HIGH LIGHT CME

Haptoglobin and the development of cerebral artery vasospasm after subarachnoid hemorrhage

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Abstract—*Background:* Vasospasm is a prolonged constriction of a cerebral artery that is induced by hemoglobin after subarachnoid hemorrhage (SAH). The subarachnoid blood clot also contains the protein haptoglobin, which acts to neutralize hemoglobin. Because the haptoglobin α gene is dimorphic, a person can expresses only one of three types of haptoglobin (α1–α1, α1–α2, or α2–α2) depending on the α subunit genes he or she inherits. Each of these three haptoglobin types has different antihemoglobin activities; therefore, haptoglobin may influence the development of vasospasm differently in various patients with SAH. *Objective:* To determine whether SAH patients who have haptoglobin containing the α2 subunit would be more likely to develop vasospasm than would be SAH patients who have haptoglobin α1–α1. *Methods and Results:* A total of 32 patients with Fisher Grade 3 SAH were enrolled in this study. Haptoglobin type was determined by polyacrylamide gel electrophoresis. The primary measure for vasospasm was increased blood flow velocities as detected by daily transcranial Doppler ultrasonography (TCD). The authors found that only 2 of 9 patients with haptoglobin α1–α1 (22%) had development of "possible" vasospasm as measured by TCD, whereas 20 of 23 patients with the haptoglobin α2 subunit (either the α1–α2 or α2–α2 haptoglobin types) had development of "possible" vasospasm (87%). The secondary measure for vasospasm was cerebral angiography performed between 3 and 14 days after SAH. Similar results (17% vs 56%) were seen between these groups in those patients who underwent cerebral angiography, although its inconsistent use limited the strength of the statistical comparison. *Conclusions:* Haptoglobins containing the α2 subunit seem to be associated with a higher rate of vasospasm than is haptoglobin α1–α1.

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In the days that follow aneurysmal subarachnoid hemorrhage (SAH), hemoglobin is released from decaying red blood cells that are trapped in the subarachnoid clot. It is this extracorpuscular hemoglobin that is thought to trigger a condition of delayed cerebral artery constriction called vasospasm.[1] In this situation, hemoglobin likely affects the artery indirectly via free radicals, prostaglandins, nitric oxide absorption, and a local inflammatory reaction in the subarachnoid space.[2-5]

Early cerebral angiography studies performed by Fisher et al. concluded that the development of vasospasm in patients with SAH was predicted by the size of the subarachnoid blood clot.[6,7] In their seminal 1980 publication, hemorrhages that were associated with vasospasm were described as "localized clots and/or vertical layers of blood 1 mm or greater in thickness"[6] (i.e., Fisher Grade 3 SAH). However, similar studies that involved larger patient populations found a considerably weaker relationship between subarachnoid clot size and the likelihood of development of vasospasm.[8,9] Although all these studies agree that the amount of blood in the subarachnoid space is a major risk factor for development of vasospasm, sufficient room exists for other factors to be influential therein. The only factors other than subarachnoid clot size that have been consistently shown to increase vasospasm risk are patient age (young > old) and a history of cigarette smoking,[10-12] although there is some skepticism even about this data among vasospasm experts.[13]

The type of haptoglobin that is expressed by a

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patient with SAH may also be a risk factor for vasospasm. Haptoglobin is an abundant serum protein whose chief action is to bind extracorpuscular hemoglobin. The binding of haptoglobin to hemoglobin interferes with the ability of hemoglobin to induce free radical production and alter prostaglandin levels.[14-16] Haptoglobin also facilitates the uptake and degradation of the hemoglobin by reticuloendothelial cells.[17,18] Because of its antihemoglobin activity and its presence in the subarachnoid space after SAH,[19] haptoglobin likely neutralizes extracorpuscular hemoglobin as the hemoglobin is released from the decaying red blood cells. Administration of haptoglobin into the subarachnoid space of patients with SAH has been tested as a treatment for vasospasm in uncontrolled studies where it was reported to have some therapeutic benefit.[20-22]

Considering that a person can expresses only one of three types of haptoglobin (α1–α1, α1–α2, or α2–α2) depending on the α subunit genes he or she inherits, we evaluated the possibility that haptoglobin type might affect the development of vasospasm after SAH.

