Posttraumatic vasospasm: the epidemiology, severity, and time course of an underestimated phenomenon: a prospective study performed in 299 patients

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Object. The purpose of this prospective study was to evaluate the cumulative incidence, duration, and time course of cerebral vasospasm after traumatic brain injury (TBI) in a cohort of 299 patients.

Methods. Transcranial Doppler (TCD) ultrasonography studies of blood flow velocity in the middle cerebral and basilar arteries (V\text{\textsubscript{MCA}} and V\text{\textsubscript{BA}}, respectively) were performed at regular intervals during the first 2 weeks posttrauma in association with \textsuperscript{133}Xe cerebral blood flow (CBF) measurements. According to current definitions of vasospasm, five different criteria were used to classify the patients: A (V\text{\textsubscript{MCA}} > 120 cm/second); B (V\text{\textsubscript{MCA}} > 120 cm/second and a Lindegaard ratio [LR] > 3); C (spasm index [SI] in the anterior circulation > 3.4); D (V\text{\textsubscript{MCA}} > 90 cm/second); and E (SI in the posterior circulation > 2.5). Criteria C and E were considered to represent hemodynamically significant vasospasm. Mixed-effects spline models were used to analyze the data of multiple measurements with an inconsistent sampling rate.

Overall 45.2\% of the patients demonstrated at least one criterion for vasospasm. The patients in whom vasospasm developed were significantly younger and had lower Glasgow Coma Scale scores on admission. The normalized cumulative incidences were 36.9 and 36.2\% for patients with Criteria A and B, respectively. Hemodynamically significant vasospasm in the anterior circulation (Criterion C) was found in 44.6\% of the patients, whereas vasospasm in the BA—Criterion D or E—was found in only 19 and 22.5\% of the patients, respectively. The most common day of onset for Criteria A, B, D, and E was postinjury Day 2. The highest risk of developing hemodynamically significant vasospasm in the anterior circulation was found on Day 3. The daily prevalence of vasospasm in patients in the intensive care unit was 30\% from postinjury Day 2 to Day 13. Vasospasm resolved after a duration of 5 days in 50\% of the patients with Criterion A or B and after a period of 3.5 days in 50\% of those patients with Criterion D or E. Hemodynamically significant vasospasm in the anterior circulation resolved after 2.5 days in 50\% of the patients. The time course of that vasospasm was primarily determined by a decrease in CBF.

Conclusions. The incidence of vasospasm after TBI is similar to that following aneurysmal subarachnoid hemorrhage. Because vasospasm is a significant event in a high proportion of patients after severe head injury, close TCD and CBF monitoring is recommended for the treatment of such patients.

Key Words: cerebral blood flow • head injury • transcranial Doppler ultrasonography • time course

Cerebral vasospasm is generally accepted to be a major cause of disability and long-term neurological deficits after aneurysmal SAH. According to one study, radiographic evidence of vasospasm was identified in 40 to 70\% of patients, yet symptomatic vasospasm with neurological deterioration occurred in only 20 to 30\% of patients after aneurysmal SAH. In 7\% of patients with this type of hemorrhage, vasospasm was severe enough to cause permanent ischemic deficits and in another 7\% it was fatal. Traumatic brain injury is frequently associated with SAH. Traumatic SAH has been reported in 33 to 60\% of patients who have sustained a TBI. Despite some controversy, there is increasing evidence that traumatic SAH is associated with an unfavorable outcome.

Posttraumatic vasospasm has been confirmed by both angiography and TCD ultrasonography; however, the incidence of posttraumatic vasospasm varies widely across prior studies. Based on TCD studies, vasospasm in the anterior circulation was identified in 27 to 40\% of cases of head injury. With respect to the posterior circulation, vasospasm of the BA was found in an estimated 33\% of all pa-
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Patients. The duration and time course of posttraumatic vasospasm have varied among reports. The durations cited have ranged from 12 hours to 3 weeks, and a high V<sub>MCA</sub> has been recorded from postinjury Day 3 to Day 12. In the majority of patients the onset of vasospasm was observed after postinjury Day 3.

Cerebral vasospasm after trauma has been found to be a significant predictor of poor outcome, independent of clinical factors such as the patient’s GCS score and age; however, for most clinicians cerebral vasospasm is not the primary focus in the treatment of a patient who has suffered multiple traumatic events. The primary focus of this study was to analyze the incidence, daily prevalence, time course, and spectrum of severity of posttraumatic vasospasm in the largest population studied to date by performing both TCD ultrasonography and CBF monitoring. Five different criteria of vasospasm in the anterior and posterior circulations were compared. In addition, CT findings and their predictive value of cerebral vasospasm were analyzed. A mixed-effects spline model was used to analyze repeated measures in a cohort with an inconstant sampling rate.

