**Clot volume and rate as independent predictors of vasospasm after aneurysmal subarachnoid hemorrhage**

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**Object.** This study was conducted for two purposes. The first was to determine whether a combination of measurements of subarachnoid clot volume, clearance rate, and density could improve prediction of which patients experience vasospasm. The second was to determine if each of these three measures could be used independently to predict vasospasm.

**Methods.** Digital files of the cranial computerized tomography (CT) scans obtained in 75 consecutive patients admitted within 24 hours of subarachnoid hemorrhage (SAH) were analyzed in a blinded fashion by an observer who used quantitative imaging software to measure the volume of SAH and its density. Clot clearance rates were measured by quantifying SAH volume on subsequent CT scans. Vasospasm was defined as new onset of focal neurological deficit or altered consciousness 5 to 12 days after SAH in the absence of other causes of deterioration, diagnosed with the aid of or exclusively by confirmatory transcranial Doppler ultrasonography and/or cerebral angiography.

Univariate analysis showed that vasospasm was significantly associated with the SAH grade as classified on the Fisher scale, the initial clot volume, initial clot density, and percentage of clot cleared per day (p < 0.05). In multivariate analysis, initial clot volume and percentage of clot cleared per day were significant predictors of vasospasm (p < 0.05), whereas Fisher grade and initial clot density were not.

**Conclusions.** Quantitative analysis of subarachnoid clot shows that vasospasm is best predicted by initial subarachnoid clot volume and the percentage of clot cleared per day.

**Key Words • aneurysm • Fisher grade • subarachnoid hemorrhage • vasospasm • volumetric measurement**

The most frequent modifiable factor contributing to poor outcome after aneurysmal SAH is cerebral vasospasm. Methods for predicting which patients will experience this complication, however, remain imprecise. Factors consistently associated with cerebral vasospasm in multivariate analysis include thicker clot on the admission cranial CT scan, worse neurological grade, a history of hypertension, and IVH. The most powerful predictor by far, however, is the thickness of subarachnoid clot on the admission CT scan, which is usually graded according to the Fisher scale. This scale has several limitations, however. The measurements used are increments displayed on printed CT scans that have no relationship to the real clot thickness. It is not clear how to classify patients with thick SAH and intracerebral or intraventricular blood compared with those who have ICH or IVH alone. In the original description by Fisher, et al., Grade 4 included patients with intracerebral or intraventricular blood and only diffuse, thin SAH. Nevertheless, confusion has arisen because some patients have thick SAH and ICH or IVH, and grading of these cases is difficult. Grade 4 could be considered pure ICH, pure IVH, or one of these plus some measurement of subarachnoid clot. Therefore, a quantitative method of measuring subarachnoid clot might improve our ability to predict vasospasm.

A second issue of interest from a clinical and scientific perspective is that other features of the clot may be important contributors to the development of vasospasm. These include clot density and the rate of clot clearance. Although several neurosurgeons have investigated the role of these factors in relation to vasospasm, there are no studies in which the relationships between vasospasm and initial clot volume, clearance, and density have been examined simultaneously and quantitatively. Because larger volumes of clot might clear more slowly, a multivariate analysis would be needed to determine whether clot volume and clearance are independent factors associated with vasospasm.

**Clinical Material and Methods**

**Patient Characteristics and Clinical Variables** After approval of the protocol by the Institutional Review Board, consecutive patients with SAH admitted to the University of Chicago Hospitals between January 2002 and May 2003 were screened for inclusion in this study. The
Intraventricular hemorrhage was coded “yes” for 3, completely filled. This scale led to scores ranging from 0, no blood; 1, layers of blood in the dependent part of the ventricle; 2, moderately filled; and 3, completely filled. The IVH was measured on a semiquantitative scale with clots thicker than this, and Grade 4 to those with only blood visible in any of these unassigned areas, it was quantified using the technique described earlier. Nonblood hyperdense areas such as bone were not included only subarachnoid blood. Subarachnoid blood conferred a grade for each CT slice that included the basal cisterns. All slice volumes were summed noninfused patients. Each CT slice was calibrated for millimeters from the University of Chicago (admission scans and 52 postadmission scans) were obtained in a lossless raw data format from the DICOM storage system (Kodak 9410 picture archiving and communication system; Eastman Kodak, Rochester, NY). All scans that were available digitally were analyzed in their original format, scaled to Level 15/Window 100 (−15 to 85 HU) in a Floating Point image DICOM browser (version 0.05). The DICOM header was stripped after exporting the patient number, study date, millimeters per pixel, and slice thickness. Slice thickness was calculated from the distance between scans and was almost always 7 mm on CT scans obtained at the University of Chicago. The CT scans obtained at other institutions (admission and no postadmission scans) and those unavailable in the DICOM format (31 admission and 23 postadmission scans) were digitized using a laser scanner (version 4.7.0, Pierre E. Gougelet, Reims, France). Density was recorded as the mean of all selected pixels. The process was repeated for each CT slice that included the basal cisterns. All slice volumes were summed for each study. The output text file resulting from this process was imported into Microsoft Excel (version XP; Microsoft Corp., Ashville, NC) to calibrate the density function. A single examiner found the best position possible for the blood clot using the IPTK measuring function. If the selection did not match the estimated values for laser-scanned images; the difference in blood density between scans was minimal (<15 HU in general) and irregularities in printing and scanning were routinely encountered. These irregularities had no impact on volume measurements because each slice was standardized to its adjacent distance marker.