Methods. *Subjects.* This study was approved by the Institutional Review Boards of the Northwestern Memorial Hospital and the Detroit Medical Center, where consecutive patients were enrolled in 2003–04 (Northwestern) and 2004–05 (the Detroit Medical Center). All patients enrolled in the study provided informed consent. Patients were eligible for enrollment if they were older than 18 years and if they had 1) a known date of onset of the SAH, 2) aneurysmal rupture as the suspected cause for the SAH, and 3) SAH of Fisher Grade 3 severity (i.e., greater than 1-mm-thick blood layers or clots[6]) as detected by CT scan within 48 hours of admission to the hospital. Extension of the hemorrhage into the brain parenchyma or ventricular system was acceptable as long as the other CT criteria were met. Patients were included in this study irrespective of sex or race. Patients who had diseases that can be associated with abnormal haptoglobin expression or that affect the likelihood of development of vasospasm (i.e., hemolytic conditions, liver disease or liver transplantation, autoimmune diseases, leukemias, endometriosis) were planned exclusions from this study, but no such exclusions were necessary.

Of the 44 patients who were enrolled in the study, 12 were removed after enrollment, leaving 32 patients for the final analysis. These patients were removed from the study because they had received blood-product transfusions before providing the blood sample for haptoglobin analysis (n = 5), they were ahaptoglobinemic (n = 1), they were actively using cocaine or amphetamines (n = 3), or they could not provide sufficient (n = 2) or reliable (n = 1) transcranial Doppler ultrasonography (TCD) data. Because anemia or abnormal blood gas content can make the detection of vasospasm by TCD unreliable, we removed patients from the study if they exhibited a hemoglobin concentration less than 8 g/dL, a P_{O_2} less than 80 mm Hg, or a P_{CO_2} greater than 45 or less than 30 mm Hg at any time during the period of TCD evaluation. This occurred in only a single patient who had severe anemia, who is accounted for under "unreliable" TCD data as described above.

Enrollment in the study did not influence the patients' treatment course. Haptoglobin typing was performed only after the completion of patient enrollment at each of the participating institutions.

Measurements and data collection. In this study, we considered only the development of arterial constriction as vasospasm, i.e., we did not measure the development of delayed neurologic injury. We chose TCD as our primary measure and cerebral angiography as our secondary measure of vasospasm. Bilateral TCD measurements of the flow velocities in nine cerebral arteries were performed daily between the 2nd and 14th days after hemorrhage. The following cerebral arteries were assessed: from a temporal window, the middle cerebral, anterior cerebral, and posterior cerebral arteries; and from a foramen magnum window, the vertebral and basilar arteries. Technical limitations prevented a reliable daily measurement of one of the posterior cerebral arteries in six patients; however, it seems unlikely this was due to the development of severe vasospasm because 1) the inability to locate the artery occurred sporadically, and usually the artery was identified on the next day's examination; 2) there was no increase in flow velocities before or after the inability to detect the artery, suggesting the development of vasospasm; and 3) there was no evidence of vasospasm in other cerebral arteries in these patients. Anterior cerebral arteries were consistently measured in all patients.

Flow velocities in the extracranial carotid artery were measured daily, but we did not use the Lindegaard ratio as a criterion for vasospasm. All measures reported in this study represent mean flow velocities.

Artery-specific thresholds for detecting vasospasm were used according to established criteria.[10] Based on their diagnostic accuracy in comparison with cerebral angiography, threshold flow velocities were used to indicate "possible" vasospasm (table 1). Flow velocities above the threshold for "possible" vasospasm are a common clinical indication to perform cerebral angiography to confirm the diagnosis of vasospasm. We defined a positive TCD test result for vasospasm using the "possible" thresholds as 2 consecutive days of increased flow velocities. It should be noted that flow velocities become decreased with very severe vasospasm and may in fact become unmeasurable; however, we did not observe any incidence in which a previously detected flow signal from a cerebral artery became consistently unobtainable during subsequent TCD examinations.

