Global Cerebral Edema and Brain Metabolism After Subarachnoid Hemorrhage

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Background and Purpose—Global cerebral edema is common among patients with poor-grade subarachnoid hemorrhage and is associated with poor outcome. Currently no targeted therapy exists largely due to an incomplete understanding of the underlying mechanisms.

Methods—This is a prospective observational study including 39 consecutive patients with poor-grade subarachnoid hemorrhage with multimodal neuromonitoring. Levels of microdialysate lactate–pyruvate ratio, episodes of cerebral metabolic crisis (lactate-pyruvate ratio >40 and brain glucose <0.7 mmol/L), brain tissue oxygen tension, cerebral perfusion pressure, and transcranial Doppler sonography flow velocities were analyzed.

Results—Median age was 54 years (range, 45 to 61 years) and 62% were female. Patients with global cerebral edema on admission (n=24 [62%]) had a higher incidence of metabolic crisis in the first 12 hours of monitoring (n=15 [15% versus 2%], P<0.05) and during the total time of neuromonitoring (20% versus 3%, P<0.001) when compared to those without global cerebral edema. There was no difference in brain tissue oxygen tension or cerebral perfusion pressure between the groups; however, in patients with global cerebral edema, a higher cerebral perfusion pressure was associated with lower lactate–pyruvate ratio (P<0.05). Episodes of metabolic crisis were associated with poor outcome (modified Rankin Scale score 5 or 6, P<0.05).

Conclusions—In patients with poor-grade subarachnoid hemorrhage, global cerebral edema is associated with early brain metabolic distress. (Stroke. 2011;42:00-00.)

Key Words: global cerebral edema ■ microdialysis ■ subarachnoid hemorrhage

Global cerebral edema is common among patients with poor-grade subarachnoid hemorrhage (SAH) and significantly impacts outcome.1 Pathophysiological mechanisms are incompletely understood. The initial bleeding is associated with a rapid increase in intracranial pressure (ICP) and reduction in cerebral blood flow,2,3 leading to decreased substrate delivery to the brain during a time of increased demand. Animal data suggest that rising intracellular Ca++, excitotoxicity, and mitochondrial dysfunction may contribute to cellular distress resulting in cytotoxic brain edema.4 Currently available animal models, however, do not convincingly replicate the pathophysiology occurring in the setting of spontaneous aneurysmal SAH in humans. This is why human physiological data may be central to better understand mechanisms seen early after SAH. Invasive brain monitoring can assess brain metabolism and indicate brain tissue in metabolic distress based on energy supply deficiency (glucose, oxygen), mitochondrial dysfunction, or increased cellular demand hours before the irreversible damage occurs.5,6 Recently, global cerebral edema (GCE) after SAH was associated with increased cerebral energy metabolism indicated by increased cerebral extracellular levels of lactate and pyruvate.7 There was no association with GCE and lactate–pyruvate ratio (LPR) and data on cerebral perfusion and brain tissue oxygenation (PbtO2) are not reported.7

We examine patterns in brain metabolism in combination with PbtO2 and cerebral perfusion in patients with GCE after SAH. We tested the hypothesis that GCE is associated with cerebral metabolic distress in the setting of brain hypoperfusion.

Materials and Methods

Patients

Between June 2006 and December 2008, 39 patients with poor-grade SAH admitted to the neurological intensive care unit at Columbia University Medical Center underwent brain multimodality monitoring according to our institutional protocol. Data were collected as

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The online-only Data Supplement is available at http://stroke.ahajournals.org/cgi/content/full/STROKEAHA.110.604488/DC1.

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Stroke is available at http://stroke.ahajournals.org

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part of an ongoing prospective database approved by the local Institutional Review Board.

