Quantitative Analysis of Hemorrhage Volume for Predicting Delayed Cerebral Ischemia After Subarachnoid Hemorrhage

Sang-Bae Ko, MD, PhD; H. Alex Choi, MD; Amanda Mary Carpenter, BA; Raimund Helbok, MD; J. Michael Schmidt, PhD; Neeraj Badjatia, MD, MS; Jan Claassen, MD, PhD; E. Sander Connolly, MD; Stephan A. Mayer, MD; Kiwon Lee, MD

Background and Purpose—Delayed cerebral ischemia (DCI) is an important complication after subarachnoid hemorrhage and appears to be associated with clot burden on CT. Quantification of hemorrhage on digitized images may be a more accurate method for predicting DCI than qualitative scales.

Methods—Quantitative analysis of clot burden on CT was performed in 160 subarachnoid hemorrhage patients who were scanned within 24 hours from the symptom onset between June 25, 2005 and July 19, 2009. Cisternal plus intraventricular hemorrhage volumes (CIHV) were classified into quartiles to evaluate their association with DCI. DCI was defined as neurological deterioration or cerebral infarction, or both attributable to vasospasm.

Results—DCI occurred in 25% of the patients included (age, 55.4±14.5; male, 36.3%). Compared to the lowest quartile of CIHV (<9.6 mL), the higher quartile (9.6 mL–16.5 mL, 16.5 mL–31.0 mL, and ≥31.0 mL) was associated with a greater risk of DCI (odds ratio, 2.6, 4.1, and 6.1, respectively; P=0.01). Receiver-operating characteristic curve analysis showed that quantitative CIHV performed equivalently to the modified Fisher scale. Patients who had DCI develop in a specific vascular territory had higher amounts of blood volume in the corresponding cisterns. Patients in the highest quartile of CIHV also had a higher risk of death or severe disability at 3 months (71%) compared to other groups (23%, 19%, and 40% for first, second, and third quartiles, respectively).

Conclusions—CIHV is a reasonable predictor for DCI and 3-month functional outcome in subarachnoid hemorrhage patients. (Stroke. 2011;42:00-00.)

Key Words: cisternal blood ■ functional outcome ■ delayed cerebral ischemia ■ subarachnoid hemorrhage ■ volumetric analysis

Cerebral vasospasm is a well-recognized complication contributing to secondary brain injury after subarachnoid hemorrhage (SAH). Although several definitions exist, only delayed cerebral ischemia (DCI), characterized by symptomatic vasospasm and/or new infarction seen on radiographic evidence attributable to vasospasm, is associated with death or disability at 3 months. Based on previous reports, initial hemorrhage burden is likely to be associated with the development of vasospasm. The Fisher scale (FS) indicated that the presence of thick cisternal or sylvian clot seen on admission CT is associated with the development of vasospasm. Moreover, presence of bilateral intraventricular hemorrhage (IVH) has been identified as an independent risk factor for DCI, and this has been reflected in the new modified FS (mFS). However, the mFS also has some caveats; large unilateral IVH can be similarly regarded as no IVH, and the risk of DCI developing overlaps in patients with mFS score 2 and 3. This raises the question whether the true predictor of DCI developing may be more related to total amount of cisternal and ventricular hemorrhage rather than the anatomic location of blood.

Volumetric analysis of blood in SAH patients has been reported previously. The importance of total cisternal hemorrhage volume or total hemorrhage volume in the development of DCI has been stressed. However, these studies were limited because of a small sample size (N=40), differences in timing of obtaining CT scans, exclusion of patients with high grades, and exclusion of IVH volumes. The purpose of this study is to determine the impact of quantitative hemorrhage in predicting DCI and functional outcome.