After all CT studies were digitized, each slice contain-
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...level of consciousness 2 days after SAH; degrees of neurological impairment, initial hemorrhage, identifiable cause of vasospasm, electrolyte disturbance, duration of vasospasm studies. Neuroangiography was defined as a 2-point or a 2-point reference study of the National Institutes of Health and monitored for more hours. The duration of the follow-up was not demonstrated in the aforementioned studies. Neuroangiography demonstrated on a major cerebral artery was done 23 postadmission days. Vasospasm was defined as a decrease in subarachnoid hemorrhage area and uniformly found to be 1:1. The subarachnoid clot then was selected as described earlier. Volume was calculated by multiplying the number of selected pixels by the area per pixel (as given by the calibrated IPTK measure function). If the selection did not include only subarachnoid blood, the range of the wand tool was changed and the selection was repeated until the examiner found the best position possible for the blood clot in that slice. The output file resulting from this process was imported into Microsoft Excel (version XP; Microsoft Corp., Redmond, WA), in which program the total number of selected pixels was multiplied by the millimeters per pixel number and density in the selected area were quantified using the IPTK. If the selection was judged to be accurate—it included the basal cisterns. All slice volumes were summed and all densities were averaged. Density was weighted by the number of pixels each slice represented, resulting in a single volume and density for each study.

Stored CT scans were analyzed in similar fashion with a few modifications. Without altering leveling, the scans were imported into Photoshop by using the program XiView (version 1.37; Pierre E. Gougelet, Reims, France). Density values were not standardized or included in the study for these patients. Each CT slice was calibrated for millimeters per pixel within Photoshop by using the distance guide adjacent to the image (usually an 8- to 12-cm bar) and the IPTK to calibrate the distance function. Most images included a horizontal and a vertical guide. As a check of the CT data, the ratio of width to height was calculated on these images and uniformly found to be 1:1. The subarachnoid clot then was selected as described earlier. Volume was calculated by multiplying the number of selected pixels by the area per pixel (as given by the calibrated IPTK measure function) and by the slice thickness. Slice thickness was recorded by the examiner after calculating the distance between slices for each study.

One challenge to the method of blood selection defined earlier was the presence of clip artifacts on almost all of the 67 CT scans obtained subsequent to the admission studies. Most scans exhibited clip artifact on one slice. If there was no subarachnoid blood clot on the slice above or below the slice containing the clip artifact and there was no substantial clot visible outside the area of artifact on the slice that contained the clip, the volume was considered to have 0 clot volume. If there was blood visible in any of these unaffected areas, it was quantified using the technique described earlier. All clip artifacts were removed manually. No blood was assumed to be present in the area of clip artifact if the following conditions were met: 1) the region was completely inaccessible because the clip was relatively small and by definition could not itself contain blood; 2) the area where the clip was inserted was necessarily one that was surgically accessible and therefore most commonly had a marked reduction in subarachnoid clot after surgery; and 3) the hyperdensity caused by the clip artifact was likely to cause a slight increase in the measurement of blood around it, despite the best efforts of the examiner to minimize such increases.

