph-
ically demonstrated vasospasm and neurological deterio-
ration30,52 as well as noncontusion related infarct.7,28,30 The
detrimental effects of vasospasm are presumably related
to impaired cerebral blood flow (CBF), as indicated by
the slowing of the circulation and poor filling seen on
angiograms in patients with vasospasm.30,48 Following
its introduction in 1982, transcranial Doppler (TCD) ul-
trasonography has largely superseded angiography as a
convenient technique for detecting vasospasm of the large
basal cerebral arteries.1–3,7,10,17,24,33,34,36,44,47,50,53 Transcranial
Doppler ultrasonography is noninvasive and particularly
well suited for serial monitoring, which are valuable qual-
ities because vasospasm that occurs after traumatic brain
injury appears to be a delayed phenomenon.11,33,34,44,47,50,53
as is the case after aneurysmal subarachnoid hemorrhage
(SAH).51 Numerous previous TCD investigations have
failed to demonstrate convincingly an independent, statisti-
cally significant association between posttraumatic vaso-
spasm and outcome;10,12,34,44,47,50 however, part of the prob-
lem has been the absence of any large prospective studies.
The primary purpose of our current study was to inves-
tigate in a prospective manner the relationship between
posttraumatic cerebral vasospasm and outcome in a large
sample population.

It appears that the disadvantages of the various TCD-
derived diagnostic criteria have contributed to the prob-
lem of defining the relationship between vasospasm and outcome. The TCD criteria for diagnosing cerebral vasospasm
have undergone an evolution of sorts since the in-
troduction of the technique. Early studies simply used
threshold flow velocities (for example, a middle cerebral
artery [MCA] velocity greater than 120 cm/second) to de-
fine vasospasm. Elevated flow velocity, however, can result from elevated CBF or changes in perfusion territory, as well as from arterial narrowing. In 1989, Lindegaard, et al. demonstrated a substantial agreement between angiographic vasospasm and a ratio, defined as the mean MCA velocity (V<sub>MCA</sub>) divided by the ipsilateral extracranial internal carotid artery (EC–ICA) velocity (V<sub>EC–ICA</sub>), resulting in a number greater than 3. This V<sub>MCA</sub>/V<sub>EC–ICA</sub> ratio, or hemispheric ratio (HR; also known as the “Lindegaard ratio”), was found to correlate better with angiographic findings than the absolute V<sub>MCA</sub> alone and was also much less influenced by the patient’s age.

Because the EC–ICA is not narrowed by SAH-induced vasospasm, a linear relationship between V<sub>MCA</sub>/<sub>EC–ICA</sub> and CBF is assumed and the HR is presumed to help compensate for alterations in CBF. It has been shown, however, that the ICA diameter can vary widely with gender and skull size. The variation in ICA diameter within the population makes it difficult to define clinically meaningful diagnostic criteria for vasospasm using the HR. In a study of patients with SAH, Jakobsen, et al. avoided some of these problems by quantitatively measuring regional CBF in the MCA territory, specifically the initial slope index (SI), with the 133Xe inhalation technique. These CBF data were then used with absolute V<sub>MCA</sub> to calculate a “spasm index” (SI) defined as V<sub>MCA</sub>/CBF<sub>ISI</sub>. Although their study population was small, their results suggested a relationship between SI and outcome, with all patients having a peak SI lower than 3.1 demonstrating good recovery. Furthermore, the SI was found to be inversely related to CBF and directly related to the arteriovenous difference in oxygen (AVDO<sub>2</sub>), indicating that elevations in the SI reflected pathologically significant hemodynamic changes.

To relate our current study to previous reports, we have investigated these various diagnostic parameters to determine their relative value in predicting outcome.

The current report is a follow up to preliminary results already published. We used TCD ultrasonography and intravenous 133Xe regional CBF studies to investigate in a prospective manner cerebral hemodynamic changes in 152 patients with head injuries. Our main goal was to clarify the relationship between postransient cerebral vasospasm and outcome, with a secondary goal of determining the most relevant criteria for diagnosing clinically significant cerebral vasospasm.

Clinical Material and Methods

Patient Population

In a prospective longitudinal cohort study, we evaluated 152 patients with traumatic brain injuries (139 with closed head injuries and 13 with penetrating head injuries) admitted to the Harbor–University of California at Los Angeles (UCLA) and UCLA Medical Centers between July 1992 and December 1994. These patients were selected from a larger cohort of 274 patients who were admitted during the same time period and recruited for enrollment in the clinical head trauma investigation at the UCLA Brain Injury Research Center; all research protocols were reviewed and approved by the UCLA and Harbor-UCLA Human Research Committees. Inclusion criteria for the current study consisted of patient consent to, and enrollment in, the Brain Injury Research Center protocol; patient having undergone at least one TCD recording or 133Xe-CBF measurement during the hospital stay; and patient outcome being evaluated at 6 months postinjury. Twenty-eight female and 124 male patients were included in this study; their ages ranged from 16 to 80 years with a mean of 33.5 years (standard deviation 15.6 years). Postresuscitation admission Glasgow Coma Scale (GCS) scores ranged from 3 to 15 with a median GCS score of 7. There were no statistically significant differences in age, gender ratio, or GCS score between the larger recruited cohort and the enrolled study population.

General Management Protocol

After the initial computerized tomography scan or surgery, patients were admitted directly to the intensive care unit. All received routine intensive care management, which, when clinically indicated, included: intracranial pressure (ICP) monitoring, central venous catheter placement, arterial pressure monitoring, electroencephalography, and mechanical ventilation. Sedatives, vasopressors (such as dopamine and levophed), mannitol, barbiturates, albumin, and blood products were administered as necessary. Nimodipine was not routinely administered to patients in this study. Among the 152 patients in the present study, only two men (one, aged 37 years, with an admGCS score of 6, and the other, aged 54 years, with an admGCS score of 13) were given nimodipine. Both had good recovery at 6 months.