Patients and Methods

Patient Population

Study subjects were a subset of patients enrolled in the Columbia University SAH Outcomes Database Project (SHOP), a single-
Table 1. Baseline Characteristics of Study Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Patients (N=160)</th>
<th>Excluded Patients (N=100)</th>
<th>Delayed Cerebral Ischemia (Yes, N=40)</th>
<th>No (N=120)</th>
<th>P</th>
<th>Vasospasm-Related Infarction (Yes, N=14)</th>
<th>No (N=146)</th>
<th>P</th>
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<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>55.4 (14.5)</td>
<td>53.5 (11.7)</td>
<td>54.5 (16.8)</td>
<td>55.7 (13.7)</td>
<td>0.66</td>
<td>57.5 (18.6)</td>
<td>55.2 (14.1)</td>
<td>0.57</td>
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<td>Male, N (%)</td>
<td>58 (36.3)</td>
<td>35 (35.0)</td>
<td>12 (31.6)</td>
<td>46 (37.7)</td>
<td>0.49</td>
<td>5 (35.7)</td>
<td>53 (36.3)</td>
<td>0.97</td>
</tr>
<tr>
<td>Race, N (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.22</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>White</td>
<td>60 (37.5)</td>
<td>33 (33.0)</td>
<td>14 (36.8)</td>
<td>46 (37.7)</td>
<td>0.60</td>
<td>5 (35.7)</td>
<td>55 (37.7)</td>
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<td>Hispanic</td>
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<td>32 (32.0)</td>
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<td>Black</td>
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<td>5 (13.2)</td>
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<tr>
<td>Asian</td>
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<td>8 (8.0)</td>
<td>5 (13.2)</td>
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<td>0.04</td>
<td>2 (14.3)</td>
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<td>Other</td>
<td>4 (2.5)</td>
<td>9 (9.0)</td>
<td>2 (5.3)</td>
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<td>0.36</td>
<td>1 (7.1)</td>
<td>3 (2.1)</td>
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<td>Hypertension, N (%)</td>
<td>75 (46.9)</td>
<td>43 (43.0)</td>
<td>21 (55.3)</td>
<td>64 (52.5)</td>
<td>0.54</td>
<td>9 (64.3)</td>
<td>66 (45.2)</td>
<td>0.17</td>
</tr>
<tr>
<td>Diabetes mellitus, N (%)</td>
<td>14 (8.8)</td>
<td>11 (11.0)</td>
<td>2 (5.3)</td>
<td>12 (9.8)</td>
<td>0.52</td>
<td>1 (7.1)</td>
<td>13 (8.9)</td>
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<td>Smoking</td>
<td>0.47</td>
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<td>0.42</td>
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<td></td>
<td>0.73*</td>
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<tr>
<td>Nonsmoker</td>
<td>87 (54.4)</td>
<td>58 (58.0)</td>
<td>21 (55.3)</td>
<td>66 (54.1)</td>
<td>8 (57.1)</td>
<td>62 (54.1)</td>
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<tr>
<td>Ex-smoker</td>
<td>27 (16.9)</td>
<td>14 (14.0)</td>
<td>4 (10.5)</td>
<td>23 (18.9)</td>
<td>3 (21.4)</td>
<td>20 (16.4)</td>
<td></td>
<td></td>
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<tr>
<td>Current smoker</td>
<td>46 (28.8)</td>
<td>28 (28.0)</td>
<td>13 (34.2)</td>
<td>33 (27.0)</td>
<td>3 (21.4)</td>
<td>35 (29.5)</td>
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<td></td>
</tr>
<tr>
<td>Alcohol use</td>
<td>73 (45.6)</td>
<td>51 (51.0)</td>
<td>17 (44.7)</td>
<td>56 (45.9)</td>
<td>0.9</td>
<td>5 (35.7)</td>
<td>68 (46.6)</td>
<td>0.44</td>
</tr>
<tr>
<td>Acute Physiology and Chronic</td>
<td>16.2 (8.7)</td>
<td>14.3 (8.3)</td>
<td>17.1 (8.1)</td>
<td>15.9 (8.8)</td>
<td>0.45</td>
<td>19.1 (8.1)</td>
<td>16.0 (8.7)</td>
<td>0.2</td>
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<tr>
<td>Health Evaluation II, mean (SD)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Admission Hunt-Hess score, mean (interquartile range)</td>
<td>3 (1–4)</td>
<td>3 (2–4)</td>
<td>0.33†</td>
<td>3 (2–4)</td>
<td>3 (1–4)</td>
<td>0.15</td>
<td>3 (2–5)</td>
<td>3 (1–4)</td>
</tr>
</tbody>
</table>

†Fisher exact test.  
*Mann-Whitney U test.

**Definition of DCI**

DCI was defined as clinical deterioration attributable to vasospasm (clinical vasospasm) or a new infarct on brain CT related to vasospasm that was not visible on the admission or immediate postoperative scan (new infarction attributable to vasospasm) or both.5 DCI was diagnosed by the treating neurointensivist and adjudicated by senior SHOP study team members on a weekly basis after review of all pertinent clinical and radiographic data, as described previously.5 Other potential causes of clinical deterioration, such as hydrocephalus, rebleeding, or seizures, were meticulously excluded.

**Radiological Image Analysis**

CT scans were analyzed using MIPAV software package (Medical Image Processing, Analysis, and Visualization, version 4.3; National Institutes of Health).11 Regions of hemorrhage on CT scan were outlined slice-by-slice using a semiautomatic threshold approach by a rater blinded to all clinical information. Supplemental Figure 1 (available online at http://stroke.ahajournals.org) showing representative region of interest selection by MIPAV software is available. Hemorrhage volumes were calculated by multiplying slice thickness by the hemorrhage area.4 After measuring blood volume in each cistern, ventricle, parenchyma, and sulci near the cortex, any blood in the cisterns or ventricles were merged as a new volume variable called cisternal blood plus IVH volume (CIHV). This volume variable was categorized into quartiles based on its distribution. To assess the reliability among different observers, hemorrhage volumes were measured by an independent rater (A.M.C.) on a randomly selected subset of 20 patients. Inter-rater reliability for the assessment of hemorrhagic volume was good (interclass correlation coefficient=0.95).

