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-
center, prospective, observational cohort study that collects demographic, clinical, radiographic, and outcome data for all adult (age older than 18) spontaneous SAH patients. Patients were included in the present analysis when CT was performed at our institution within 24 hours of symptom onset. Two hundred sixty consecutive patients were enrolled in SHOP between June 25, 2005, and July 19, 2009. For this study, we excluded the following patients: those with presentation after 24 hours (N=52); those with unavailability of initial scan (N=160); those with no measurable blood on CT scan (N=38); those who died within 48 hours of symptom onset (N=40) No (N=146) P

<table>
<thead>
<tr>
<th></th>
<th>Total Patients (N=160)</th>
<th>Excluded Patients (N=100)</th>
<th>P</th>
<th>Delayed Cerebral Ischemia</th>
<th>Vasospasm-Related Infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes (N=40)</td>
<td>No (N=120)</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>55.4 (14.5)</td>
<td>53.5 (11.7)</td>
<td>0.24</td>
<td>54.5 (16.8)</td>
<td>55.7 (13.7)</td>
</tr>
<tr>
<td>Male, N (%)</td>
<td>58 (36.3)</td>
<td>35 (35.0)</td>
<td>0.84</td>
<td>12 (31.6)</td>
<td>46 (37.7)</td>
</tr>
<tr>
<td>Race, N (%)</td>
<td></td>
<td></td>
<td>0.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>60 (37.5)</td>
<td>33 (33.0)</td>
<td></td>
<td>14 (36.8)</td>
<td>46 (37.7)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>54 (33.8)</td>
<td>32 (32.0)</td>
<td></td>
<td>12 (31.6)</td>
<td>42 (34.4)</td>
</tr>
<tr>
<td>Black</td>
<td>27 (16.9)</td>
<td>18 (18.0)</td>
<td></td>
<td>5 (13.2)</td>
<td>22 (18.0)</td>
</tr>
<tr>
<td>Asian</td>
<td>15 (9.4)</td>
<td>8 (8.0)</td>
<td></td>
<td>5 (13.2)</td>
<td>10 (8.2)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (2.5)</td>
<td>9 (9.0)</td>
<td></td>
<td>2 (5.3)</td>
<td>2 (1.6)</td>
</tr>
<tr>
<td>Hypertension, N (%)</td>
<td>75 (46.9)</td>
<td>43 (43.0)</td>
<td>0.54</td>
<td>21 (55.3)</td>
<td>64 (52.5)</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.47</td>
<td>0.42</td>
<td>0.73*</td>
<td>0.47</td>
<td>0.42</td>
</tr>
<tr>
<td>Diagnosed with diabetes</td>
<td>14 (8.8)</td>
<td>11 (11.0)</td>
<td>0.55</td>
<td>2 (5.3)</td>
<td>12 (9.8)</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>73 (45.6)</td>
<td>51 (51.0)</td>
<td>0.39</td>
<td>17 (44.7)</td>
<td>56 (45.9)</td>
</tr>
<tr>
<td>Acute Physiology and Chronic</td>
<td>16.2 (8.7)</td>
<td>14.3 (8.3)</td>
<td>0.03</td>
<td>17.1 (8.1)</td>
<td>15.9 (8.8)</td>
</tr>
<tr>
<td>Health Evaluation II, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission Hunt-Hess score,</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>
</tr>
</tbody>
</table>


Table 1. Baseline Characteristics of Study Patients

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.3 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. 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 semiautomated 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.8 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 analysis 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 & 11006 8.3 vs 16.2 & 11006 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).

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.

Hemorrhage Volume and the Timing of Delayed Cerebral Ischemia
Higher CIHV volumes (\( \geq 16.5 \text{ mL} \)) 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 \( \approx 1.5 \) days earlier than the lower blood burden groups (median, 6.5; IQR, 5.3–8.8) with regard to time to DCI.