Statistical Analysis

Initial scans were recorded as Day 0 and the number of days from the initial scan was calculated for all subsequent ones analyzed (mean 3.8 ± 2.8 days, range 1–16 days, 56 patients with one, 18 with three, and one with four postadmission scans analyzed). Each Day 0 scan provided the initial clot volume and density. The final study analyzed was used to measure the final volume and total time in days. A variety of factors relating to clot clearance were examined to account for the possibility that clearance rates were nonlinear or were related in some way to the initial clot volume. Log transforms of some variables were studied to see whether the relationship between vasospasm and clot volume might resemble a pharmacological dose–response curve in which this volume is best expressed logarithmically. Clearance volume was calculated as the initial minus final volume and clearance amount per day was clearance volume divided by time between scans in days. Similarly, the percentage of clot cleared was calculated by dividing the cleared amount by the initial amount and the percentage cleared per day was calculated by dividing the percentage cleared by time between scans. All percentages were limited to 0 to 100 because small changes in patients with very little blood (for example, < 2 ml) on the initial scan occasionally resulted in highly negative values for percentage of clot cleared, as noted by Brouwers, et al. Comparisons of each variable between patients with and without vasospasm was made by using the Chi-square and Student t-tests.

The primary question asked at the outset of this study was: what factors are associated with development of vasospasm? Vasospasm was treated as the dependent variable and as dichotomous (present or absent) throughout the study and the variables identified earlier that were potentially associated with vasospasm were analyzed using logistic regression models (version 8.2; SAS, Cary, NC). Univariate analysis of each variable was performed before beginning the selection process. Dummy variables based on quartiles were used to assess the assumption of linearity for continuous variables such as patient age, initial clot volume, and clot clearance rates and percentages. Univariate logistic regression modeling was then used to obtain the estimated coefficients, estimated standard error, likelihood ratio test for significance of the coefficient, and the univariate Wald statistic. Statistically significant variables (p < 0.1 both to enter and to stay in analysis) in the simple logistic regressions were then entered into multivariate logistic models by using stepwise selection, forward selection, and backward elimination procedures. The significance of each variable included in the model was verified using the Wald statistic. The
Overall fit was then assessed between several different models by using the likelihood ratio test. Unadjusted and adjusted odds ratios and 95% confidence intervals for occurrence of vasospasm were derived from the logistic regression models. Tests for interaction were conducted between each variable entered into the multivariate models and the study indicator. Finally, a composite variable of initial volume and percentage of clot cleared per day was determined by examining the distribution of the study population and by using a scatterplot diagram. Data are given as mean ± standard deviation.

Results

Clinical grade, aneurysm location, Fisher grade, and treatment factors are shown in Table 1. Overall, vasospasm developed in 26 patients (35%). The mean initial clot volume was 10.4 ± 8.7 ml (range 2.8–38 ml) and the mean volume of clot cleared per day was 2.8 ± 3.5 ml (range 0–21 ml). The mean percentage of clot cleared per day was 35 ± 21% (range 0–92%). Comparison of these values between patients with and without vasospasm showed no significant difference in mean values between groups. Tests of linearity showed that for age, the rate of vasospasm was highest for patients 40 to 59 years of age, suggesting an inverted U-shaped relationship between age and vasospasm. Therefore, in the logistic regression analysis, age was entered into 3 categories (<1 ml, 1–10 ml, >10 ml). The transfor-
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Discussion

Few investigators have used image analysis to quantify subarachnoid clot volumes. Friedman, et al.,14 reported a method of quantification of SAH and noted that volumes more than 20 ml were highly likely to be associated with delayed ischemic neurological deficits. The new findings in this study are the identification, using multivariate analysis, of the independent predictive power of purely quantitative measurements of subarachnoid clot volume, density, and clearance rate for vasospasm after SAH.

Experimental studies of vasospasm are widely believed to have shown that the volume of blood injected or placed into the subarachnoid space of animals as well as the time that it remains there are important factors that influence the severity and duration of vasospasm. This assumption, however, has seldom been tested systematically. Furthermore, there are clinical reports of a lack of correlation between subarachnoid blood location and clearance rate and vasospasm. Thus, an important scientific tenet that remained to be proven clinically and that was proven in this study is whether vasospasm is independently associated with the volume, duration of presence, and density of subarachnoid blood clot.