**Statistical Analysis**

Differences between continuous variables were analyzed using the t test, Mann-Whitney U test, or rank-sum test, as appropriate, and differences between categorical variables were analyzed using the χ² test or Fisher exact test, as appropriate. Logistic regression analysis was used for predicting DCI risk in different blood burden groups. Any variables with significant probability values on univariate analysis, or ones that were considered clinically meaningful, were adjusted for in the multivariate logistic regression analysis. Analysis of linear trends was used to assess associations between increasing amount of blood volume and risk of DCI. Cox regression analysis was used for comparing the timing of DCI. SPSS statistical package for Windows (version 17.0; SPSS) was used for statistical analyses and statistical significance was set at P<0.05.
Results

Demographics
A total of 160 consecutively admitted patients were included. Excluded patients had lower Acute Physiology and Chronic Health Evaluation II scores compared to study subjects (14.3 ± 8.3 vs 16.2 ± 8.7; P = 0.03). All other baseline characteristics were not different between the 2 groups (Table 1). Among included patients, distribution of vascular risk factors, such as hypertension, diabetes, smoking, or alcohol use, was not statistically different between patients with or without DCI or new infarction. In total, DCI occurred in 25% (40/160) of patients and the risk of DCI was 13% (2/16) in mFS score 1, 20% (1/5) in mFS score 2, 20% (16/81) in mFS score 3, and 36% (21/58) in mFS score 4 groups. When stratified by CIHV, no significant differences between risk factors were found (Supplemental Table available online at http://stroke.ahajournals.org).

Prediction of DCI by CIHV
Increased CIHV volume was associated with an increased odds for the development of DCI (P for trend = 0.01; Table 2). Compared to patients in the lowest quartile, the odds ratio (OR) for DCI increased in a dose-related manner in the higher groups (OR, 2.6, 4.5, and 6.1 in second, third, and fourth quartiles; P = 0.18, 0.03, and 0.02, respectively) after adjusting for age, sex, race, hypertension, diabetes, smoking, alcohol use, and admission Hunt-Hess scale. When stratified by CIHV, no significant differences between risk factors were found (Supplemental Table available online at http://stroke.ahajournals.org).

Hemorrhage Volume and the Timing of Delayed Cerebral Ischemia
Higher CIHV volumes (>16.5 mL) were associated with earlier development of DCI compared to lower blood volumes (<16.5 mL; hazard ratio, 2.41; 95% CI, 2.13–5.18; P = 0.024) using Cox regression analysis controlled for age, sex, race, hypertension, diabetes, smoking, alcohol use, and admission Hunt-Hess (Figure 2). The higher blood burden group developed DCI within 5 days after hemorrhage (median, 5; interquartile range [IQR], 4.0–7.8), which was 1.5 days earlier than the lower blood burden groups (median, 6.5; IQR, 5.3–8.8) with regard to time to DCI.

Comparison of Quantitative and Qualitative Scales
CIHV volumes to predict DCI were compared to the mFS using receiver-operator curve analysis. Area under the curve values were 0.62 (95% CI, 0.52–0.72; P = 0.03) for mFS and 0.65 (95% CI, 0.56–0.74; P = 0.005) for CIHV volume (Supplement Figure 2 available online at http://stroke.ahajournals.org). Two receiver-operator curves were not statistically different (P = 0.11), which indicates that 2 volume criteria had similar discriminating powers.

Table 2. Risk of Delayed Cerebral Ischemia Associated With the Hemorrhage Volume

<table>
<thead>
<tr>
<th>Cisternal and Intraventricular Hemorrhage Volumes (mL)</th>
<th>Total Patients (N=160)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCI (+) (N=40)</td>
<td>DCI (-) (N=120)</td>
</tr>
<tr>
<td>&lt;9.6</td>
<td>4</td>
</tr>
<tr>
<td>9.6–16.5</td>
<td>8</td>
</tr>
<tr>
<td>16.5–31.0</td>
<td>14</td>
</tr>
<tr>
<td>≥31.0</td>
<td>14</td>
</tr>
</tbody>
</table>

DCI indicates delayed cerebral ischemia; +, positive; −, negative.
*Adjusted for age, sex, race, hypertension, diabetes, smoking, alcohol use, and admission Hunt-Hess scale score.

Figure 1. Blood volumes in patients with or without delayed cerebral ischemia. Patients with delayed cerebral ischemia had higher blood volume with regard to intraventricular hemorrhage (IVH), total cisternal blood volume, cisternal blood plus IVH volume, or total hemorrhage volume, which was statistically significant (P < 0.05). Values are presented with median with quartiles.
Location of Blood and Risk of DCI in Specific Vascular Distributions

The amount of blood in specific cisterns was compared between patients with DCI and those without DCI in the corresponding vascular territories (Figure 3). In patients with DCI in the anterior cerebral artery distribution, composite hemorrhage volumes in the interhemispheric and bilateral suprasellar cisterns (median volume, 9.4 mL; IQR, 5.7–15.4 mL) were higher than those of patients without DCI (median 5.7 mL; IQR, 2.2–9.9 mL) in the anterior cerebral artery territory (Mann-Whitney test, P = 0.02). Likewise, patients with DCI in the right middle cerebral artery territory had a higher blood burden (median volume, 5.8 mL; IQR, 4.7–10.3 mL) defined by the composite amount of blood in the right basal and lateral sylvian cisterns and ipsilateral suprasellar cistern compared to those without DCI (median volume, 3.7 mL; IQR, 1.5–6.9 mL; Mann-Whitney test, P = 0.02). Composite blood burdens in the left basal and lateral sylvian cisterns and ipsilateral suprasellar cistern were higher in patients with DCI in the left middle cerebral artery (median, 6.4 mL; IQR, 3.5–10.9 mL) compared to those without DCI (median, 3.8 mL; IQR, 1.2–6.8 mL) in the left middle cerebral artery (Mann-Whitney test, P = 0.026). Because of the small numbers of patients who had DCI develop in the posterior cerebral artery territory (right = 1, left = 1) and basilar artery territory (N = 4), statistical analysis was not performed.