Clinical Material and Methods

Management Protocol

Patients with TBI were enrolled in the UCLA Brain Injury Research Center Program. They were treated either at the UCLA Health Science Center in Los Angeles, or at the Harbor–UCLA Medical Center in Torrance, California. An informed consent form approved by the UCLA Human Subject Protection Committee was signed by family members of all patients. After hospital admission, the patients immediately underwent cranial CT scanning. Depending on the nature and severity of the injury, the patients either underwent surgery or were directly transported to the neurosurgical ICU. Treatment in the ICU followed the recommendations set forth in the article, “Guidelines for the management of severe head injury.” Arterial pressure monitoring, mechanical ventilation, continuous electroencephalography, central venous pressure, and continuous ICP monitoring were performed. Sedatives, vasopressors (such as dopamine and norepinephrine), mannitol, barbiturates, propofol, albumin, and blood products were administered and hyperventilation was induced as needed. The head-injury management protocols at the UCLA and Harbor–UCLA Medical Centers included intensive cerebral hemodynamic monitoring. Both TCD and CBF studies were performed as soon as possible following the patient’s admission to the hospital. They were performed at regular intervals in accordance with the Brain Injury Research Center’s research protocol over a 15-day period, or as indicated clinically, until the patient died, recovered, was transferred, or was discharged. Significant abnormalities in CBF or TCD flow velocities prompted a careful assessment of relevant physiological parameters (such as MABP, ICP, arterial blood gas levels, and hematocrit). These parameters were adjusted to optimize the patient’s CPP at no less than 70 mm Hg (through cerebral spinal fluid drainage and mannitol administration to lower the ICP or by the use of vasopressors).

Measurement Techniques of Physiological Parameters

Transcranial Doppler Ultrasonography. Vessels including the MCA, the extracranial ICA, and the BA were insonated bilaterally by using the general method described by Aaslid and associates. Recordings were performed using a 2-MHz pulsed probe and a commercially available TCD ultrasonography unit (Neuroguard Cerebrovascular Diagnostic System; Nicolet Biomedical, Inc., Madison, WI). The mean flow velocity values represent an average over four cardiac cycles. The Gosling pulsatility index was calculated automatically for each recording. Physiological data were recorded with each TCD and CBF study, and included ICP, MABP, CPP, and arterial PCO<sub>2</sub> measurements. The number of patients studied on each postinjury day with TCD ultrasonography were as follows: Day 0, 117 patients; Day 1, 173; Day 2, 162; Day 3, 166; Day 5, 238; Day 7, 179; Day 9, 151; Day 11, 139; Day 13, 112; and Day 15, 89 patients.

Cerebral Blood Flow Measurements. Cerebral blood flow was measured using the intravenous 133Xe clearance technique with a portable, commercially available apparatus (Cerebrograph Cortexplorer; Ceretronix, Randers, Denmark) as previously described. The CBF<sub>a</sub>, an index of mean gray and white matter flow, was determined according to Obrist and Wilkinson. Both mean right- and left-sided CBF<sub>a</sub> values (uncorrected for arterial PCO<sub>2</sub>) were obtained by averaging five regional detectors placed over each hemisphere. Coordinated TCD and CBF studies were performed sequentially because simultaneous measurements were technically not feasible.

Definition of Diagnostic Criteria and Calculations

Table 1 presents the definition of the five hemodynamic criteria used to diagnose vasospasm: Criteria A, B, and C for the anterior circulation and Criteria D and E for the posterior circulation.

Vasospasm and TCD Measurements. The methods used to assess vasospasm have evolved since TCD ultrasonography was first introduced. Initially, vasospasm was defined by blood flow velocity alone. Comparing angiography with
found that all patients is defined as the ratio of empirically defined hemodynamic threshold for the BA was defined as a $V_{MCA} > 200$ cm/sec and LR $> 6$. Table 2 indicates the severity of vasospasm in the anterior circulation along with that considered to be hemodynamically significant.

**Bilateral Vasospasm.** Vasospasm can develop in both hemispheres simultaneously or sequentially. Patients in whom vasospasm developed first in one hemisphere and later in the other were classified as being in spasm the first time a given criterion was met, regardless of the laterality. Vasospasm was considered present as long as one hemisphere displayed at least one of the criteria.