Extent and Volume of SAH

Takemae and colleagues38 and Fisher, et al.,12 recognized the principle of the dependence of vasospasm on initial clot volume and generated the Fisher scale. A relationship between the amount and location of subarachnoid clot and vasospasm as assessed using various clinical, angiographic, and TCD criteria has been confirmed in almost all subsequent investigations.2,7,8,14,15,17,19,31,34,36 In some studies, however, investigators have not been able to demonstrate such a relationship or have noted only a relatively weak correlation. Although there are several possible reasons for this, the results of our study indicate that other factors, such as clot clearance rate and density, need to be taken into account.

Broderick and colleagues3 used analysis of digitized CT scans to measure the volume of subarachnoid blood in patients with aneurysmal SAH. The mean volume of SAH was 21 ± 22 ml and served as a powerful predictor of mortality rates in multivariate analysis, whereas the Fisher scale

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fisher grade</td>
<td>2.22</td>
<td>9.24</td>
<td>1.25-68.3</td>
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<tr>
<td>initial clot vol</td>
<td>0.08</td>
<td>1.08</td>
<td>1.02-1.15</td>
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<td>log initial clot vol</td>
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<td>composite variable†</td>
<td>1.28</td>
<td>3.60</td>
<td>1.69-7.65</td>
</tr>
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</table>

† Consists of log initial clot volume and percentage of clot cleared per day.

All measurements were made in 75 patients.

FIG. 1. Bar graph showing the clot volume by day post-SAH in patients in whom vasospasm did or did not develop. The initial clot volume is larger in patients with vasospasm and this tends to persist for a longer time.

FIG. 2. Graphs showing the relationship between initial clot volume and the log odds ratio for risk of vasospasm. Upper: A plot of the initial clot volume as a linear variable shows a saturating trend in the risk of vasospasm with higher clot volumes. Lower: Log transformation of initial clot volume produces a more linear relationship between clot volume and risk of vasospasm.

TABLE 3
Multivariate logistic regression models for prediction of vasospasm

<table>
<thead>
<tr>
<th>Variable</th>
<th>β Coefficient</th>
<th>OR</th>
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<td>1.25-68.3</td>
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<td>0.0009</td>
</tr>
</tbody>
</table>

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8. Claassen J, Bernardini GL, Kreiter K, et al: Effect of cisternal pooling of high values was associated with vasospasm compared with intrathecal fibrinolytic agents, in preventing vasospasm. In addition, persistence of high values was associated with vasospasm, and clot density and rate of clot clearance contribute independently to vasospasm.

Clot Density

Suzuki, et al.,37 noted that Hounsfield values higher than 60 on CT scans taken within 24 hours of aneurysmal SAH were associated with vasospasm. In addition, persistence of high values was associated with vasospasm, and clot density and rate of clot clearance were not accounted for, and vasospasm was diagnosed simply based on rapid loss of consciousness and/or motor disturbance 4 to 14 days post-SAH. In their study Suzuki, et al., report that clot density is an important additional predictor of vasospasm.

limitations of the study

In this study we measured basal cisternal SAH and not the total volume of SAH that would include the clot over the convexities and some clot in the posterior fossa. It has been shown previously that basal volumes are important in predicting vasospasm and that the convexity SAH can be ignored.3,18 Other factors may be associated with vasospasm, including IVH.3,18 We did not quantify IVH but classification based on a commonly used qualitative scale did not demonstrate significance in multivariate analysis, likely because of the small number of patients examined in this study and the relatively weaker role of IVH in contributing to vasospasm. Most of the patients in the study underwent surgery to clip ruptured aneurysms. Although no specific effort was made to evacuate subarachnoid clot of aneurysms surgically other than in the cisterns that needed to be opened for clip occlusion of aneurysms, it must be stated that the clot clearance rates noted therefore may not reflect the natural history of clot clearance. Clearance rates after endovascular treatment may also be different. Surgery has no effect on vasospasm per se37 and does not alter the fundamental conclusions about the roles of clot volume, clearance, and density on the development of vasospasm. The day on which the second CT scan was obtained was variable. Clot clearance was calculated as a percentage change per day, although in the absence of multiple CT scans for each patient it is impossible to derive the function that best describes clot clearance in any one patient. Our results indicate, however, that the function differs between patients with and without vasospasm. Finally, because this is a retrospective study there is variability, in addition to other factors mentioned earlier, in the facilities where initial CT scans were performed and in the methods used to diagnose vasospasm. Therefore, it would be optimal to develop software to allow measurement of the aforementioned parameters easily at the CT workstation. Such software would increase the utility of the method and facilitate performance of a prospective study to confirm or modify the findings described here.

References

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