Blood Volume and Functional Outcome at 3 Months

The 3-month follow-up for functional outcome was completed in 132 patients (82.5%). The rate of failure to follow-up was not different among the 4 quartiles (25%, 20%, 12.5%, and 15%, first, second, third, and fourth quartiles, respectively; χ² test, P = 0.48). Based on CIHV criteria, patients in higher quartiles of blood volume were more likely to be dead or severely disabled (modified Rankin scale score, 4–6; 70.6% and 40.0% in fourth and third quartiles) compared to those in lower quartiles (23.3% and 18.8% in first and second quartiles; χ² test, P < 0.01; Figure 4). Patients in the highest quartile had an increased risk for death or severe disability (OR, 5.9; 95% CI, 1.7–20.4; P = 0.005) when compared with the first quartile after controlling age, sex, hypertension, diabetes mellitus, smoking, and alcohol use. Other quartiles of CIHV failed to reach statistical significance (OR, 0.63; 95% CI, 0.16–2.4; P = 0.51; and OR, 2.1; 95% CI, 0.63–6.8; P = 0.23; for second and third quartiles). The receiver-operator curve analysis was performed to compare 2 volume criteria in predicting functional outcome at 3 months. Area under the curve was 0.72 (95% CI, 0.63–0.81; P < 0.01) for CIHV and 0.61 (95% CI, 0.52–0.71; P = 0.03) for mFS. Statistical analysis showed that CIHV was superior compared to mFS in predicting a state of death or severe disability at 3 months (P = 0.02).

Discussion

Our primary finding is that CIHV is a good predictor of DCI and death or severe disability at 3 months. Second, patients
with larger CIHV had DCI develop, on average, 1.5 days earlier than patients in the smaller CIHV group. Third, patients were more likely to have DCI develop in specific vessels in concordance to the specific location of cisternal blood.

Although the FS and the mFS have demonstrated the association between blood burden and DCI, questions regarding the location of blood and thresholds of blood volume have not been addressed. Our data show that the quantitative blood volume in contact with the cisternal space, whether directly in the cisternal subarachnoid space or in the intraventricular space, acts as cumulative blood burden and is associated with an increased risk for DCI. The quantitative volume scale and the mFS were equivalent in predicting DCI, validating the accuracy of the mFS. However, no overlaps in the OR for DCI were seen in different blood burden groups, which may suggest the robust association between blood burden and DCI. We also showed that patients with DCI in a specific vascular territory had a larger amount of blood in the concordant cistern compared to those without DCI. Moreover, the higher blood burden group had DCI develop more often and earlier than the lower blood burden group. More studies are needed to examine the possible causal relationship between blood burden and development of DCI.

Our data suggest that quantitative blood burden may be a better predictor of death or severe disability 3 months after SAH compared to the mFS. Although it was not statistically significant, more patients left the low blood burden group. For the most conservative estimate of effect, if we were to consider that all patients who were lost to follow-up had a poor outcome, then the proportion of patients with poor outcome would be calculated as 60%, 47.5%, 50%, and 75% (first, second, third, and fourth CIHV quartiles, respectively), which still suggested that the higher blood burden group had poorer outcome, albeit with marginal significance ($\chi^2$ test, $P=0.05$). However, discharge Glasgow coma scale and modified Rankin scale scores of the patients who were lost during follow-up were not different from those who were followed-up. Therefore, it is highly unlikely that all patients lost to follow-up would have modified Rankin scale score 4 to 6, especially in the low blood burden group.

Taken together, measuring quantitative blood burden is not only a good research tool but also a good predictor of DCI and clinical outcomes in SAH patients. Measuring the amount of blood in a semiautomatic technique might be regarded as cumbersome. However, this limitation may be solved with the development of automatic systems for quantifying lesion volume.

This study has multiple strengths. As opposed to previous articles that only included FS score 3 group patients, we included every possible consecutive SAH patient across all grades of SAH from a prospectively collected registry. This is the first study to our knowledge to quantify the amount of IVH and analyze its association with clinical outcomes. Finally, we used DCI as the primary clinical end point, which is the most relevant clinical outcome scale in regard to vasospasm-related clinical research.

There are several limitations of this study. First, this study is a retrospective analysis based on a prospectively collected registry. Therefore, some degree of bias is inevitable. To partially address this issue, the rater was blinded to clinical outcome when quantifying the scans and DCI was judged prospectively by 3 or 4 physicians in consensus. Second, functional outcome data at 3 months were not completed for all of the patients. However, drop-out rates were similar across CIHV groups. Therefore, it is unlikely that different functional outcomes were caused by selection bias.

### Conclusion

In conclusion, to the best of our knowledge, this is the first article to correlate quantitative hemorrhagic burden, including quantification of ventricular hemorrhage with the risk of DCI in SAH patients. Based on the results, CIHV is a good predictor of DCI, equivalent to mFS, and a better predictor of death or severe disability at 3 months after SAH.

### Sources of Funding

This study was supported in part by Columbia University’s CTSA grant (UL1 RR024156) from NCRR/NIH and the Neuroepidemiology training program NIH grant (5T32NS007153-27).

### Disclosures

None.