Twenty patients were concurrently enrolled in the completed United States/Canadian study of tirilazad mesylate in the treatment of moderate and severe head injury, which is similar in design to a recently completed international study. Only 10 patients actually received tirilazad (10 mg/kg/day), whereas 10 received vehicle only. Compared with patients receiving vehicle only and with patients in the entire study group, the 10 tirilazad-treated patients were demographically similar, demonstrating no significant difference in age, admGCS score, or gender ratio (p > 0.1 for all comparisons). Furthermore, this small tirilazad-treated group did not display a significantly different incidence of vasospasm (whether defined by TCD criteria or SIs; p > 0.1) or poor outcome (40% for tirilazad-treated patients versus 40% in the vehicle group and 34% in the entire study group; p = 0.72 and 0.76, respectively). Because the patients who received tirilazad did not appear to represent a significant confounding factor, they were retained in the present analysis.
Posttraumatic vasospasm and outcome

**TABLE 1**

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>high mean MCA velocity</td>
<td>$V_{MCA} \geq 120$ cm/sec</td>
</tr>
<tr>
<td>very high hemispheric ratio</td>
<td>$V_{MCA}/V_{EC-ICA} \geq 6$</td>
</tr>
<tr>
<td>high hemispheric ratio</td>
<td>$V_{MCA}/V_{EC-ICA} \geq 3$</td>
</tr>
<tr>
<td>normal hemispheric ratio</td>
<td>$V_{MCA}/V_{EC-ICA} &lt; 3$</td>
</tr>
<tr>
<td>TCD-diagnosed MCA vasospasm</td>
<td>$V_{MCA} \geq 120$ cm/sec w/ an HR $\geq 3$</td>
</tr>
<tr>
<td>TCD-diagnosed BA vasospasm</td>
<td>$V_{BA} \geq 90$ cm/sec</td>
</tr>
<tr>
<td>low CBF</td>
<td>$CBF_{\text{low}} \leq 35$ ml/100 g/min</td>
</tr>
<tr>
<td>normal–high CBF</td>
<td>$CBF_{\text{normal-high}} \geq 35$ ml/100 g/min</td>
</tr>
<tr>
<td>high MCA spasm index</td>
<td>$V_{MCA}/CBF_{\text{15-H}} &gt; 3.4$</td>
</tr>
<tr>
<td>normal MCA spasm index</td>
<td>$V_{MCA}/CBF_{\text{15-H}} = 3.4$</td>
</tr>
<tr>
<td>high BA spasm index</td>
<td>$V_{BA}/CBF_{\text{15-G}} &gt; 2.5$</td>
</tr>
<tr>
<td>normal BA spasm index</td>
<td>$V_{BA}/CBF_{\text{15-G}} \leq 2.5$</td>
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**Transcranial Doppler Ultrasonography**

Recordings were made of the mean blood flow velocity in the MCA, EC–ICA, and basilar artery using a 2-MHz probe. These vessels were sonicated through temporal (MCA), submandibular (EC–ICA), and suboccipital foraminal (basilar artery [BA]) windows according to the general principles first described by Aaslid, et al. All measurements were performed with the aid of a commercially available TCD apparatus (Neuroguard Cerebrovascular Diagnostic System; Nicolet Biomedical, Inc., Madison, WI). Mean velocity recordings from this instrument represent the mean velocity averaged over four cycles. Pertinent physiological parameters (such as arterial blood pressure, ICP, and hematocrit) were recorded, when available, during all studies.

Initial TCD studies were generally performed within 24 to 48 hours after admission. Serial studies were performed at regular intervals for the first 2 weeks after admission, and thereafter when clinically indicated. Patients who had TCD evidence of vasospasm (see Definitions of Terms and Table 1) underwent serial TCD examinations until velocities decreased to normal values. A total of 149 patients underwent 918 TCD studies (mean 6.15 studies per patient) on postinjury Days 0 through 27 (median postinjury Day 5). Among those patients, all 149 obtained $V_{MCA}$ recordings and 147 obtained concurrent recordings of ipsilateral $V_{MCA}$ and $V_{EC-ICA}$, allowing calculation of an HR ($V_{MCA}/V_{EC-ICA}$). Basilar mean velocity ($V_{BA}$) was recorded in 126 patients.

**Cerebral Blood Flow Measurements**

Cerebral blood flow measurements were performed at the patient’s bedside using the intravenous $^{133}$Xe clearance technique previously described. Approximately 20 to 30 mCi of gaseous xenon-133 dissolved in saline was injected intravenously for each study. Cerebral clearance curves were recorded over 11 minutes from 10 extracranial sodium iodide detectors, five of which were located over the approximate MCA territory in each hemisphere. Analytic computer software was then used to extrapolate the data to 15 minutes, referencing the cerebral clearance curves to the clearance curve of exhaled end-tidal xenon-133 (used to estimate the arterial concentration of xenon-133). A two-compartment, modified height-over-area method was then used to calculate the hemispheric CBF ($CBF_{\text{hemi}}$, calculated from five detectors on one side) and global CBF ($CBF_{\text{global}}$, calculated from all 10 detectors). The CBF represents the mean flow of both fast- and slow-clearing compartments and is insensitive to “slippage,” more stable than single compartment parameters (such as Fl) in pathological conditions, and has been used extensively in head trauma investigations. Pertinent physiological parameters (for instance, blood pressure, ICP, arterial blood gas levels, and hematocrit) were recorded during each study. The CBF values reported here are the actual recorded values and are not corrected for PCO. Previous investigations have indicated that the standard relationship between PCO and CBF (a 3% change in CBF per millimeter of mercury change in PCO) is not always preserved after head injury (see Discussion). All CBF measurements were performed using a commercially available portable unit (Cerebrograph Cortexplorer 10; Ceretronix, Randers, Denmark).

Initial CBF measurements were generally performed within 24 to 48 hours after admission. Serial studies were performed at regular intervals during the first 2 weeks and afterward, as clinically indicated. Patients who had TCD evidence of vasospasm underwent serial studies until TCD and CBF values were normal. A total of 91 patients underwent 376 CBF studies (mean 4.13 studies per patient) on postinjury Days 0 through 41 (median postinjury Day 5). Among the 91 patients, 85 had $V_{BA}$ and hemispheric CBF recorded on the same day, allowing the calculation of an MCA SI ($V_{BA}/CBF_{\text{15-G}}$), whereas 70 patients had TCD $V_{BA}$ and CBF recorded concurrently, allowing calculation of a basilar SI ($V_{BA}/CBF_{\text{15-G}}$).