### Statistical Analysis

Individual time courses of physiological measurements (used both for estimating the timing of the beginning and resolution of vasospasm as well as the time courses of vasospasm) were estimated using a mixed-effects spline model. The model relies on the assumption that each individual time course can be described by a piecewise cubic polynomial with knots at postinjury Days 2, 4, 7, and 10 (the knots were chosen using both statistical and substantive considerations). The parameters of the splines were considered to be random effects. The estimated trajectories in this model represent smoothed versions of the raw data: for a particular patient’s data, the amount of smoothing and the amount of uncertainty in the estimated trajectory are inversely related to the number of measurements available for that patient. The estimated trajectories and their associated confidence limits were used to estimate the first (or last) time at which the measurements were likely to have exceeded a certain threshold (for example, $V_{MCA}$ on the right side $> 120$ cm/sec). In practice, we looked at when the upper limit of the 90% confidence band exceeded the threshold; this is equivalent to finding the first (or last) time at which the null hypothesis that the patient’s measurement is above the threshold can no longer be rejected at a one-sided level of 0.05.

Kaplan–Meier curves for the cumulative normalized incidence were computed using the imputed time of onset of vasospasm for each patient. Some patients did not have a time of onset under the several criteria and were regarded as free from vasospasm. Patients who died during the study were treated as censored at the time of death. Values for the daily risk of developing vasospasm were derived directly from the Kaplan–Meier curves. Similar Kaplan–Meier curves were constructed for the proportion of patients remaining in vasospasm by using an imputed time of vasospasm resolution to estimate the duration of vasospasm.

### Results

**Description of the Sample**

A total of 299 patients were included in this study. The mean age of these patients was 35 ± 16 years (range 16–87 years) with a male/female ratio of 4:1. The median GCS score on admission was 7 and the scores ranged from 3 to 15.
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15. A comparison was made between patients with and without vasospasm. As shown in Table 3, patients in whom vasospasm developed according to at least one criterion were significantly younger and had a lower GCS score on admission (p < 0.001, two-tailed t-test). The two groups were not significantly different in terms of sex, MABP, ICP, or CPP. From postinjury Day 0 to Day 15, a total of 1526 TCD ultrasoundography studies were performed on supratentorial vessels including the MCA, and 921 studies were performed on posterior circulation vessels including the BA. Overall 572 133Xe CBF studies were performed. Concurrent TCD and CBF measurements were not possible for all studies because of logistic and technical issues such as depletion of 133Xe supplies, computer failure, or lack of technical staff. The anterior circulation SI was calculated from 389 CBF measurements with concurrent TCD ultrasoundography studies, whereas the posterior circulation SI was calculated from 285 concurrent CBF and TCD ultrasoundography studies. As shown in Table 1, in only 130 patients were CBF measurements obtained at the time of TCD value determination, which means that the SI was calculated based on a subgroup of the total 298 TCD patients. Comparisons between this subgroup and the larger TCD sample revealed no significant differences in MABP, CPP, admission GCS score, age, right- and left-sided V_{MCA}, V_{BA} or right- and left-sided LR. Thus, it should be possible to generalize the SI findings to the entire study cohort. A total of 135 patients (45.2%) met at least one of the criteria of vasospasm (Table 1). One, two, three, and four or more criteria were met by 21, 37, 27, and 15% of patients, respectively. Vasospasm in both the anterior and posterior circulations was present in 36% of those patients who experienced spasm.

Normalized Cumulative Incidence and the Daily Risk of Vasospasm

Figure 1 presents the cumulative incidence of vasospasm occurring in the anterior (Fig. 1 upper) and posterior (Fig. 1 lower) circulations. Relative to Criteria A and B, Criterion C (top graph) showed a steep rise between postinjury Days 2 and 4, and a higher total incidence (44.6%). The probability of vasospasm commencing on a given day (daily hazard) is shown in Fig. 2. In the anterior circulation the highest risk of vasospasm development was on postinjury Days 2 and 3 for Criterion A (0.12 and 0.08, respectively) and Criterion B (0.13 and 0.11, respectively). Note that on postinjury Day 1 the probability of vasospasm was higher for Criterion A than for B (0.07 compared with 0.02), the highest probability of hemodynamically significant vasospasm (Criterion C) developing was recorded on postinjury Days 3 and 4 (0.14 and 0.11, respectively). After Day 5 the risk of vasospasm development was less than 0.05 regardless of which criterion was used. In the posterior circulation, Criterion D showed the highest probability of vasospasm development on postinjury Day 2 (0.07). For Criterion E, the highest risk of hemodynamically significant vasospasm development was found on postinjury Days 2 and 4 (0.05 on both days).