### References


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Stroke. published online January 21, 2011;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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Delayed Cerebral Ischemia after Subarachnoid Hemorrhage

Running title: Quantitative volumetric analysis of SAH

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S1. Representative figure for quantitative measurement of hemorrhagic volume.

Cisternal (A and B) and intraventricular blood (C and D) were marked by region of interests (ROIs), drawn by semiautomated methods based on voxel intensity threshold algorithm
S2. Distribution of risk factors in patients with different blood burden group.

<table>
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<tr>
<th>CIHV Q1</th>
<th>Age</th>
<th>Sex (male)</th>
<th>DCI (-)</th>
<th>DCI (+)</th>
<th>P value</th>
<th>DCI (-)</th>
<th>DCI (+)</th>
<th>P value</th>
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<td>CIHV Q2</td>
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<td>41.5(3.4)</td>
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<td>1(12.5)</td>
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<td>CIHV Q3</td>
<td>52.2(2.8)</td>
<td>55.3(4.7)</td>
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<td>6(42.9)</td>
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<tr>
<td>CIHV Q4</td>
<td>59.0(2.9)</td>
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<td>7(26.9)</td>
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<thead>
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<th>DM (yes)</th>
<th>Alcohol (yes)</th>
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<th>P value</th>
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<th>P value</th>
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<th>P value</th>
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<td>0.002</td>
<td>3(75.0)</td>
<td>0.38</td>
<td>34(94.4)</td>
<td>0.55</td>
<td>4(100.0)</td>
<td>0.95</td>
<td>21(58.3)</td>
<td>0.79</td>
<td>3(75.0)</td>
<td>0.78</td>
</tr>
<tr>
<td>CIHV Q2</td>
<td>15(46.9)</td>
<td>5(62.5)</td>
<td>27(84.4)</td>
<td>7(87.5)</td>
<td>15(46.9)</td>
<td>3(37.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIHV Q3</td>
<td>14(53.8)</td>
<td>9(64.3)</td>
<td>23(88.5)</td>
<td>14(100.0)</td>
<td>14(53.8)</td>
<td>8(57.1)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>CIHV Q4</td>
<td>7(26.9)</td>
<td>5(35.7)</td>
<td>24(92.3)</td>
<td>13(92.9)</td>
<td>15(57.7)</td>
<td>8(57.1)</td>
<td></td>
<td></td>
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</tbody>
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<table>
<thead>
<tr>
<th>CIHV Q1</th>
<th>Smoking</th>
<th>DCI (-)</th>
<th>DCI (+)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>24(66.6)</td>
<td>6(16.7)</td>
<td>6(16.7)</td>
<td>0.18</td>
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</tr>
<tr>
<td>CIHV Q2</td>
<td>12(37.5)</td>
<td>9(28.1)</td>
<td>11(34.4)</td>
<td>3(37.5)</td>
</tr>
<tr>
<td>CIHV Q3</td>
<td>16(61.5)</td>
<td>2(7.7)</td>
<td>8(30.8)</td>
<td>8(57.1)</td>
</tr>
<tr>
<td>CIHV Q4</td>
<td>13(54.2)</td>
<td>6(23.1)</td>
<td>7(26.7)</td>
<td>9(64.3)</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>CIHV Q1</th>
<th>Hunt-Hess Scale</th>
<th>DCI (-)</th>
<th>DCI (+)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>20(55.6)</td>
<td>6(16.7)</td>
<td>4(11.1)</td>
<td>2(5.6)</td>
<td>4(11.1)</td>
</tr>
<tr>
<td>CIHV Q2</td>
<td>12(37.5)</td>
<td>4(12.5)</td>
<td>10(31.3)</td>
<td>5(15.6)</td>
</tr>
<tr>
<td>CIHV Q3</td>
<td>3(11.5)</td>
<td>3(11.5)</td>
<td>11(42.3)</td>
<td>5(19.2)</td>
</tr>
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<td>CIHV Q4</td>
<td>1(3.8)</td>
<td>5(19.2)</td>
<td>4(15.4)</td>
<td>4(15.4)</td>
</tr>
</tbody>
</table>

*: Fisher’s exact test
S3. Receiver operated curve analysis of quantitative blood volume criteria and mFS.

Area under the curve analysis showed that cisternal and intraventricular hemorrhage (CIVH) criteria and modified Fisher scale were equally powerful in predicting delayed cerebral ischemia.
定量分析出血量用于预测蛛网膜下腔出血后迟发性脑缺血

Quantitative Analysis of Hemorrhage Volume for Predicting Delayed Cerebral Ischemia After Subarachnoid Hemorrhage

Sang-Bae Ko, MD, PhD; H. Alex Choi, MD; Amanda Mary Carpenter, BA; Raimund Helbok, MD; J. Michael Schmidt, PhD; Neeraj Badjatia, MD, MS; Jan Claassen, MD, PhD; E. Sander Connolly, MD; Stephan A. Mayer, MD; Kiwon Lee, MD

背景和目的：迟发性脑缺血 (DCI) 是一种重要的蛛网膜下腔出血后并发症，与 CT 所示血块负荷量相关。与定性评测相比，经数字化图像对出血的量化可能是更加准确预测 DCI 的一种方法。