**Clinical Outcome**

A Glasgow Outcome Scale (GOS) score was determined for all 152 patients approximately 6 months after injury. Outcome has been shown to stabilize after 6 months and this time span appears to be an appropriate end point for clinical studies in head injury. Scores were determined on the basis of interviews with patients or their families, questioning of rehabilitation therapists involved in patients’ extended care, or analyzing discharge reports from rehabilitation facilities. Patients were assigned to one of five categories: death, persistent vegetative state, severe disability, moderate disability, or good recovery. Patients were considered to have achieved a “good” outcome if they were assigned to the moderate disability or good recovery categories, and a “poor” outcome if they died or were assigned to the persistent vegetative state or severe disability groups.

**Definitions of Terms**

**High Mean MCA Velocity**

In 1984, Aaslid, et al. report-
ed an association between angiographically diagnosed MCA vasospasm and a $V_{\text{mca}}$ greater than 120 cm/second. This current report, therefore, uses a threshold velocity of 120 cm/second to define a significantly elevated mean $V_{\text{mca}}$.

**Hemispheric Ratio.** Lindegaard and colleagues found an association between moderate angiographic vasospasm and an HR ($V_{\text{mca}}/V_{\text{ec-ica}}$) greater than 3, and between severe angiographic vasospasm and an HR greater than 6. The same threshold values are used in this current report to define, respectively, “high” and “very high” HRs.

**Transcranial Doppler–Diagnosed MCA Vasospasm.** Previous studies by Martin and colleagues have reported both a threshold MCA velocity of 120 cm/second and an HR of greater than 3 to diagnose MCA vasospasm using TCD ultrasonography alone. The use of the HR in combination with an absolute $V_{\text{mca}}$ aids in differentiating between elevated velocities that are secondary to elevated CBF and those that are elevated primarily as a result of vasospasm. These criteria are used in the current report to define TCD-diagnosed MCA vasospasm.

**Transcranial Doppler–Diagnosed BA Vasospasm.** Sloan, et al. reported 100% specificity but only 39% sensitivity for the diagnosis of angiographically confirmed BA vasospasm when the BA threshold velocity was 95 cm/second. In this current report, a threshold velocity of 90 cm/second is used to define TCD-diagnosed BA vasospasm to maintain a high degree of specificity (93% as reported by Sloan, et al.) while presumably improving sensitivity.

**Cerebral Blood Flow.** In 1984, Obrist and associates reported a normal value for $CBF_{\text{mca}}$ of 44.1 ml/100 g/minute with a standard deviation of 5.6 at a PaCO$_2$ of 34 mm Hg. If the normal range is defined as the mean ± 2 standard deviations, then the normal range is approximately 33 to 55 ml/100 g/minute. In this current report, low CBF is generally defined as a $CBF_{\text{mca}}$ of 35 ml/100 g/minute or less and absolute hyperemia as a $CBF_{\text{mca}}$ of more than 55 ml/100 g/minute.

**Middle Cerebral Artery SI.** In 1990, Jakobsen, et al. reported using a unitless SI in patients with SAH. They defined this index as the $V_{\text{mca}}$ divided by the regional CBF, represented by the ISI. For the current study, we substituted the $CBF_{\text{mca}}$ for ISI (see Discussion), defining MCA SI as $V_{\text{mca}}/CBF_{\text{mca}}$. To determine a meaningful threshold for high MCA SI, we took our threshold for high $V_{\text{mca}}$, 120 cm/second and divided that by our threshold value for low CBF, 35 ml/100 g/minute, arriving at a value of approximately 3.4.

**Basilar SI.** In the current report, the definition of an SI for the posterior circulation was derived by dividing the $V_{\text{bas}}$ by the $CBF_{\text{bas}}$ ($V_{\text{bas}}/CBF_{\text{bas}}$). One difficulty with this index is that the $CBF_{\text{bas}}$ does not specifically represent the CBF in the posterior circulation, which is not directly quantitated by our technique for CBF measurement. Studies using the stable Xe-CT technique in head-injured patients have shown, however, that the CBF in posterior fossa structures is quantitatively similar to that in the cerebral hemispheres (that is, cerebral hemorrhagic oligemia or hyperemia is generally accompanied by cerebellar/brainstem oligemia or hyperemia). We therefore believe that $CBF_{\text{bas}}$ is the most reasonable substitute available. We defined the threshold for high BA SI as the quotient derived by dividing our threshold value for high $V_{\text{bas}}$, 120 cm/second by our threshold value for low CBF (35 ml/100 g/minute); that is, approximately 3.4.

**Statistical Analysis**

For correlation with GOS score at 6 months, we used the nonparametric Spearman correlation analysis. Significant differences between groups for continuous variables (such as age, CBF, and flow velocities) were determined using a two-tailed t-test for independent samples. Significant differences between groups for nonparametric variables (such as GOS score and admGCS score) were determined using the Mann–Whitney U-test. Comparisons between ratios (for example, gender ratios and incidence of low CBF) were performed using chi-square
analysis. Stepwise logistic regression analysis was used to confirm the independent contribution of the following parameters to outcome at 6 months: admGCS score, age, MCA SI, and BA SI. It should be noted that whenever a probability value is given for differences in outcome, this represents the value obtained by Mann–Whitney U analysis of all GOS scores and not a chi-square analysis of the percentage of poor or good outcome. The following were used as threshold p values: p < 0.01, highly significant; p < 0.05, significant; p < 0.1, statistical trend; p ≥ 0.1, not significant. All statistical analyses were performed using commercially available computer software (Statistica; StatSoft, Inc., Tulsa, OK; Excel; Microsoft, Inc., Redmond, WA; and Epistat; Epistat Services, Seattle, WA).

Results
Correlation of Clinical and Hemodynamic Variables With Outcome
We performed Spearman correlation analysis to determine which parameters, among the eight tested, had the best correlation with GOS score at 6 months (Table 2). Highly significant or significant correlations were demonstrated for the following variables (listed in descending order of the absolute Spearman r): admGCS score, lowest CBF, highest BA SI, highest MCA SI, and highest HR. Age and highest Vmax demonstrated only a statistical trend toward correlation with outcome. The highest Vmax displayed no statistically significant correlation with GOS score at 6 months.