### 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>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>DCI (+) (N=40)</td>
<td>DCI (−) (N=120)</td>
<td>Crude OR (95% CI)</td>
<td>Adjusted OR* (95% CI)</td>
<td></td>
</tr>
<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 (1.34–27.33)</td>
</tr>
</tbody>
</table>

\( P \) for trend \( 0.003 \) \( 0.01 \)

DCI indicates delayed cerebral ischemia; +, positive; −, negative.

*Adjusted for age, sex, race, hypertension, diabetes, smoking, alcohol use, and admission Hunt-Hess scale.

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.
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**


Quantitative Analysis of Hemorrhage Volume for Predicting Delayed Cerebral Ischemia After Subarachnoid Hemorrhage
Sang-Bae Ko, H. Alex Choi, Amanda Mary Carpenter, Raimund Helbok, J. Michael Schmidt, Neeraj Badjatia, Jan Claassen, E. Sander Connolly, Stephan A. Mayer and Kiwon Lee

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

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/early/2011/01/21/STROKEAHA.110.600775

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2011/01/20/STROKEAHA.110.600775.DC1
http://stroke.ahajournals.org/content/suppl/2012/02/28/STROKEAHA.110.600775.DC2

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/
ON LINE SUPPLEMENT

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

Running title: Quantitative volumetric analysis of SAH

Sang-Bae Ko, MD, PhD¹, H. Alex Choi, MD¹, Amanda Mary Carpenter, BA¹, Raimund Helbok, MD²,
J. Michael Schmidt, PhD¹, Neeraj Badjatia, MD, MS¹, Jan Claassen MD, PhD¹,
E. Sander Connolly, MD³, Stephan Mayer, MD¹, Kiwon Lee, MD¹.

¹: Department of Neurology, Columbia University College of Physicians and Surgeons, New York, NY, USA

²: Clinical Department of Neurology, Neurological Intensive Care Unit, Medical University
Innsbruck, Innsbruck, Austria

³: Department of Neurosurgery, Columbia University College of Physicians and Surgeons, New York, NY, USA

Address for Correspondence

Kiwon Lee, MD, KL2356@columbia.edu

Division of Neurocritical Care, Department of Neurology,

Columbia University College of Physicians and Surgeons,

Milstein Hospital Building 8 Center, 177 Fort Washington Ave,

New York, NY 10032, USA

Tel: 1-212-305-7236

Fax: 1-212-305-2792
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.

|         | Age  | Sex (male) |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        | four tabular data with columns for Age, Sex (male), DCI (-), DCI (+), P value, HT (yes), DM (yes), Alcohol (yes), Smoking, and Hunt-Hess Scale. The table includes data for CIHV Q1 to Q4 with specific values for each category and their corresponding P values. A note at the bottom indicates that Fisher’s exact test was used for certain comparisons.
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.
Original Contributions

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 Objectives: Delayed cerebral ischemia (DCI) is an important complication after subarachnoid hemorrhage, and it is related to the load of blood in CT scans. Quantitative analysis of hemorrhage volume may be a more accurate way to predict DCI compared to traditional assessments.

Methods: From June 25, 2005, to July 19, 2009, 160 patients with subarachnoid hemorrhage were treated, and CT scans were performed within 24 hours of symptom onset. The hemorrhage volumes in the brain parenchyma and intraventricular spaces were quantitatively analyzed. The hemorrhage load (Cisternal plus Intraventricular Hemorrhage Volumes, CIHV) was divided into four quartiles, and the association with DCI was assessed. DCI was defined as neurologic deterioration or brain infarction, or both, due to vasospasm.

Results: Among the treated patients, 25% developed DCI, with an average age of 55.4 ± 14.5 years, and 36.3% were male. Compared to the lowest quartile (CIHV < 9.6 mL), the risk of DCI increased with higher quartiles (CIHV: 9.6 mL to 16.5 mL, 16.5 mL to 31.0 mL, ≥ 31.0 mL), with corresponding odds ratios of 2.6, 4.1, 6.1, and P = 0.01. ROC curve analysis showed that quantified CIHV was equivalent to a modified Fisher scale. Patients with DCI had more blood in the corresponding brain compartments. At 3 months, the risk of death or severe disability in the first, second, and third quartiles was 23%, 19%, and 40%, respectively, while in the highest CIHV quartile, it was 71%.