方法：2005 年 6 月 25 日至 2009 年 7 月 19 日收治蛛网膜下腔出血住院患者 160 例，症状发生后 24 小时内行 CT 扫描，对 CT 片上的血块负荷量进行定量分析。按照四分位距划分为四个等级，评估脑池加脑室内出血量 (Cisternal plus intraventricular hemorrhage volumes, CIHV) 与 DCI 的关联。DCI 被定义为神经功能恶化或脑梗死，或者归因于血管痉挛的神经功能恶化或脑梗死。

结果：收治患者中有 25% 发生 DCI，平均年龄 55.4±14.5，男性占 36.3%。相比最低四分位组 (CIHV<9.6 毫升)，其它高四分位出血量组 (CIHV 分别为 9.6 毫升-16.5 毫升，16.5 毫升-31.0 毫升，≥31.0 毫升) 发生 DCI 的风险增加，并且随着出血量增加而增大 (对应的优势比分别为 2.6，4.1，6.1；P=0.01)。ROC 曲线分析表明，量化的 CIHV 等效于一个改良的 Fisher 量表。特定的血管领域发展为 DCI 的患者在相应的脑池会存在较大的血量。在 3 个月时，在第一、第二和第三分位组的患者的死亡或严重残疾的风险分别为 23%，19% 和 40%，而最高 CIHV 四分位组患者的死亡或严重残疾的风险则更高，达 71%。

结论：CIHV 可以合理的预测蛛网膜下腔出血患者 DCI 发生及其 3 个月时功能结局。

关键词：脑池出血，功能结局，迟发性脑缺血，蛛网膜下腔出血，容量分析

(Stroke. 2011;42:669-674. 北京市神经外科研究所 刘红梅 译 江滨 校)

脑血管痉挛是公认的蛛网膜下腔出血 (subarachnoid hemorrhage, SAH) 后并发症[1]，导致继发性脑损伤。尽管有好几种定义，只有以症状性血管痉挛和 / 或在影像上发现归因于血管痉挛的新鲜梗死为特征而定义的迟发性脑缺血 (delayed cerebral ischemia, DCI) 与 3 个月时的死亡或残疾有关联[1]。根据以往报道，最初的出血量可能与血管痉挛的发展有关。Fisher 量表 (Fisher scale, FS) 表明，入院时 CT 所示脑池内存在较厚的血块与血管痉挛的发展有关联[3]。此外，存在双侧脑室内出血 (intraventricular hemorrhage, IVH) 已被确认为 DCI 的一个独立的危险因素，这一点已经在新的改良 Fisher 量表 (modified FS，mFS) 中有所反映[4,5]。然而，mFS 的应用有些问题，如大的单侧 IVH 同样能被视为没有 IVH，mFS 得 2 分和 3 分的患者发生 DCI 的风险有重叠[6]。这就提出了一个问题，是否预测 DCI 的发生可能与脑池和脑室的出血总量更相关，而不是出血的解剖位置。

SAH 患者血量分析过去已有报道[7-10]，总的脑池出血量或总出血量在 DCI 发展中的重要性一直被强调。然而，这些研究存在样本量小 (N=40)、CT 扫描的时间不同[8]、除外了高级别的患者、不包括 IVH 的出血量[10]，因此均有一定的局限性。本研究的目的就是明确定量分析出血量对预测 DCI 发生和功能结局的作用。

患者与方法

患者人群

哥伦比亚大学蛛网膜下腔出血患者预后数据库
项目 (SAH Outcomes Database Project，SHOP) 是一项单中心、前瞻性观察队列研究。该队列研究收集所有成年(年龄大于18岁)自发性SAH患者的人口学、临床、放射学和预后数据。本项研究的对象就是该项研究在册登记中的一部分患者。纳入本项研究的患者都是SAH发病后24小时内入本单位行CT检查者。2005年6月25日至2009年7月19日期间，SHOP共登记260例连续患者。在此研究中，我们除外了以下患者：24小时以后CT扫描患者(N=52例)；初次扫描无效患者(N=38例)；1例CT扫描中未显示可测量到血的患者(N=1例)；或症状出现后48小时内死亡患者(N=9例)。其余160例患者最终成为本研究的对象。患者的人口学资料和社会及医学史信息是入院后不久通过患者及家属获得。入院时，患者经由当时参研的神经重症专科医师进行神经科和全身性体格检查。治疗3个月时，通过电话或面见患者及其陪护者，获得改良的Rankin量表评分。4-6分者为死亡或重度残疾。该项研究经伦理委员会批准。

DCI 由神经科重症监护专科医师诊断，每周由研究团队的高级成员审查患者全部的有关临床和影像学资料后裁定，先前已有描述[5]。谨慎地排除其他导致临床恶化的潜在原因，如脑积水、再出血，或者癫痫发作。

放射影像分析

应用MIPAV软件包(医学图像处理、分析和可视化,4.3版，美国国立卫生研究院)分析CT扫描[1]。使用半自动阈值逐层扫描，由不知情的评定者逐层圈出CT扫描。补充图1(见http://stroke.ahajournals.org)显示由MIPAV软件选中的代表区域是有效的。出血量的计算由该层的出血面积乘以层厚度[8]。在测量每一个脑池、脑室、脑实质、皮层附近脑沟的出血量以后，在脑池或脑室的任何血液被合并为一个新的出血量变量称为脑池加脑室内出血量(cisternal blood plus IVH volume, CIHV)。基于这一出血量变量的分布，将其分为四组。为评测不同观察者间的可靠性，随机选取20例患者，由名叫A.M.C.的操作者独立评测出血量。评测者之间评估出血量的可靠性很好(组间相关系数0.95)。