Clinical and Hemodynamic Differences Between Good and Poor Outcome Groups
To determine which parameters varied most significantly between good and poor outcome groups, we calculated the mean or median values of eight variables in the two outcome groups (Table 3). Highly significant differences between good and poor outcome groups were found for admGCS scores and the highest BA SI, whereas significant differences were demonstrated for lowest CBF and age. The difference in the mean highest MCA SI between good and poor outcome groups represents a statistical trend. No statistically significant difference was found for highest Vmax, Vmean, or HR between good and poor outcome groups. In addition, there was no significant difference in gender between good and poor outcome groups (p > 0.1; data not shown).

Middle Cerebral Artery Vasospasm and Outcome
We evaluated the relationship between MCA vasospasm and outcome (Table 4). The MCA vasospasm was defined in four ways by means of criteria that are currently in clinical use and have been used in previous studies:

1. Vmax alone (Vmax ≥ 120 cm/second); 2) HR alone (Vmax/Vmean ≥ 3 and ≥ 6); 3) Vmax and HR together (Vmax ≥ 120 cm/second with Vmax/Vmean ≥ 3); and 4) MCA SI, combining Vmax and CBF (Vmax/CBF > 3.4).

Middle Cerebral Artery Vasospasm Diagnosed by MCA Velocity Alone. At least one recording of Vmax was performed in 149 patients. Of these, 64 (43%) had at least one Vmax greater than or equal to 120 cm/second. The worse outcome among patients with a high Vmax represents a statistical trend (p = 0.069; Table 4).

Middle Cerebral Artery Vasospasm Diagnosed by HR Alone. Concurrent mean Vmax and ipsilateral Vmean recordings were made in 147 patients, allowing the calculation of an HR. Ninety-seven patients (66%) had at least one HR of 3 or higher (high HR group), whereas 50 patients (34%) always had an HR less than 3 (normal HR group). There was no statistically significant difference between the two groups (p = 0.18; Table 4). When the 14 patients (9.5%) who had an HR that was at least 6 (very high HR group) were compared with the normal HR group, a statistical trend (p = 0.069) toward worse outcome was demonstrated for the very high HR group.

Middle Cerebral Artery Vasospasm Diagnosed by MCA Velocity With HR. At least one set of MCA TCD data with HR was obtained in 149 patients. Of these, 86 patients (59%) had no MCA or BA vasospasm. Sixty patients (41%) had TCD-diagnosed MCA vasospasm, with 35 developing unilateral vasospasm and 25 developing bilateral vasospasm. Twenty-two patients with TCD-diagnosed MCA vasospasm also had TCD-diagnosed BA vasospasm at some time. One patient had BA vasospasm alone (see Basilar Artery Vasospasm Diagnosed by TCD Ultrasonography Alone). The group of patients with TCD-diagnosed MCA vasospasm had a significantly worse outcome compared with the group with no TCD-diagnosed vasospasm (p = 0.020; Table 4). There was no significant difference in outcome between the groups of patients with unilateral and bilateral MCA vasospasm (p = 0.5). Similarly, there was no significant difference in outcome between the 22 patients who developed both MCA and BA vasospasm and the 38 who developed MCA vasospasm alone (p = 0.29).

Middle Cerebral Artery Vasospasm Diagnosed by MCA Spasm Index: Combined Use of MCA Velocity and Hemispheric CBF. Thirty-three (39%) of 85 patients had at least one MCA SI greater than 3.4 (high MCA SI group); 52 patients (61%) never had an MCA SI exceed 3.4 (normal MCA SI group). The worse outcome associated with the high MCA SI group was highly significant (p = 0.006; Fig. 1 upper and Table 4).

Basilar Artery Vasospasm and Outcome
We evaluated the relationship between BA vasospasm and outcome (Table 4). Basilar artery vasospasm was defined in two ways using the following criteria: 1) Vmax alone (Vmax ≥ 90 cm/second) and 2) BA SI combining Vmax and CBF (Vmax/CBF > 2.5).

Basilar Artery Vasospasm Diagnosed by TCD Ultrasonography Alone. One hundred twenty-six patients had at least one set of TCD BA data. Seventy-four (59%) of these demonstrated no BA or MCA vasospasm; 23 (18%) had TCD-diagnosed BA vasospasm. In the latter group, 22 of 23 also had TCD-diagnosed MCA vasospasm, essentially representing a group of patients with both anterior and posterior circulation vasospasm. Only one patient, a 37-year-old man who died on postinjury Day 48, developed BA vasospasm alone (see Addendum). The group of patients with TCD-diagnosed BA vasospasm demonstrated a significantly worse outcome when compared with the group without BA vasospasm (p = 0.013; Table 4).
Basilar Artery Vasospasm Diagnosed by BA SI: Combined Use of BA Velocity and Global CBF. Among 70 patients with at least one calculated BA SI, 13 (19%) had at least one BA SI greater than 2.5 (high BA SI group) and 57 (81%) never had a BA SI exceed 2.5 (normal BA SI group). The worse outcome associated with patients in the high BA SI group was highly significant (p = 0.0023; Fig. 1 lower and Table 4).

Cerebral Blood Flow and Outcome

We evaluated the relationship between CBF and outcome (Table 4). Among 91 patients in whom CBF was measured, 58 (64%) had at least one measurement of 35 ml/100 g/minute or lower (low CBF group), whereas 33 (36%) maintained CBF above 35 ml/100 g/minute (normal–high CBF group). The worse outcome associated with patients in the high BA SI group was highly significant (p = 0.0023; Fig. 1 lower and Table 4).

Relationships Among Flow Velocity, CBF, and Outcome

To determine the importance of considering CBF when interpreting elevated flow velocities, we investigated the incidence of elevated \( V_{\text{mca}} \) and \( V_{\text{ba}} \) associated with absolute hyperemia (CBF\(_{\text{abs}}\) > 55 ml/100 g/minute). In addition, we examined the relationship between elevated \( V_{\text{mca}} \) with and without low CBF, and outcome.

Elevated Flow Velocities Associated With Hyperemia. Thirty-four patients had 92 \( V_{\text{mca}} \) measurements of 120 cm/second or greater with a concurrent ipsilateral CBF\(_{\text{abs}}\) measurement. Seventeen (18%) of 92 instances of elevated \( V_{\text{mca}} \) in 10 patients (29%) were associated with concurrent absolute hyperemia. Similarly, 16 patients had 33 \( V_{\text{ba}} \) measurements of 90 cm/second or more with a concurrent CBF\(_{\text{abs}}\) measurement. Eight (24%) of these 33 instances of elevated \( V_{\text{ba}} \) in five patients (31%) were associated with concurrent absolute hyperemia.