Conclusions: Quantitative analysis of hemorrhage volume can reasonably predict subarachnoid hemorrhage patients' DCI occurrence and its 3-month functional outcomes.

Keywords: Subarachnoid hemorrhage, functional outcomes, delayed cerebral ischemia, subarachnoid hemorrhage, quantification

From the Department of Neurology (S.B.K., H.A.C., J.M.S., N.B., J.C., S.A.M., K.L.) and Neurosurgery (A.M.C., E.S.C.), Columbia University College of Physicians and Surgeons, New York, NY; Clinical Department of Neurology (R.H.), Neurological Intensive Care Unit, Medical University Innsbruck, Innsbruck, Austria.

The online-only Data Supplement is available at http://stroke.ahajournals.org/cgi/content/full/STROKEAHA.110.600775/DC1.

Address correspondence to Kiwon Lee, MD, Division of Critical Care, Department of Neurology, Columbia University College of Physicians and Surgeons, Milstein Hospital Building 8 Center, 177 Fort Washington Avenue, New York, NY 10032. E-mail KL2356@columbia.edu

© 2011 American Heart Association, Inc.
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 小时内在本单位行 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其家属获得。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, 通过电话或见面患者及其陪护者, 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 的定义
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 扫描的出血区。补充图 1 (见 http://stroke.ahajournals.org) 显示由 MIPAV 软件所选择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)。基干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。评测者之间估计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。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; $P=0.03$)。所有其他的基线特征两组间没有差异（见表 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，有或没有 DCI 或新发梗死的患者之间无统计学差异。总的来说，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)。当依照 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。

采用 CIHV 预测 DCI

CIHV 血量的增加与发生 DCI 的机率增加有关 (趋势检验，$P=0.01$; 见表 2)。在调整了年龄、性别、种族、高血压、糖尿病、吸烟、饮酒和入院时 Hunt-Hess 量表评分后，与 CIHV 最低四分位组的患者相比，高 CIHV 四分位组患者发生 DCI 的可能性增加，且呈线性关系。第二、三、四四分位组与最低 (第一) 四分位组患者比较发生 DCI 的优势比分别为 2.6 ($P=0.18$)、4.5 ($P=0.03$)、6.1 ($P=0.02$)。当以 CIHV 的中位数 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 患者在脑室、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：$P<0.01$）；脑池的出血量比较结果为 $P=0.03$。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。

表 2 与出血量相关的迟发性脑缺血的风险

<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>

趋势检验，$P$ 值

表 DCI 表示迟发性脑缺血；+，阳性；-，阴性。

* 调整年龄、性别、种族、高血压、糖尿病、吸烟、饮酒和入院时 Hunt-Hess 量表评分。
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出血量。在大脑前动脉发生 DCI 的患者中，大脑半球间和双侧蝶鞍上池内的混合出血量（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<0.024)。同样，在右侧大脑中动脉区域发生 DCI 的患者，右侧基底和侧面粗池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=0.026)。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、四分位组的失访率分别为 25%，20%，12.5% 和 15%，未见统计学差异 (χ² 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 ($\chi^2$ 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疾的风险增加 ($OR$, 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 曲线下面积为是 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疾方面 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疾状态。其次，大的 CIHV 患者会发生 DCI, DCI 的发生平均早于较小 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血量的血容量，不论是直接在蛛网膜下腔池空间内的还是在室内空间，均作为累加血负荷量，并且与增加 DCI 的风险有关。量化血容量测得和 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。

本项研究数据显示，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，更多的患者留在血负荷量组。最保守地估计效果，如果我们考虑将失访患者算作坏的预后，那么 CIHV 第一、二、三及第四四分位组坏结局患者的百分比分别为 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 ($\chi^2$ 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，不太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，而且能很好地预测 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的功能结局。

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，同时也很好地预测 SAH 患者 3 个月时的死亡或重度残疾。

参考文献