As a secondary measure of vasospasm, we evaluated any cerebral angiograms taken between the 3rd and 14th days after SAH for a reduction in artery caliber of at least 50% (measured as the fraction of the diameter at the site of maximal constriction divided by the diameter at the point immediately upstream from the constriction at which the artery walls were parallel). Evaluation of the cerebral angiograms was performed without knowledge of the haptoglobin type.

Not every patient received a cerebral angiogram between posthemorrhage days 3 through 14. In these patients, we evaluated the available TCD data for convincing evidence of vasospasm that would forgo the necessity of cerebral angiography. Artery-specific flow velocity thresholds greater than those for "possible" vasospasm have been found to indicate "presumed definite" vasospasm[10] (see table 1), because the additional use of cerebral angiography in SAH patients with such greatly increased TCD flow velocities would be unlikely to improve the diagnostic accuracy. The evaluation for "presumed definite" TCD vasospasm was performed only for those patients who did not receive cerebral angiograms. A positive TCD test using the "presumed definite" thresholds required only 1 day of increased flow velocities.

Determination of haptoglobin type. Blood was drawn from the patients immediately after their enrollment into the study. After centrifugation, the plasma fraction was stored at −80 °C until it was shipped to the Technion Institute of Technology (Haifa, Israel) for haptoglobin typing. Haptoglobin typing was performed without any knowledge of the patient's clinical course. Haptoglobin typing was performed on 10 μL of plasma by means of polyacrylamide gel electrophoresis as described elsewhere.[23] A

Table 1 *Transcranial Doppler mean flow velocity criteria for "possible" and "presumed definite" vasospasm, according to Sloan et al.[10]*

	"Possible" vasospasm	"Presumed definite" vasospasm
Middle cerebral artery	120	200
Anterior cerebral artery	100	150
Posterior cerebral artery	80	160
Vertebral artery	60	105
Basilar artery	75	140

Values are in cm/second.

Table 2 *Characteristics of patients grouped according to haptoglobin type*

	Haptoglobin α1–α1 (n = 9)	Haptoglobin α1–α2 (n = 12)	Haptoglobin α2–α2 (n = 11)	Haptoglobin α1–α2 or α2–α2 (n = 23)
Age, y (no. of patients aged >55 y)	51.6 ± 6.7 (4)	50.2 ± 1.7 (3)	52.9 ± 3.1 (4)	51.5 ± 1.7 (7)
Sex				
M	4	4	3	7
F	5	8	8	16
Race				
White	5	7	9	16
Black	3	2	1	3
Asian	1	1	1	2
Hispanic		2		2
Premorbid medical conditions				
Hypertension	3	6	5	11
Ischemic stroke	0	0	1	1
Hemorrhagic stroke	1	0	0	0
Coronary artery disease	2	0	0	0
Diabetes	1	1	1	2
Dyslipidemia	1	2	1	3
Premorbid medication use				
Antihypertensives	2	3	3	6
Antiplatelet agents	2	1	3	4
Anticoagulants	0	0	0	0
Hypoglycemics	1	0	1	1
Lipid lowering	0	1	1	2
Drug use				
Smoking	3	3	7	10
Alcohol	2	1	1	2
Drugs of abuse*	1	0	1	0

* Both were marijuana.

signature banding pattern was obtained for each of the three possible haptoglobin types: haptoglobin α1–α1 (patients homozygous for the haptoglobin α1 allele), haptoglobin α2–α2 (patients homozygous for the haptoglobin α2 allele), or haptoglobin α1–α2 (heterozygous patients). This technique has 100% concordance with the haptoglobin genotype as determined by PCR.[23] An unambiguous haptoglobin type was obtained in all but one patient sample, and that sample had haptoglobin levels below the detection limit of the assay (i.e., ahaptoglobinemia); the patient from whom this sample was taken was subsequently removed from the study as previously noted.

Data analysis. We evaluated our data using the Fisher exact test because we did not accrue a large enough patient population for regression analysis. This plan for statistical analysis was developed in accordance with the recommendations of biostatisticians from the Wayne State University department of statistics. TCD and cerebral angiography measures of vasospasm were evaluated separately and in various combinations, reflecting the variability of use of these diagnostic tests in clinical practice. The haptoglobin α1–α1 type was used as the referent group in all analyses; statistical comparison was then made against the combined group of patients who had α1–α2 or α2–α2 haptoglobin types. A two-sided p value less than 0.05 was considered significant. All data are presented as mean ± SEM.