Elevated MCA Velocities, Low CBF, and Outcome. Thirty-four patients had a recorded \( V_{\text{mca}} \) of 120 cm/second or greater with a concurrent CBF measurement. Sixteen patients (47%) had an elevated \( V_{\text{mca}} \) that was never accompanied by low CBF, whereas 18 patients (53%) had at least one elevated \( V_{\text{mca}} \) with concurrent low CBF. When compared with a group of 85 patients who maintained \( V_{\text{mca}} \) below 120 cm/second (with or without low CBF), there was a significantly worse outcome in patients with elevated \( V_{\text{mca}} \) accompanied by low CBF (p = 0.025) but no difference in outcome for patients who did not develop low CBF.
CBF (p = 0.29, Fig. 2). Although a greater percentage of patients with both elevated V_MCA and low CBF had a poor outcome compared with those with elevated velocity and normal/high CBF (50% vs. 44%), this difference did not reach statistical significance (p = 0.53).

Relationship Between SI and CBF

To elucidate the relationship between elevated SIs and CBF, we compared the incidence of low CBF among patients with elevated and normal SIs. Among 33 patients with a high MCA SI, 28 (85%) had simultaneously low ipsilateral CBF. In contrast, only 22 (42%) of 52 patients with a normal MCA SI had low CBF (Fig. 3). Twelve (92%) of 13 patients with a high BA SI had simultaneously low CBF. Twenty-six (46%) of 57 patients who did not have a high BA SI developed low CBF. The higher incidence of low CBF among patients with high MCA and BA SIs compared with those with normal MCA and BA SIs was highly significant (p = 0.0001 and p = 0.0037, respectively).

Associations Among TCD-Diagnosed Vasospasm, Hemodynamically Significant Vasospasm, and CBF

Middle Cerebral Artery Vasospasm. There were 42 patients with TCD-diagnosed MCA vasospasm who also had a calculated MCA SI. Among these 42 patients, 27 (64%) developed hemodynamically significant vasospasm as defined by at least one high MCA SI (MCA vasospasm/high SI group). Twenty-two (81%) of the 27 patients had hemodynamically significant vasospasm with low CBF; whereas five maintained normal CBF. Fifteen (56%) of the 27 patients with hemodynamically significant vasospasm had poor outcome. There were 15 patients (36%) among the 42 with TCD-diagnosed vasospasm who did not have a high MCA SI (and, therefore, did not develop hemodynamically significant vasospasm [MCA vasospasm/normal SI group]). Only four (27%) of those 15 patients had a poor outcome. Outcome for patients in the MCA vasospasm/high SI group was significantly worse compared with that for the MCA vasospasm/normal SI group (p = 0.011; Fig. 4).
Basilar Artery Vasospasm. Among 18 patients who had BA vasospasm according to TCD criteria and at least one calculated BA SI, 11 (61%) developed hemodynamically significant vasospasm as defined by at least one BA SI greater than 2.5 (BA vasospasm/high SI group). Ten (91%) of these 11 patients had hemodynamically significant vasospasm with low CBF15-G and only one maintained normal CBF. Eight (73%) of the 11 patients with hemodynamically significant vasospasm had poor outcome. There were seven patients (39%) among the 18 with TCD-diagnosed BA vasospasm who did not have a BA SI greater than 2.5 and, by definition, did not develop hemodynamically significant vasospasm (BA vasospasm/normal SI group). Three (43%) of those seven patients had poor outcomes. Although the BA vasospasm/high SI group had a higher percentage of patients with poor outcome compared with the BA vasospasm/normal SI group (73% vs. 43%, respectively), this difference did not reach statistical significance (p = 0.26).

### Relationship of Age, AdmGCS, and Gender to TCD and CBF Measurements

#### Age of Patient
The influence of age on TCD and CBF measurements was assessed (Table 4). The lower mean age of patients with at least one mean V_m of 120 cm/sec or greater compared with those without an elevated V_m was highly significant (p = 0.0055). Similarly, the lower mean age for patients with TCD-diagnosed MCA vasospasm compared with that for patients without MCA vasospasm was highly significant (p = 0.0067). Patients with TCD-diagnosed BA vasospasm demonstrated a trend toward younger age than those not diagnosed with BA vasospasm (p = 0.082). In contrast, low CBF was associated with a significantly higher mean age than normal–high CBF (p = 0.015). There were no significant differences in mean age between high and normal groups for HR, MCA SI and BA SI (p = 0.37, p = 0.79, and p = 0.6, respectively).

### Admission GCS Score
The association between admGCS score and subsequent TCD and CBF measurements was assessed. The lower median admGCS score among groups of patients with high V_m, TCD-diagnosed MCA vasospasm, TCD-diagnosed BA vasospasm, very high HR, high HR, low CBF, high MCA SI, and high BA SI compared with groups of patients without high V_m, without TCD-diagnosed MCA or BA vasospasm, with normal HR, normal–high CBF, normal MCA SI, and normal BA SI was highly significant (p < 0.01 for all comparisons).

### Gender
The influence of gender on TCD and CBF measurements was assessed. There were no significant differences in the gender ratio between any of the groups compared (p > 0.1 for all comparisons).

### Stepwise Logistic Regression Analysis for Outcome at 6 Months
A stepwise logistic regression analysis was performed to test whether the influence of a high MCA or BA SI on outcome was independent of the influence of admGCS score and age (Table 5).