Duration of Posttraumatic Vasospasm

As shown in Fig. 3, 50% of patients meeting either Criteria A or B experienced resolution of vasospasm 5 days after its onset. In contrast, hemodynamically significant vasospasm (Criterion C) resolved earlier, with 50% of patients experiencing the cessation of vasospasm after 2.5 days. In the anterior circulation, vasospasm resolved in 50% of patients 3 days after its onset (Criteria D and E).

Comparison of patients with and without vasospasm

<table>
<thead>
<tr>
<th>Factor</th>
<th>No. of Patients</th>
<th>Value*</th>
<th>p Value†</th>
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<tr>
<td>patients w/o vasospasm‡</td>
<td>135</td>
<td>32 ± 14</td>
<td>0.001</td>
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<td>male/female ratio</td>
<td>135</td>
<td>4.6:1</td>
<td>0.54</td>
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<td>GCS score on admission</td>
<td>135</td>
<td>7 ± 4</td>
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<td>95 ± 9</td>
<td>0.13</td>
</tr>
<tr>
<td>ICP (mm Hg)§</td>
<td>109</td>
<td>15 ± 7</td>
<td>0.5</td>
</tr>
<tr>
<td>CPP (mm Hg)§</td>
<td>109</td>
<td>82 ± 12</td>
<td>0.11</td>
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<td>patients w/o vasospasm</td>
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<td>38 ± 17</td>
<td>0.001</td>
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<tr>
<td>male/female ratio</td>
<td>164</td>
<td>4:1</td>
<td>0.54</td>
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<td>GCS score on admission</td>
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<td>10 ± 4</td>
<td>0.001</td>
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<tr>
<td>CPP (mm Hg)§</td>
<td>81</td>
<td>78 ± 22</td>
<td>0.11</td>
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</table>

* With the exception of the male/female ratio, values are expressed as the means ± standard deviations.† Determined using t-test or chi-square test.‡ Includes all patients in whom at least one of the vasospasm criteria was identified.§ Values are based on the total observations made across individuals and time.

TABLE 3

Daily Prevalence of Vasospasm in the ICU

The daily prevalence of vasospasm is shown in Fig. 4. Patients who left the ICU are not represented in this calculation. Starting on postinjury Day 2, it is apparent that approximately 30% of all patients remaining in the neurosurgical ICU fulfilled at least one criterion of vasospasm. The percentages remained stable through postinjury Day 13 both in the anterior and posterior circulations. Severe vasospasm (V_{MCA} > 200 cm/second and LR > 6) was not seen before postinjury Day 11.

Hemodynamically Significant Vasospasm

Figure 5 presents the distribution of the SI, V_{MCA}, and CBF values in the subgroup of patients with hemodynamically significant vasospasm in the anterior circulation (SI > 3.4). In more than 50% of the studies the SI was greater than 4. In 58% of the studies in which the SI was greater than 3.4, the V_{MCA} was greater than 120 cm/second. Nevertheless, in 34% of the studies the V_{MCA} was between 90 and 120 cm/second, and in 8% of the studies the V_{MCA} was even lower than 90 cm/second. Hypoperfusion, defined as CBF lower than 30 ml/100 g/min, was observed in more than 50% of the studies.

Time Course of Hemodynamic Variables in Patients With Hemodynamically Significant Vasospasm

Figure 6 presents the time course of the V_{MCA}, CBF, and SI in the subgroup of patients with hemodynamically significant vasospasm in the anterior circulation. Whereas the V_{MCA} increased 2 days before the development of this vasospasm (time 0 on the graph), the CBF and SI did not change...
until 1 day before hemodynamically significant vasospasm appeared. The increase in the SI was primarily due to the decrease in CBF rather than the small increase in the V_{MCA}. There was no change in the ICP or in the cerebrovascular resistance assessed by using the Gosling pulsatility index.

**Vasospasm and CT Findings**

Computerized tomography scans of good quality could be reviewed in 259 patients (87%). The CT scans revealed more than one major diagnosis in 176 patients (68%). Epidural, subdural, and intracerebral hematomas or contusions were found in 20, 37, and 64% of patients, respectively. Subarachnoid and intraventricular hemorrhages were present in 57 and 21 patients, respectively. A ventriculostomy was placed in 64% of the patients who had undergone CT scanning. The occurrence of SAH was significantly greater in patients in whom vasospasm developed than in those in whom it did not (p < 0.05, chi-square test). A logistic regression analysis revealed a statistical trend for the development of vasospasm for patients with intracerebral hematomas or contusions (p = 0.09) and SAH (p = 0.13), but not for patients with subdural (p = 0.36) or epidural (p = 0.91) hematomas.