统计分析

采用t检验、Mann-Whitney U检验，或秩和检
验分析连续型变量间的差异。使用 $\chi^2$ 检验或 Fisher 精确检验分析分类变量间的差异。Logistic 回归分析用于预测不同的出血量组发生 DCI 的风险。单因素分析中 $P$ 值有意义的任何变量，或者被认为是临床有意义的变量，在多元 Logistic 回归分析中进行调整。线性趋势分析是用来评估出血量增加和 DCI 风险之间的关联。Cox 回归分析用于比较组间发生 DCI 的时机。采用 Window 系统支持下的 SPSS 17.0 统计软件包进行统计分析，$P<0.05$ 为有统计意义。

### 结果

**人口学特征**

本项研究包括 160 名连续入院患者。与纳入者相比，排除患者的急性生理和慢性健康评价 II 的分数较低 (14.3±8.3 vs 16.2±8.7; $P=0.03$)。所有其他的基础特征在两组之间没有差异 (表 1)。在纳入患者中，血管危险因素的分布，如高血压、糖尿病、吸烟和饮酒，在有或没有 DCI 或新发梗死的患者之间无统计学差异。总来说，25% (40/160) 的病人发生 DCI。在 mFS 评分分为 1 分、2 分、3 分和 4 分组中，发生 DCI 的风险分别是 13% (2/16)、20% (1/5)、20% (16/81) 和 36% (21/58)。当依据 CIHV 分层比较时，两组间已知的危险因素 (见 http://stroke.ahajournals.org 网站上的补充表) 没有显著性差异。

<table>
<thead>
<tr>
<th>出血量 (mL)</th>
<th>DCI(+)</th>
<th>DCI(-)</th>
<th>粗 OR (95% CI)</th>
<th>调整 OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;9.6</td>
<td>4</td>
<td>36</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>9.6-16.5</td>
<td>8</td>
<td>32</td>
<td>2.25 (0.62-8.18)</td>
<td>2.58 (0.64-10.49)</td>
</tr>
<tr>
<td>16.5-31.0</td>
<td>14</td>
<td>26</td>
<td>4.85 (1.43-16.42)</td>
<td>4.51 (1.14-17.87)</td>
</tr>
<tr>
<td>≥31.0</td>
<td>14</td>
<td>26</td>
<td>4.85 (1.43-16.42)</td>
<td>6.11 (1.34-27.83)</td>
</tr>
</tbody>
</table>

* 调整年龄、性别、种族、高血压、糖尿病、吸烟和入院时 Hunt-Hess 量表评分。

当以 CIHV 中位数 16.5 毫升将患者划分为两组时，出血量较大组有着较高的发生 DCI 的风险 (OR=2.9; 95% CI, 1.1-7.3; $P=0.03$)。在有无 DCI 发生的患者间进行绝对出血量的比较，DCI 患者脑室内、脑池的出血量，CIHV 以及包括颅内任意区域出血的总出血量都较高 (见图 1)。所有组间的比较统计学上有显著性差异 (IVH、CIHV 和总出血量比较的秩和检验：$P<0.01$; 脑池的血量比较结果为 $P=0.03$)。然而，在所有出血容量变量中均没有找到预测 DCI 发生的绝对截点值。

### 出血量和 DCI 的时机

使用 Cox 回归分析，控制年龄、性别、种族、高血压、糖尿病、吸烟、饮酒和入院时 Hunt-Hess (见图 2)，与较低的出血量 (<16.5 毫升) 比较，较高的出血量 (≥16.5 毫升) 较早发生 DCI 的风险增
出血部位和特定血管区域发生 DCI 的风险

图 3 比较了相应血管区域有无发生 DCI 的两组患者特定脑池中的血液量。在大前脑动脉发生 DCI 的患者中，大脑前动脉和两侧蝶鞍上池中的混合出血量（中位数血量，9.4 毫升；IQR，5.7-15.4 毫升），高于大脑前动脉没有发生 DCI 的患者（中位数血量，5.7 毫升；IQR，2.2-9.9 毫升），差异有统计学意义 (Mann-Whitney 检验，P=0.02)。同样，左侧大脑中动脉区域发生 DCI 的患者，左侧基底和侧脑室以及同侧蝶鞍上池内的混合出血量（中位数血量，5.8 毫升；IQR，4.7-10.3 毫升），高于没有发生 DCI 的患者（中位数血量，3.7 毫升；IQR，1.5-6.9 毫升），差异有统计学意义 (Mann-Whitney 检验，P=0.02)。在左侧大脑中动脉发生 DCI 的患者，在左侧基底和侧脑室以及同侧蝶鞍上池内的混合出血量（中位数血量，6.4 毫升；IQR，3.5-10.9 毫升），高于那些左侧大脑中动脉没有发生 DCI 的患者（中位数血量，3.8 毫升；IQR，1.2-6.8 毫升），差异有统计学意义 (Mann-Whitney 检验，P=0.026)。由于大脑后动脉区域（左侧 1 例，右侧 1 例）和基底节动脉区域（4 例）发生 DCI 的病例数量少，因此没有进行组间统计分析比较。