### Middle Cerebral Artery SI, AdmGCS Score, and Age
Stepwise logistic regression analysis of all 85 patients with at least one calculated MCA SI (admGCS score of 3−15) demonstrated that admGCS scores had the strongest independent influence on outcome (p = 0.0024), followed by age (p = 0.0069). The MCA SI approached, but did not achieve, a statistical trend toward an independent contribution to poor outcome when all patients were included in
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Discussion

Our primary reason for undertaking this prospective study was to investigate the relationship between posttraumatic cerebral vasospasm and clinical outcome. Previous TCD studies have failed to demonstrate a clear, independent, statistically significant association between posttraumatic cerebral vasospasm and poor outcome.10,12,34,44,47,50 This is partly attributable to the relatively small patient sample in most of these studies. It appears, however, that the disadvantages of the various TCD-derived diagnostic criteria have contributed to the problem. We have investigated the clinical significance of elevated flow velocity, HR, and SI. Our results clearly show that the SI, which takes into account the level of CBF, is the most clinically meaningful indicator of hemodynamically significant cerebral vasospasm. The data conclusively demonstrate a significant association between hemodynamically significant vasospasm, as defined by an elevated SI, and poor outcome in head-injured patients. Furthermore, the influence of hemodynamically significant vasospasm on outcome is independent of that of admGCS score and age. Our findings support a multimodal approach to the diagnosis of cerebral vasospasm. This approach, using concurrent TCD and CBF measurements, can better delineate outcome groups while avoiding the risks associated with angiography or the uncertainties associated with TCD monitoring alone.

Vasospasm Diagnosed by Cerebral Angiography

Cerebral angiography was the earliest technique used to diagnose vasospasm in head-injured patients.28,50,48,52 Early studies indicated an association of vasospasm with neurological deterioration10,52 as well as noncontusion-related infarcts.7,28,30 In the largest angiographic series, Suwanwela and Suwanwela46 reported angiographic evidence of cerebral vasospasm in 18.6% of 350 patients with head injury. This incidence of posttraumatic vasospasm is considerably lower than that reported by more recent TCD investigations.7,10,33,34,50 The most likely reason for this discrepancy is the early time in the clinical course at which most posttraumatic angiograms were performed. Angiography is difficult to repeat due to the invasive nature of the procedure. Indeed, only 40 of the 350 patients studied by Suwanwela and Suwanwela had repeated angiograms. This is a particularly significant shortcoming because it appears that the vasospasm that follows head injury, similar to the vasospasm that follows spontaneous SAH, is a delayed phenomenon.11,33,44,47,50,51,52 Thus, a single, early angiogram could miss vasospasm that develops later in the clinical course.

A second disadvantage of using angiography is that only qualitative assessments can be made of the hemodynamic effects of vasospasm. Angiographic images can illustrate impaired CBF through slowing of circulation and poor filling.28,30,48 Macpherson and Graham23 demonstrated an association between ischemic brain damage in arterial territories and the combination of high-grade arterial spasm with slowing of circulation. It is not possible, however, to assess CBF quantitatively using angiography. Our results demonstrate the importance of quantitating CBF by confirming previous studies that show an important association between low CBF and poor outcome.28,30,41

**TABLE 5**

<table>
<thead>
<tr>
<th>Variable†</th>
<th>χ²</th>
<th>p Value</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>all patients w/ at least one calculated MCA SI (admGCS score of 3–15, 85 patients)‡</td>
<td>9.23</td>
<td>0.0024</td>
<td>0.81</td>
<td>0.70–0.94</td>
</tr>
<tr>
<td>age</td>
<td>7.29</td>
<td>0.0069</td>
<td>1.04</td>
<td>1.01–1.07</td>
</tr>
<tr>
<td>MCA SI</td>
<td>2.68</td>
<td>0.1</td>
<td>1.52</td>
<td>0.92–2.50</td>
</tr>
<tr>
<td>all patients exclusive of those w/ most severe head injuries: (admGCS score 5–15, 66 patients)§</td>
<td>6.74</td>
<td>0.0094</td>
<td>0.81</td>
<td>0.68–0.96</td>
</tr>
<tr>
<td>age</td>
<td>4.61</td>
<td>0.032</td>
<td>1.03</td>
<td>1.00–1.07</td>
</tr>
<tr>
<td>MCA SI</td>
<td>3.93</td>
<td>0.047</td>
<td>1.81</td>
<td>1.00–3.26</td>
</tr>
<tr>
<td>all patients w/ at least one calculated BA SI: (admGCS score 3–15, 70 patients)†</td>
<td>10.43</td>
<td>0.0012</td>
<td>0.77</td>
<td>0.64–0.93</td>
</tr>
<tr>
<td>age</td>
<td>7.16</td>
<td>0.0074</td>
<td>1.05</td>
<td>1.01–1.10</td>
</tr>
<tr>
<td>BA SI</td>
<td>4.32</td>
<td>0.038</td>
<td>2.21</td>
<td>1.01–4.85</td>
</tr>
</tbody>
</table>

* Scoring: 1) GOS score: good = 1, poor = 0; 2) age: raw continuous values; 3) admGCS score: raw integer values, 3–15; 4) MCA SI: >3.4 = 1, ≤3.4 = –1; 5) BA SI: >2.5 = 1, ≤2.5 = –1. Chi-square values are improvement chi-square values. Abbreviation: CI = confidence interval.

† Glasgow Outcome Scale score at 6 months is the dependent variable; admGCS score, MCA SI, and BA SI serve as independent variables.

‡ U = −0.0507 + 0.0386 (age) −0.207 (admGCS score) + 0.416 (MCA SI). Model’s prediction of poor GOS score: sensitivity = 54.3%; specificity = 80.0%; correct = 69.4%.

§ U = 0.338 + 0.0328 (age) −0.216 (admGCS score) + 0.592 (MCA SI). Model’s prediction of poor GOS score: sensitivity = 45.2%; specificity = 83.3%; correct = 72.7%.

‖ U = 0.274 + 0.0529 (age) −0.261 (admGCS score) + 0.792 (BA SI). Model’s prediction of poor GOS score: sensitivity = 67.9%; specificity = 88.1%; correct = 80.0%.

the analysis (p = 0.1; Table 5). Stratification of patients by admGCS scores, however, revealed the following: 1) the MCA SI was shown to have a statistically significant independent influence on outcome when patients with the most severe injuries (admGCS scores of 3 or 4) were excluded (p = 0.072 for patients with admGCS scores of 4–15; p = 0.047 for admGCS scores of 5–15, Table 5; p = 0.047 for admGCS scores of 6–15); 2) conversely, age exhibited a significant independent contribution to outcome only when patients with the most severe injuries (admGCS scores of 3–5) were included (p = 0.08 for patients with admGCS scores of 6–15; p = 0.032 for admGCS scores of 5–15; p = 0.025 for admGCS scores of 4–15); and 3) analysis of 24 patients with very severe injuries (admGCS scores of 3–5) showed a significant independent contribution by BA SI (p = 0.038, Table 5).