**Discussion**

**Summary of Findings**

The primary purpose of this investigation was to gain a description of the incidence and time course of posttraumatic vasospasm defined by five currently used criteria. This
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![Bar graphs showing the daily probability of entering a phase of vasospasm for each of the five criteria. The highest probability is on postinjury Day 2 for Criteria A and B; however, hemodynamically significant vasospasm (Criterion C) does not develop until postinjury Day 3. Note that the overall occurrence of vasospasm is lower in the posterior circulation (Criteria D and E).]

Investigation included 299 patients, which is the largest patient sample studied to date with TCD ultrasonography and CBF studies since the first description of vasospasm following severe head injury. In this study we investigated not only TCD-diagnosed vasospasm alone, but also hemodynamically significant vasospasm. The normalized cumulative incidence of vasospasm in the anterior (Criteria A and B) and posterior (Criteria D and E) circulations were 36 to 37% and 19 to 22.5%, respectively. Hemodynamically significant vasospasm in the anterior circulation (Criterion C), defined by an SI greater than 3.4, was found in 44.6% of the patients. The highest daily risk of developing vasospasm was recorded on postinjury Day 2 for all criteria except hemodynamically significant vasospasm in the anterior circulation (Criteria D and E).

The highest daily risk of developing vasospasm was recorded on postinjury Day 2 for all criteria except hemodynamically significant vasospasm in the anterior circulation (Criteria D and E), for which the highest risk was found on postinjury Day 3. The daily prevalence of vasospasm in the ICU (number of patients in spasm divided by the number studied) remained relatively constant at 30% between 2 and 13 days postinjury. The duration of vasospasm was generally longer in the anterior circulation than in the posterior circulation. In 50% of patients with vasospasm in the anterior circulation, the condition resolved within 5 days after its onset. Here, hemodynamically significant vasospasm resolved within 2.5 days in 50% of the patients. In the posterior circulation, vasospasm resolved in 50% of the patients as early as 3 days after onset. The time course of hemodynamically significant vasospasm was primarily due to a decrease of CBF that occurred 1 day before vasospasm.
Methodological Issues

The analysis of time course data was complicated by the lack of homogeneity in the cohort. Not all patients were studied on all days. According to their clinical conditions, the patients entered or exited the cohort throughout the 15-day observation period. In attempting to correct for this nonhomogeneity, we used time course estimates, taking into account the varying amounts of information contributed by different individuals. Additional time course analyses were performed on a subsample of patients with hemodynamically significant vasospasm. When interpreting TCD velocities, it is necessary to consider the role of cerebral hyperemia (elevated CBF), which typically occurs between 2 and 4 days postinjury. Given that the onset of posttraumatic vasospasm is most probable during this time period, TCD velocities greater than 120 cm/second should be interpreted with caution. High velocities could represent hyperemia rather than a spastic narrowing of vessels. Both the LR and the SI were designed to reduce the influence of hyperemia and thus are more indicative of vasospasm. The combined use of TCD and CBF measurements has been found to improve predictions of outcome.

Cumulative Incidence of Vasospasm

The incidence of posttraumatic vasospasm has varied widely in investigative reports. This is primarily attributable to the small sample size in most studies. In the present study we found a cumulative incidence of 36 to 37% (Criteria A and B) over the first 15 days postinjury, which is consistent with previously published results. Based on TCD measurements, approximately 40% of patients experience posttraumatic vasospasm. In other studies, however, investigators have reported vasospasm in 27 and 68% of patients. These extremes may be due to small, highly select patient samples. In angiographic studies the incidence of posttraumatic vasospasm has generally been lower than the incidences recorded in TCD- and CBF-based evaluations. Although Leeds and colleagues reported an incidence as high as 31%, in other angiographic studies investigators found only 5 to 19%. Compared with our
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results, the relatively low incidence of angiographically defined vasospasm may be due to the lack of repeated measurements. The cumulative incidence of BA spasm in patients with TBI was found to be 19 to 22% (Criteria D and E). This is lower than that suggested in previous reports. In an earlier investigation vasospasm was found in the posterior circulation in 33% of patients. Hadani, et al., published an incidence of 37% in a sample of 32 patients; however, the focus of that study was on patients with severe head trauma (initial GCS score ≤ 8), in contrast to the present study in which we included some milder cases.