Results. Our group of 32 patients yielded n = 9 with haptoglobin α1–α1, n = 12 with haptoglobin α1–α2, and n = 11 with haptoglobin α2–α2. The characteristics of the patients grouped according to haptoglobin type are noted in table 2. No obvious difference between the groups was noted in terms of age, the presence of comorbid medical conditions, the prehospitalization use of major classes of medications, or drug use. There did seem to be an imbalance in the distribution of race between the groups, with whites being overrepresented in haptoglobin α1–α2 and α2–α2 groups; this was more likely due to the small number of patients in our study than to any association between race and haptoglobin type.[24,25] Overall, there was a noticeable predominance of women (21 of 32 patients) that was reflected in all three groups (p = 0.08 vs an expected even split between the sexes, although the power of this comparison is only 0.52). We have no explanation for the predominance of women in our patient population, and a similar imbalance was apparent in those patients who were removed from the study (3 men vs 9 women). As shown in table 3, the features of the SAHs and the patients' initial clinical conditions were comparable between the groups. The number of patients with intraparenchymal or intraventricular extension of the subarachnoid clot and

Table 3 *Subarachnoid hemorrhage and aneurysm features in patients grouped according to haptoglobin type*

	Haptoglobin α1–α1 (n = 9)	Haptoglobin α1–α2 (n = 12)	Haptoglobin α2–α2 (n = 11)	Haptoglobin α1–α2 or α2–α2 (n = 23)
No. with intraparenchymal or intraventricular hemorrhage	4	4	4	8
Admit Hunt and Hess score	2.7 ± 0.5	3.1 ± 0.2	2.6 ± 0.3	2.9 ± 0.2
No. of aneurysms (range)	1.3 ± 0.2 (1–2)	1.4 ± 0.4 (0–5)	1.5 ± 0.3 (1–4)	1.4 ± 0.2 (0–5)
Ruptured aneurysm site				
Middle cerebral	1	2	2	4
Anterior cerebral		1		1
Anterior communicating		2	4	6
Posterior communicating	3	4	2	6
Basilar	3	1	1	2
Ophthalmic or terminal carotid	2		2	2
None identified		2		2

the baseline Hunt and Hess scores seemed reasonably equivalent in each of the three groups, and there did not seem to be a difference in the number of aneurysms per patient identified by angiography. However, there seemed to be a relative lack of ruptured anterior communicating artery aneurysms in the group of patients with haptoglobin α1–α1.

Treatments used in the management of the aneurysm and SAH, and the application of preventative therapies against vasospasm were also evaluated (table 4). Two patients in the haptoglobin α1–α2 group did not have any surgical procedure to control the site of hemorrhage because no aneurysm could be identified on their initial angiograms; inability to identify the ruptured aneurysm did not, however, prevent the application of hypertensive–hypervolemic–hemodilution ("triple H") therapy in one of those patients who exhibited increased TCD flow velocities that were consistent with "presumed definite" vasospasm. Triple H therapy was used less frequently in patients with haptoglobin α1-α1, likely reflecting the lower incidence of vasospasm in this group. Aside from this, no obvious difference was observed between the groups in terms of any of the other common treatments used in the treatment of patients with SAH or vasospasm. As shown in table 5, there seemed to be more hospital complications in patients who had haptoglobin α1–α2 or α2–α2 (43 total complications for these 23 patients vs 14 total complications for the 9 patients who had haptoglobin α1–α1), although no category stood out in particular to account for this observation.

The development of vasospasm did seem to correlate with the haptoglobin type of the patient (table 6). Using only the TCD criteria for "possible" vasospasm as defined in the Methods section, 20 of 23 patients (87%) who had either haptoglobin α1–α2 or α2–α2 had development of

Table 4 *Treatments administered to patients grouped according to haptoglobin type*