Basilar Artery SI, AdmGCS Score, and Age. Stepwise logistic regression analysis of all 70 patients (admGCS scores of 3–15) revealed a highly significant contribution to outcome by admGCS score (p = 0.0012) and age (p = 0.0074) with a significant independent contribution by BA SI (p = 0.038, Table 5).

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Vasospasm Diagnosed by Flow Velocities Alone

Transcranial Doppler ultrasonography has proven to be a safe, noninvasive, and easily repeatable technique for detecting vasospasm of the large basal cerebral arteries.\(^\text{1-3,7,10,17,24,33,34,36,44,45,47,50}\) The TCD criteria used to diagnose vasospasm have undergone an evolution of sorts since the introduction of the technique. Many earlier studies simply used threshold velocities to define vasospasm.\(^\text{1,7,10,17}\) In theory, however, “elevated” flow velocities can result from increased CBF and increased perfusion territory in addition to vasospasm.\(^\text{40}\) Our own preliminary findings indicate that in the head-injured population, approximately one-fifth of observed elevated flow velocities are associated with absolute hyperemia. Previous reports have also shown “decreased” TCD flow velocities to be associated with elevated ICP,\(^\text{24}\) hypotension,\(^\text{7}\) and advanced age.\(^\text{16}\) Our own TCD criteria for vasospasm require a certain threshold velocity to be reached (120 cm/second for the MCA and 90 cm/second for the BA). In our report, the significantly lower mean age of patients with TCD-diagnosed MCA vasospasm, and the trend toward lower age in patients with BA vasospasm (Table 4) probably reflect a systematic bias against elderly patients who may have vasospasm but whose TCD velocities will not reach threshold levels for diagnosis because their CBF is inherently lower.\(^\text{15,37}\) However, we do not ignore the possibility that younger patients may be actually more susceptible to developing vasospasm.

These issues encourage caution when interpreting the clinical significance of elevated flow velocities. Our analysis reinforces this caveat by demonstrating relatively low correlations between the highest recorded VMCA and VEC–ICA and outcome. These findings are consistent with those of Sander and Klingelhöfer,\(^\text{44}\) who reported no significant correlation between maximum mean flow velocity and clinical outcome. The hazards associated with interpreting single-vessel flow velocities in isolation are illustrated in a previously published report.\(^\text{28}\) In that study, the authors found little correlation between absolute VMCA and the development of neurological deficits in patients with aneurysmal SAH. These results led them to the unfortunate conclusion that the “clinical value of TCD in cases of SAH is questionable.”\(^\text{26}\) We would argue that, considered alone, the clinical significance of an elevated VMCA is indeed questionable, but that the clinical value of TCD ultrasonography greatly depends on its proper application.

Vasospasm Diagnosed by Hemispheric Ratio

In 1989, Lindegaard, et al.,\(^\text{27}\) attempted to address some of the aforementioned concerns by emphasizing the utility of an HR, defined as VEC–ICA/CBF.\(^\text{15}\) Their study demonstrated a substantial agreement between a ratio measuring greater than 3 and angiographic vasospasm, with the ratio more closely correlating with angiographic findings than the absolute VMCA alone.\(^\text{27}\) The ratio was found to be much less influenced by patient age and was presumed to help compensate for alterations in CBF, assuming a linear relationship between VMCA and hemispheric CBF. Lindegaard’s group reported that with marked angiographic spasm of the MCA, the VEC–ICA was higher and the VMCA lower, confirming an earlier TCD report by Aaslid, et al.,\(^\text{2}\) indicating a measurable hemodynamic effect caused by vasospasm. As promising as these findings were, the clinical significance of an elevated HR has been difficult to define. Weber, et al.,\(^\text{45}\) found no significant difference in functional outcome between head-injured patients whose HR was greater than 3 and those whose HR did not exceed 3. Our study confirms that finding and shows no significant difference in the mean highest HR between good and poor outcome groups. Although Spearman correlation analysis does demonstrate a statistically significant correlation between the highest recorded HR and outcome, this correlation is not as high as that for lowest CBF or the SIs (Table 2).

The problem with the HR is that the VEC–ICA is not a dependable substitute for CBF.\(^\text{15}\) Although the diameter of the EC–ICA may not vary significantly in an individual with vasospasm, it clearly varies within the population depending on gender and skull width.\(^\text{16}\) Furthermore, day-to-day EC–ICA velocity measurements are particularly influenced by differences in TCD probe position and angulation. These issues explain the difficulties in defining a clinically significant threshold for an HR within a population.

In our practice, we have used the HR only in combination with measurements of absolute VMCA to help differentiate elevated flow velocities primarily due to increased CBF from elevated velocities caused primarily by vasospasm.\(^\text{33,34}\) Using this definition of vasospasm, which includes both an absolute threshold VMCA and a threshold HR, we have demonstrated a significantly worse outcome in patients who develop TCD-diagnosed MCA vasospasm (Table 4). In the absence of available CBF measurements, we recommend this set of criteria as the most clinically meaningful, especially in the generally young head-injured population.

Elderly patients may pose a special problem because of some of the confounding issues mentioned earlier. If CBF measurements are not available in older individuals, somewhat greater emphasis may be placed on the more age-independent HR, with the important sign being a significant rise from baseline (perhaps a 100% increase) rather than the crossing of any specific threshold value.

Vasospasm Diagnosed by SI: a Multimodal Approach Using Concurrent TCD and CBF Measurements

Jakobsen, et al.,\(^\text{31}\) avoided some of the difficulties encountered using the HR by directly measuring hemispheric CBF, specifically the ISI, and using it to calculate an SI defined as VMCA/CBF.\(^\text{15}\) Although their sample of 24 patients with spontaneous SAH was too small to draw broad conclusions, their results suggested a relationship between SI and outcome: all patients who maintained a peak SI less than 3.1 experienced a good recovery. Furthermore, the SI was found to be inversely related to CBF and directly related to AVDO₂, suggesting that changes in the SI reflected significant hemodynamic changes. We have slightly modified the SI proposed by Jakobsen, et al., by substituting CBF for the ISI. We chose the CBF, because it appears to be more stable than the ISI in pathological conditions with low CBF.\(^\text{40}\)

Combining TCD flow velocities with concurrent quantitative CBF measurements in an SI allows the easy identification of high flow velocities due primarily to hyper-
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emia rather than vasospasm (the value of the index would remain low in cases of hyperemia). Direct measurement of CBF eliminates reliance on indirect approaches for identifying hyperemia, such as monitoring for low AVDO₂ and analyzing TCD waveforms, as used in previous reports. Low AVDO₂ may also result from a low cerebral metabolic rate of oxygen consumption, which is quite common after head injury. Furthermore, AVDO₂ used alone has been found to be unreliable in estimating CBF. Similarly, TCD waveform analysis has been found to be unreliable in differentiating between hyperemia and vasospasm.