Daily Risk of Vasospasm

In our sample the highest daily risk of developing vasospasm (Criteria A and B) was found on postinjury Day 2, with a probability of 0.12 to 0.13. The risk of hemodynamically significant vasospasm (Criterion C) was highest on postinjury Day 3, with a probability of 0.14. In the literature the onset of posttraumatic vasospasm (mostly defined as \( V_{\text{MCA}} > 120 \text{ cm/second} \)) was recorded between postinjury Day 2 and Day 4. The highest risk of onset of BA spasm was found on postinjury Day 2, with a probability of 0.07 for Criterion D. Nevertheless, even on Day 1 the risk was 0.03. In contrast to other investigations, the day of onset in our sample was earlier. In a previous study investigators reported that the \( V_{\text{MCA}} \) was greater than 90 cm/second starting on postinjury Day 4.

Duration of Vasospasm

Among patients with vasospasm in the anterior circulation (Criteria A and B) 50% experienced resolution of the condition within 5 days of onset, whereas among patients with vasospasm in the posterior circulation (Criteria D and E) 50% experienced resolution within 3 days. Hemodynamically...
day before the SI crossed the vasospasm threshold, whereas the \(V_{\text{MCA}}\) displayed an unremarkable increase. In fact, the \(V_{\text{MCA}}\) was less than 120 cm/second in 42% of studies when the SI exceeded 3.4 (Fig. 5). The reduction in CBF with little or no change in the \(V_{\text{MCA}}\) explains why hemodynamically significant vasospasm (SI > 3.4) occurred more frequently than an elevated \(V_{\text{MCA}}\) as shown in Table 1. The finding of hemodynamically significant vasospasm in the presence of normal \(V_{\text{MCA}}\) may be explained by the pathophysiological characteristics of cerebral vasospasm as proposed by Jakobsen.\(^{31}\) Given \(FV = CBF/A\) (where \(FV\) = flow velocity and \(A\) = the cross-sectional area of the vessel), the following stages of vasospasm can be postulated. In mild stenosis (Stage 1) the flow velocity will increase, but because of peripheral vasodilation (an increase in blood volume) CBF will be unchanged.\(^{32}\) In this stage, flow velocity is a good indicator of vasospasm. With increasing stenosis and a reduction in the cross-sectional area of the vessel (Stage 2), peripheral vasodilation can no longer compensate and CBF will decrease. Consequently, in a setting of low CBF and reduced cross-sectional area of the vessel, the flow velocity will be normal or only slightly elevated. In this stage the SI is a good indicator of vasospasm.\(^{44}\) Ischemia (Stage 3) may develop when the AVDO\(_2\) can no longer compensate for the reduction in CBF, so that the CMRO\(_2\) decreases. In accordance with the previous definition of the SI and the aforementioned pathophysiological concepts, the SI becomes elevated when the degree of arterial narrowing is sufficient to reduce blood flow (Stage 2). This explains not only the later onset of SI-defined vasospasm, but also its hemodynamic significance.

**Vasospasm and CT Findings**

After aneurysmal SAH occurs, the amount of blood on the first CT scan can be predictive of the development of cerebral vasospasm.\(^{21}\) In only a few studies have investigators examined CT findings and vasospasm after trauma. In a sample of 99 patients with TBI, vasospasm was independently predicted in patients with SAH, subdural hematoma, and intraventricular hemorrhage on CT scans.\(^{49}\) In the present study, only SAH was significantly related to the development of vasospasm, although intracerebral hematomas or contusions revealed a trend. The presence of traumatic SAH on a CT scan occurred in 57% of our sample, a value that agrees with the 61% rate reported recently.\(^{53}\) A multicenter study of 750 patients with TBI found that traumatic SAH was associated with a poor outcome,\(^{67}\) which is consistent with the finding that posttraumatic vasospasm is predictive of outcomes.\(^{17,44}\) After trauma, other factors need to be considered in the genesis of vasospasm. Direct stretching or mechanical irritation of cerebral arteries may enhance the early development of posttraumatic vasospasm.\(^{6,72}\) This may explain why posttraumatic vasospasm was found in patients whose CT scans or lumbar punctures demonstrated no blood in the cerebrospinal fluid.\(^{10,80,70}\)