	Haptoglobin α1–α1 (n = 9)	Haptoglobin α1–α2 (n = 12)	Haptoglobin α2–α2 (n = 11)	Haptoglobin α1–α2 or α2–α2 (n = 23)
Time to intervention from diagnosis, d	1.6 ± 0.2	2.3 ± 0.5	1.1 ± 0.1	1.7 ± 0.3
Type of surgical intervention				
No. coiled	4	4	5	9
No. clipped	5	6	6	12
No. untreated	0	2	0	2
Other treatments				
Antiepileptics	6	12	8	20
Calcium-channel blockers	9	12	11	23
Triple H therapy	2	8	8	16
Glucocorticoids	6	8	9	17
Antibiotics	8	10	8	18
Antihypertensives	7	7	5	12
Anticoagulation	2	1	3	4
Antiplatelet agents	1	4	0	4
Pressor agents	2	3	6	9

Table 5 *Hospital complications in patients grouped according to haptoglobin type*

	Haptoglobin α1–α1 (n = 9)	Haptoglobin α1–α2 (n = 12)	Haptoglobin α2–α2 (n = 11)	Haptoglobin α1–α2 or α2–α2 (n = 23)
Infection				
Systemic	3	4	7	11
Intracranial	0	2	1	3
Deep venous thrombosis	2	2	1	3
Hyponatremia	2	1	2	3
Seizure	0	4	1	5
Hydrocephalus	6	10	8	19

"possible" vasospasm, in comparison with 2 of 9 patients (22%) who had haptoglobin α1–α1. Comparing the incidence of vasospasm in these two groups with a Fisher exact test found them to be different ($p = 0.001$). It did not seem that increased TCD flow velocities were attributable to the use of triple H therapy because this treatment was initiated after the onset of the increased flow velocities in every patient in which it was used.

Results from cerebral angiograms were also collected, although angiograms were not performed for the purpose of vasospasm diagnosis in every patient enrolled in this study. Angiograms were available from 6 patients with haptoglobin α1–α1, 11 patients with haptoglobin α1–α2, and 7 patients with haptoglobin α2–α2. Evaluation of the angiogram results also suggests an association between haptoglobin containing the α2 subunit and higher rates of vasospasm. Of the 18 patients with haptoglobin α1–α2 or α2–α2 who had angiograms, n = 10 exhibited vasospasm (56%), whereas only 1 of the 6 patients who had angiograms from the haptoglobin α1–α1 group exhibited vasospasm (17%). However, the comparison of these two incidences with a Fisher exact test showed them to be indistinguishable ($p = 0.16$). Combining both "possible" TCD and angiography measures also did not seem to affect the association between haptoglobin type and vasospasm (see table 6). As shown at the bottom of table 6, using either a positive angiogram or the "presumed definite" TCD measure as proof of vasospasm again demonstrated a statistical association between vasospasm and haptoglobin type (vasospasm rate in patients with haptoglobin α1–α1 = 11%; vasospasm rate in patients with haptoglobin α1–α2 or α2–α2 = 65%; $p = 0.02$).

Discussion. In all animals, haptoglobin is composed of two subunits—α and β—that form the four-subunit structure $(\alpha\beta)_2$. In humans, the haptoglobin α gene locus is dimorphic with two alleles denoted α1 and α2.[26] Because each person has an α subunit gene on each of two chromosomes that are both continuously transcribed to make protein subunits, three major types of haptoglobin are found in the general population: these are haptoglobin α1–α1, α1–α2, and α2–α2 (the β subunit is invariable and so is not written here). These three types of haptoglobin neutralize hemoglobin to different degrees. In general, haptoglobin containing the α2 gene product does not inhibit hemoglobin's effects on free radical production and prostaglandin levels as well as does haptoglobin α1–α1.[14-16,18,26,27] Furthermore, haptoglobin α2–α2 may worsen the local inflammatory response in the subarachnoid space after SAH, as is suggested by the recent observations that the complex of hemoglobin with haptoglobin α2–α2 is 1) more potent than that with haptoglobin α1–α1 at activating the monocyte/macrophage CD163 receptor[18] and 2) less able to stimulate production of anti-inflammatory cytokines from cultured monocytes (A. Levy, PhD, unpublished data, 2005). Finally, haptoglobin α1–α2 and α2–α2 likely have worse tissue permeability than haptoglobin α1–α1 because the α2 subunit promotes the aggregation of those types of haptoglobin into large polymers.[28] The tissue permeability of haptoglobin may be important in the context of vasospasm because extracorpuscular hemoglobin is known to penetrate deep into the walls of the cerebral arteries after experimental SAH.[29] Therefore, we hypothesized that haptoglobin containing the α2 subunit would be associated with higher rates of vasospasm than would haptoglobin α1–α1.