Our study demonstrates a significantly worse outcome for head-injured patients who develop either an elevated MCA SI or an elevated BA SI, illustrating the clinical significance of these indices. We also show that patients with a high SI are twice as likely to have low CBF as those with a normal SI, indicating that an elevated SI represents vasospasm severe enough to impair CBF: hemodynamically significant cerebral vasospasm. Our findings shown in Figs. 2 and 4 (and detailed in the text) clearly imply that the factor impacting on outcome is not vasospasm per se, but hemodynamically significant vasospasm with low CBF.

It should be emphasized that an elevated SI is not always associated with low CBF. A patient can have vasospasm severe enough to affect CBF and yet maintain adequate blood flow. The patients who have hemodynamically significant cerebral vasospasm without critically low CBF are possibly the most important to identify, for although they may not yet have been injured by ischemia, they are at high risk. These patients may be the most amenable to aggressive medical therapy.

Identifying patients with vasospasm and low CBF is not easy without direct quantitative CBF measurement. A poor correlation between the level of consciousness and the level of CBF after head injury has been previously reported. Furthermore, the symptoms and signs of cerebral vasospasm are not very specific, and the clinical examination is complicated and insensitive to subtle changes in comatose head-injured patients. It can therefore be argued that the important and pragmatic distinction to be made in posttraumatic cerebral vasospasm is between hemodynamically significant and hemodynamically nonsignificant vasospasm, rather than between symptomatic and nonsymptomatic vasospasm.

Relative Contribution of SI, Age, and AdmGCS to Outcome

It should be emphasized that the difference in outcome between high and normal SI groups is not primarily due to differences in age or admGCS score. Advanced age has been associated with decreased baseline CBF in healthy individuals. It might therefore be expected that older patients would be more vulnerable to developing low CBF postinjury and suffer worse outcome. Our results tend to support this proposition (Table 4). However, there was no significant difference in mean age between high and normal SI groups, despite the fact that those two groups had very different outcomes (Table 4). As for admGCS score, one would expect progressively worse outcome with lower admGCS scores, and our findings confirm this relationship (Tables 2 and 3). Stepwise logistic regression analy-
sis confirms the intuitive and clinically supported notion that the severity of head injury, represented by the admGCS score, is the most important predictor of outcome (Table 5). Our results also show that high SIs exert a relatively greater influence on outcome, compared with age, in mild and moderately head injured patients, and relatively less influence in patients with more severe head injuries. This makes sense: one would expect most patients with very severe primary brain injuries to have a poor outcome regardless of whether they develop cerebral vasospasm. It is in those patients with less severe initial injuries, who might do well without secondary insults, that cerebral vasospasm has its greatest impact. To summarize, the development of hemodynamically significant cerebral vasospasm (as defined by an elevated SI) is a risk factor for poor outcome relatively independent of age and admGCS score, with its relative importance increasing with decreasing severity of head injury.

Implications for Treatment of Head-Injured Patients

The results presented here clearly show that cerebral vasospasm that occurs after traumatic brain injury, like vasospasm that occurs following aneurysmal SAH, is a potentially important contributor to secondary ischemic injury. Recognition of this similarity compels one to ask whether therapies proven to be efficacious in patients with aneurysmal SAH might not also produce benefits in the head-injured population. Indeed, such a supposition has been the inspiration for recent trials investigating the utility of nimodipine in patients with traumatic brain injury. Nimodipine has long been known to produce beneficial effects in patients with aneurysmal SAH. A similar benefit has been seen in patients with posttraumatic SAH, but not in the general head-injured population. Our present report, unfortunately, cannot address the issue of whether nimodipine bestows its benefits through ameliorating effects on vasospasm or by modifying cellular metabolism (or a combination of both). Investigation of the cerebral hemodynamic effects of nimodipine and the efficacy of other therapies should prove to be fruitful areas for future study.

Confounding Issues

One potential criticism of this study is our decision not to use CBF values corrected for PCO₂. We believe that in correlating CBF or an SI to outcome, it is important to use the actual CBF. Brain tissue is presumably indifferent to the exact cause of inadequate CBF. In addition, CO₂ reactivity has been shown to vary after head injury, with markedly diminished reactivity associated with poor outcome. Standard formulas used to adjust CBF values for PCO₂ may, therefore, make assumptions that simply are not true for the head-injured population.

A second criticism may center on the absence of data for AVDO₂ and cerebral metabolic rate of oxygen consumption. Measuring these parameters requires the use of jugular venous catheters. Placement of these catheters is difficult to justify in patients with a GCS score greater than 8, and difficult to continue for the 10 to 14 days necessary to include the period of spasm. A third criticism may focus on our decision not to include data on ICP, hypotension, and other factors that are associated with
clinical outcome. Our research group is currently investigating many of these parameters for correlation and logistic regression analysis, and we plan to report the findings in a future article.

Conclusions

Our findings strongly support a multimodal approach to diagnosing vasospasm, which combines TCD flow velocities, and direct, quantitative CBF measurements. We have demonstrated a strong association between hemodynamically significant cerebral vasospasm, as defined by an elevated SI, and poor outcome. Early identification of patients with hemodynamically significant vasospasm could allow preemptive measures to be undertaken that may prevent critical impairment of CBF and poor outcome.

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Addendum

Twenty-nine (23%) of the 126 patients in whom TCD ultrasound alone was used to diagnose BA vasospasm had no BA vasospasm but did develop TCD-diagnosed MCA vasospasm. These 29 patients were excluded from this particular analysis so as to obtain a normal group that was completely free of TCD-demonstrated vasospasm.

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