**Comparison of Vasospasm After Trauma and After Aneurysmal SAH**

In the present study, the cumulative incidence of posttraumatic vasospasm (across all criteria) is comparable to the incidence following aneurysmal SAH, for both the anterior\(^{40,76}\) and posterior\(^{13,68}\) circulations. Although the genesis
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of vasospasm may be different after trauma and SAH, little
difference has been found in the morphological appearances
of the vessels in these two conditions.77

Posttraumatic vasospasm may occur earlier than vasos-
spasm that follows aneurysmal SAH. Vasospasm was not
seen on angiograms within the first 72 hours after aneurysm
rupture, when the vessels may even be dilated.88 Weir and
colleagues89 reported that following aneurysmal SAH vaso-
spasm started on Day 3 and concluded by Day 12. In con-
trast, after severe head injury vasospasm was seen within 12
hours on TCD ultrasonograms.15 In a cohort of 130 patients
with TBI, an angiographic study provided the diagnosis of
vasospasm between postinjury Days 0 and 2 in seven of 18
patients in whom ischemic symptoms developed.72 The ear-
lier onset of vasospasm after trauma is in accord with the
present findings, in which the highest risk of vasospasm de-
velopment occurred on postinjury Day 2. The duration of
vasospasm may be shorter after TBI than after aneurysmal
SAH. Several investigators have reported that the vaso-
spasm associated with aneurysmal SAH can last longer than
3 weeks.30,43

Across studies the duration of vasospasm varied from 8
to 20 days.30,43,76 These investigations encountered the prob-
lem of loss of patients over time. We used the mixed-effects
model to try to correct for this. Unfortunately, in none of the
studies was the duration of vasospasm reported in a surviv-
al-type analysis, as performed in the present study. Despite
the fact that vasospasm can be seen up to 14 days after tra-
ma, it resolved in 50% of our patients within 5 days. The
prevalence of hemodynamically significant vasospasm is
approximately the same following trauma and aneurysmal
SAH, but maximum velocities may be higher after aneu-
rysmal SAH. According to an unpublished UCLA study
(Glenn, et al.), hemodynamically significant vasospasm oc-
curred in 43.4% of 378 patients with aneurysmal SAH com-
pared with 46.6% in the present sample of patients with
TBI. Nevertheless, moderate (V_{MCA} > 150 cm/second and
LR < 4–6) and severe (V_{MCA} > 200 cm/second and LR > 6)
vasospasm were found, respectively, in 14.2 and 2.9% of
patients with aneurysmal SAH, compared with only 8.9 and
0.8% in the present study (Table 2).

Clinical Significance of the Physiological Indices
of Vasospasm

Secondary neurological deterioration caused by vaso-
spasm is difficult to detect in comatose patients with TBI
and thus the immediate effects of spasm cannot be assessed.
Because cerebral angiography is not routinely performed
in patients with TBI, the extent of arterial spasm is usually
unknown. The question arises whether clinically significant
information can be derived from the physiological indices
used in the present study (the V_{MCA}, LR, and SI), as previ-
ously reported for patients with aneurysmal SAH.

By using a V_{MCA} criterion greater than 120 cm/second,
Suarez and colleagues40 predicted symptomatic vasospasm
in 55 of 199 patients with aneurysmal SAH with a sensiti-
ity of 64% and a specificity of 78%. In a sample of 25 pa-
ients with aneurysmal SAH, Mascia and coworkers22 found
that all six patients with a V_{MCA} greater than 160 cm/second
had both clinically and angiographically determined vaso-
spasm, although six other patients in whom there was a clin-
ical deterioration did not reach this threshold. As noted ear-
lier, approximately 10% of patients with TBI in the present
study were classified as having moderate to severe vaso-
spasm, based on their MCA velocities and LRs. In 10% of
these patients the SI values were in excess of 5, which was
suggestive of more severe vasospasm. Using these criteria,
it should be possible to identify patients with TBI who are
at greater risk for the development of clinically significant
vasospasm. In such cases, more aggressive therapy may be
considered.

Of particular relevance is the possibility of vasospasm-
induced cerebral infarction. In a study of aneurysmal SAH,
Rabinstein and associates61 found evidence of infarction on
later CT scans in 55% of 85 patients with a V_{MCA} greater
than 120 cm/second. In the present TBI study, 36.9% of the
patients had V_{MCA} values higher than this level. Extrapolat-
ing from the data on aneurysmal SAH, vasospasm-induced
infarction might be expected in as many as 20% of the pres-
ent trauma patients (55 × 37%).