We demonstrate here that patients with SAH who

Table 6 *Development of vasospasm in patients grouped according to haptoglobin type*

	Haptoglobin α1–α1	Haptoglobin α1–α2	Haptoglobin α2–α2	Haptoglobin α1–α2 or α2–α2
TCD "possible"	2 of 9	11 of 12	9 of 11	20 of 23
Angiography	1 of 6	6 of 11	4 of 7	10 of 18
TCD "possible" *or* angiography	2 of 9	11 of 12	9 of 11	20 of 23
TCD "possible" *and* angiography	1 of 6	6 of 11	4 of 7	10 of 18
TCD "presumed definite" or angiography	1 of 9	7 of 12	8 of 11	15 of 23

express haptoglobin α1–α2 or α2–α2 have a higher incidence of vasospasm than do patients who express haptoglobin α1–α1. This association seemed to be true using TCD or cerebral angiography measures of vasospasm, although the evaluation of cerebral angiography data was weakened by the inconsistent use of this diagnostic technique in our patient population. We suspect that haptoglobin containing the α2 subunit is associated with an increased risk of vasospasm because it does not effectively neutralize the hemoglobin that is released from the subarachnoid clot. In this regard, haptoglobin may interfere with hemoglobin's ability to affect prostaglandin or free radical production, absorb nitric oxide, or induce an inflammatory response. Alternatively, haptoglobin type may affect the cerebral arteries in a way that predisposes them to vasospasm after SAH without influencing the vasoconstrictive factors that directly cause vasospasm. In the context of atherosclerosis—which is also a disease of cerebral arteries that involves free radicals, prostaglandins, nitric oxide, and inflammation[13,30-32] but that develops chronically—haptoglobin α1–α2 and α2–α2 have been associated with an increased rate of plaque progression.[33] Lower levels of such chronic injury to the cerebral arteries in a patient with SAH may increase the arteries' sensitivity to the subarachnoid blood, thereby increasing the patient's risk for vasospasm. As an example of this kind of phenomenon, atherosclerotic cerebral arteries are known to become increasingly sensitive to the vasoconstrictive effects of the blood-borne protein thrombin as the severity of the atherosclerosis progresses.[34]

We chose to use TCD as our primary measure of vasospasm because of its widely accepted role as a screening test for vasospasm.[35] The blood flow velocities for "possible" vasospasm that we used cannot reliably establish the diagnosis but instead are used as an indication for angiography that will then confirm the suspicion of vasospasm. Mean blood flow velocities greater than 120 cm/second in the middle cerebral artery, for example, have a specificity of 85% to 100% for ruling out vasospasm but a sensitivity of only 39% to 86% in comparison with cerebral angiography (reviewed in Sloan et al.[10]). Flow velocity thresholds above those for "possible" vasospasm are more specific, however, and at very high flow velocities (e.g., >200 cm/second for the middle cerebral artery), the correlation between TCD and cerebral angiography becomes sufficient so that vasospasm can be "presumed definite" with just the TCD measure alone.

We were not able to demonstrate a significant association between the measure of vasospasm by cerebral angiography and haptoglobin type, but this was likely due to the unbalanced use of this diagnostic test in our patient population. Of our 32 patients, only 24 received cerebral angiograms within the time frame laid out for vasospasm (i.e., 3 to 14 days after hemorrhage). Cerebral angiograms were not performed in every patient for one of two reasons: 1) there was no clinical deterioration or TCD evidence of vasospasm to justify the risk of angiography, and 2) the TCD studies were sufficiently indicative of vasospasm to forgo angiographic confirmation. TCD measurements high enough to be considered "presumed definite" vasospasm according to the criteria of Sloan et al.[10] were, in fact, observed in at least one cerebral artery from all five patients with haptoglobin α1–α2 or α2–α2 who did not receive angiograms (figure). In comparison, the three patients with haptoglobin α1–α1 who did not receive angiograms always had blood flow velocities safely in the normal range, not even close to indicating "possible" vasospasm. Identifying vasospasm, then, according to either a positive angiogram or "presumed definite" TCD flow velocity is essentially what occurs in clinical practice, and doing so with our data again demonstrated a statistical association between vasospasm and haptoglobin type.