出血量和治疗 3 个月时的功能结局

对 132 例 (82.5%) 患者完成了 3 个月的功能结局随访。第一、二、三、四分位数组的失访率分别为 25%，20%，12.5% 和 15%，未见统计学差异 ($\chi^2$ 检验，P=0.48)。基于 CIHV 标准分组，高血量组死亡
或重度致残 (mRS 评分 4-6 分) 比例高 (第四、四分位组死亡或重度致残率分别为 70.6% 和 40.0%), 与低血量组 (第一、二四分位组死亡或重度致残率分别为 23.3%, 18.8%) 比较, 有统计学意义 (χ² 检验, P<0.01; 见图 4). 结果显示, 在控制了年龄、性别、高血压、糖尿病、吸烟、饮酒之后, 血量最高四分位组与第一四分位组比较, 最高四分位组患者的死亡或重度残废的风险增加 (OR, 5.9; 95% CI, 1.7-20.4; P=0.005). CIHV 其他四分位组与第一四分位组比较未见有统计学意义 (第二四分位组 OR, 0.63; 95% CI, 0.16-2.4; P=0.51; 第三四分位组 OR, 2.1; 95% CI, 0.63-6.8; P=0.23). 应用 ROC 曲线分析比较两个评估血量标准用于预测 3 个月时的功能预后, 结果显示, CIHV 曲线下面积为 0.72 (95% CI, 0.63-0.81; P=0.01), mFS 曲线下面积是 0.61 (95% CI, 0.52-0.71; P=0.03). 统计分析显示, 在预测 3 个月时患者死亡或重度残废方面 CIHV 优于 mFS (P=0.02).

讨论

我们最主要的发现是 CIHV 能很好预测 DCI 发生和患者 3 个月时死亡或重度残废状态。其次, 大的 CIHV 患者会发生 DCI. DCI 发生平均早于较小 CIHV 组患者 1.5 天。再次, 患者更有可能在与其对应脑池内有出血的特定血管发生 DCI.

虽然 FS 和 mFS 已证明血负荷量与 DCI 之间有关联, 然而, 关于血量的位置及其血容量的阈值问题还没有被解决。我们的数据表明包括脑池空间内的血量, 不论是直接在蛛网膜下腔池空间内的还是在室内空间, 均作为累积血负荷量, 并且与增加 DCI 的风险有关。量化血容量评测和 mFS 用于预测 DCI 是等效的, 也验证了 mFS 的准确性。不同血负荷量组间发生 DCI 的 OR 值没有重叠, 可能提示在血负荷量和 DCI 之间存在很强的关联。我们同样发现, 与那些没有发生 DCI 的患者相比, 在特定血管领域发生 DCI 的患者在与血管对应的脑池中有较大的血量。而且, 较高的血负荷量组比较低组更经常和更早发生 DCI。更多的研究需要检查在血负荷量和发生 DCI 之间可能的因果关系。

本项研究数据提示, 发生 SAH 以后 3 个月时, 与 mFS 比较, 量化的血负荷量能更好地预测死亡或重度残疾。虽然差异没有统计学意义, 更多的患者留在低血负荷量组。最保守地估计效果, 如果我们考虑将失访者算作坏的预后, 那么 CIHV 第一、二、三及第四四分位组患者百分比分别为 60%、47.5%、50% 和 75%, 这表明较高的血负荷量组有较好的预后, 虽然有临界意义 (χ² 检验, P=0.05). 然而, 那些后来失访患者出院时的 Glasgow 昏迷量表和改良的 Rankin 量表评分与随访到的患者没有什么不同。因此, 不可能所有失访患者改良的 Rankin 量表评分都在 4-6 分, 尤其是在低血负荷量组。

总的来说, 测量血负荷量不仅是一个好的研究工具, 而且能很好预测 SAH 患者 DCI 的发生和临床预后。不过用半自动技术测量血量仍是一件很麻烦的事情, 然而, 为量化病变体积而开发的自动化系统可以解决这种缺陷。

本研究有多重优势。相对于以前的研究只包括 FS 评分为 3 分组的患者, 我们的研究对象来自前瞻性登记, 包括不同评分的每一例可能的 SAH 连续入院患者。据我们所知, 这是首次量化 IVH 并分析其与临床预后的关联。最后, 我们使用 DCI 为主要临床终点, 这是与血管痉挛相关且在临床研究中最相关的临床结局评测 [2]。

本项研究有一些局限性。第一, 本研究是一项基于前瞻性登记项目的回顾性分析。因此, 一定程
度的偏倚是不可避免的。为了部分地解决这一问题，对 CT 扫描做量化分析的评定人不知道患者的临床预后，并且 DCI 的诊断要由 3 或 4 个医生一致做出决定。第二，并没有收集到所有患者的 3 个月时功能预后数据。然而，在 CIHV 各组间失访率是相似的。因此，不太可能是由选择偏倚导致的不同功能结局。

结论
总之，据我们所知，这是首次关于 SAH 患者的出血负荷量，包括脑室出血量与发生 DCI 风险关系的文章。基于本研究结果，CIHV 能很好预测 SAH 患者 DCI 的发生，其预测能力等效于 mFS，同时也能很好地预测 SAH 患者 3 个月时的死亡或重度残疾。

参考文献