In patients with TBI, the 6-month outcome, determined
using the Glasgow Outcome Scale, was found to be signifi-
cantly related to the SI, independent of the patient’s age and
admission GCS score: patients with an SI greater than 3.4
had poorer outcomes.41 In a subsequent study by the au-
thors,23,29 patients with TBI were examined on the day of
spasm onset and 1 day earlier. Compared with the previ-
ous day, the CMRO$_2$ declined significantly with spasm on-
set: in the right hemisphere, 1.44 ml/100 g/min compared
with 1.09 ml/100 g/min (p < 0.02, 18 patients); and in the
left hemisphere, 1.22 ml/100/min compared with 0.88 ml/
100 g/min (p < 0.04, 12 patients). These observations are
consistent with previous AVDO$_2$, CMRO$_2$, and outcome
findings in patients with aneurysmal SAH,33,34 which were
interpreted as evidence of cerebral ischemia.32 The afore-
mentioned preliminary findings on outcome and CMRO$_2$
indicate that posttraumatic vasospasm may also induce ce-
bral ischemia and a lower CMRO$_2$, which could then lead
to poorer outcomes. Thus vasospasm may be considered a
secondary insult to a traumatized brain that is already in a
state of increased vulnerability.32 Further research (includ-
ing positron emission tomography and magnetic resonance
imaging studies) is clearly needed to determine the extent to
which posttraumatic vasospasm causes cerebral ischemia
and infarction.

Implications for Treatment

Although the current guidelines for the management of
severe brain injury$^8$ recognize that traumatic SAH is asso-
ciated with a delayed ischemic deficit,72 there are no spe-
cific recommendations for the treatment of posttraumatic
vasospasm. Treatment of vasospasm after aneurysmal SAH
presently includes triple-H therapy (hypertension, hyper-
volemia, and hemodilution),27,28 administration of calcium
channel blockers (such as nimodipine),32,42 angioplasty,29,36
and intraarterial administration of papaverine.29,36

Treatment of vasospasm after TBI is complicated by
multiple factors, however, and cannot simply follow the
recommendations for treatment after aneurysmal SAH. Be-
cause angiography is not routinely performed after trauma,
the efficacy of angioplasty and intraarterial papaverine has
not been clearly demonstrated, as in the case of aneurysmal
SAH, in which 90% of the patients have benefited8 and
vessel diameter increased by 42%.81 It is quite possible that
the 10% of patients with TBI who display more severe vasospasm could benefit from endovascular therapy.

Consideration should also be given to the hemodynamic phases after TBI; that is, initial hypoperfusion followed by hyperemia and its resolution. These phases require different treatments. Without TCD and CBF studies, the transition from one phase to the next may not be detected. Triple-H therapy is clearly not suitable for patients with hyperemia or high ICP due to brain edema; however, elevation of blood pressure may be necessary in patients with hypoperfusion. Secondary insults such as hypotension and hypoxia should be avoided after TBI. In this regard, hypotension is a major side effect of nimodipine therapy. Hypoxia caused by nimodipine has also been reported. The efficacy of nimodipine administration in patients with TBI is controversial. Whereas the European Study Group found no significant benefit of nimodipine, the German trial of traumatic SAH demonstrated a more favorable outcome and lower ICP with nimodipine. Based on the high prevalence of posttraumatic vasospasm reported here and its potential effect on outcome, further research is clearly needed to establish guidelines for its appropriate treatment.

**Conclusions**

Our investigation revealed that vasospasm occurs in more than one third of all patients with TBI. Patients in whom vasospasm developed were younger and more severely injured than patients who did not experience vasospasm after head injury. The onset of vasospasm following TBI may be earlier than the onset of vasospasm following aneurysmal SAH. The duration of vasospasm in the anterior circulation is longer than that in the posterior circulation. Despite the fact that the maximum $V_{max}$ was lower after trauma than after aneurysmal SAH, hemodynamically significant vasospasm more frequently occurred. Although in the present study we did not assess the effect of vasospasm on outcome, findings from our previous studies of posttraumatic vasospasm and other reports described earlier indicate that moderate-to-severe vasospasm (present in 10% of our patients) may be sufficient to cause ischemic damage and poorer outcomes.

Overall, we consider posttraumatic vasospasm to be a potentially significant secondary insult after TBI, and recommend close TCD and CBF monitoring of patients with this type of injury.

**Acknowledgments**

We thank Maria Etchepare and Kathy Langlois for their help in data collection, and we greatly appreciate the technical support of Brenda Rinsky, Oscar Barcenas, Chris Hanuscin, and So-Youin Lee from the UCLA Cerebral Blood Flow Laboratory.

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