Our results suggest that haptoglobin containing

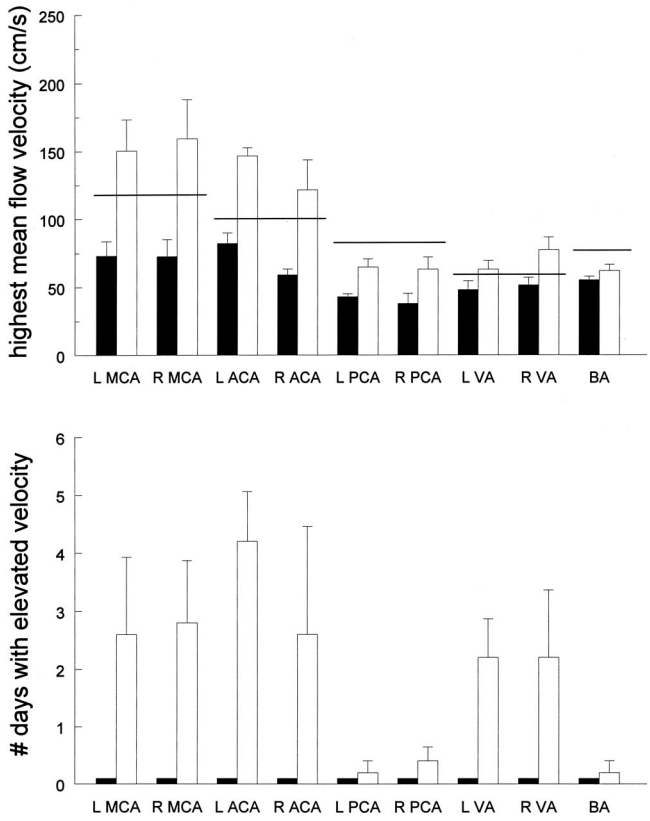

Figure. Transcranial Doppler (TCD) measures in patients who were not evaluated with cerebral angiography. (A) The highest mean flow velocities observed in patients with haptoglobin α1–α1 (filled bars) and in patients with haptoglobin α1–α2 or α2–α2 (open bars) who were not evaluated with cerebral angiography. Horizontal lines represent the artery-specific thresholds for "possible" vasospasm. (B) The total duration of increased flow velocities in patients with haptoglobin α1–α1 (filled bars) and in patients with haptoglobin α1–α2 or α2–α2 (open bars) who were not evaluated with cerebral angiography. In no instance was a TCD measurement above the threshold for vasospasm in the group of patients with haptoglobin α1–α1.

the α2 subunit should be considered as a biomarker for SAH patients who are at high risk for development of vasospasm. Detecting patients at high risk for vasospasm shortly after SAH could improve the clinical treatment of these patients because vasospasm develops in an unpredictable manner that is often difficult to differentiate from other forms of delayed neurologic injury. Furthermore, many of the available treatments for vasospasm involve serious side effects and complications, and most treatments for vasospasm are maximally effective when administered prophylactically. Identifying SAH patients who are at high risk for development of vasospasm would allow for the selective administration of aggressive treatments to those patients who clearly would benefit from them. Although haptoglobin typing is not widely available, the haptoglobin type of a patient with SAH could easily and rapidly be determined by most medical laboratories with a minimal investment in equipment and training.

Despite our positive results, we recognize the limitations in the sample size of our study. Furthermore, the results we presented here do not consider the development of neurologic injury from vasospasm ("symptomatic vasospasm"), which does not always correlate with angiographic measures of vasospasm. Evaluating the relationship of haptoglobin type to symptomatic vasospasm would be important for understanding the relationship between the two forms of vasospasm, and it would provide greater meaning to any prognostic value for haptoglobin type. To take into account these concerns, we are currently in the process of developing a larger study that will evaluate the relation between haptoglobin type and symptomatic and angiographic measures of vasospasm, and we welcome collaboration in this effort.

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