**Global Cerebral Edema**

GCE was diagnosed by senior researchers (J.C., N.B., K.L., S.A.M.) based on the initial cerebral CT scan as previously described: (1) complete or near-complete effacement of the hemispheric sulci and basal cisterns; and (2) bilateral and extensive disruption of the hemispheric gray–white matter junction at the level of the centrum semiovale, which was due to either blurring or diffuse peripheral “finger-like” extension of the normal demarcation between gray and white matter.1

**General Management**

Patient care for SAH conformed to guidelines.8 Hemodynamic and fluid management was targeted to maintain cerebral perfusion pressure (CPP) >60 mm Hg and ICP <20 mm Hg.9

**Intracranial Monitoring**

At the time monitoring was started, all patients had a Glasgow Coma Scale (GCS) ≤8. Multimodality monitoring was initiated if (1) it was unlikely that the patient gains consciousness within the following 48 hours; and (2) the patient had a high probability to survive for the next 48 hours. This decision was made by the attending neurointensive care unit physician and head neurosurgeon. Through a burr hole, a triple-lumen bolt was affixed with a frontal approach (in patients who underwent aneurysm clipping contralateral to craniotomy [n=22; 56%]; after endovascular treatment in the nondominant frontal lobe in diffuse SAH or ipsilateral in lateralized SAH). A CMA-70 microdialysis catheter (CMA/Microdialysis, Stockholm, Sweden) was inserted into the brain parenchyma and hourly samples were analyzed (CMA-600; CMA/Microdialysis). At least 1 hour passed after the insertion of the probe and the start of the sampling to allow for normalization of changes due to probe insertion. PbtO2 was measured with a Licox Clark-type probe (Licox GMBHTM, Kiel-Germany: Integra Neurosciences, Plainsborough, NJ). ICP monitoring was performed using a parenchymal probe (Integra Neurosciences). The location of the monitoring catheters in the white matter was confirmed by brain CT scan immediately after the procedure. Metabolic crisis (MC) was defined as a microdialysate glucose <0.7 mmol/L together with LPR >40.10,11

**Statistical Analysis**

Microdialysis, PbtO2, and cerebral perfusion measurements were averaged daily and time-locked to the onset of Group. Comparisons were performed using Mann-Whitney U (Bonferroni-corrected), Student t test, χ², and Fisher exact tests as appropriate. The percentage of hours spent in metabolic distress (LPR >40) and MC over the entire neuromonitoring time was calculated for every patient. Data are expressed as mean±SD or median (interquartile range) unless otherwise indicated. Multivariable general linear models were calculated to determine the relationship over time of GCE to cerebral metabolism, PbtO2, and cerebral perfusion. Multiple observations per subject were handled by using generalized estimating equations with an autoregressive working correlation matrix. Continuous variables that were not normally distributed were normalized using logarithmic transformations. All statistical comparisons were done using SPSS 18 (SPSS Inc, Chicago, IL). Differences were considered significant at P<0.05.

**Results**

**Patient Characteristics and Clinical Course**

Patient baseline characteristics are given in the Table. A total of 3402 microdialysate samples from 39 patients with SAH were analyzed. Admission Glasgow Coma Scale was not different between groups (P=0.2). All of the 9 patients with admission Hunt & Hess grades 1 to 3 deteriorated during hospitalization to a Hunt & Hess grade of 4 or 5 due to hydrocephalus, rebleeding, and cerebral ischemia (3 patients each). Patients with GCE (n=24 [62%]) were younger (49±13 versus 61±14 years, P<0.01), and all had reported loss of consciousness at ictus (versus 33%, P<0.01). Other admission variables and treatment choice (clipping versus coiling) did not differ between groups. Initial CT scanning revealed lateralized SAH in 12 patients equally distributed in both groups (GCE/non-GCE: n=7/5 [29%/33%], P=0.8). Insertion hematoma (<1 cm) was observed in 2 patients in the cortical area distant to the catheter tip. Median time to neuromonitoring was 2 days in both groups (P=0.9). In-hospital complications did not differ significantly between groups (Table S1; http://stroke.ahajournals.org).

**GCE and Brain Metabolism**

In the first 12 hours of neuromonitoring, admission GCE was associated with lower brain pyruvate (102±48 μmol/L; versus 137±38 μmol/L, P<0.05) and glucose levels (1.3±0.7 mmol/L versus 1.8±1.1 mmol/L, P=0.07) resulting in a higher frequency of episodes of MC (15% versus 2%, P<0.05). During monitoring Days 2 and 10 after SAH, patients with GCE had a higher percentage of episodes in MC (20% versus 3%, P<0.001), of LPR >40 (42% versus 9%, P=0.001; Figure 1 A),

<table>
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<th>Table. Baseline Characteristics (N=39)</th>
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<td><strong>Demographics and medical history</strong></td>
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<tr>
<td>Age, y</td>
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<td>Gender (female)</td>
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<tr>
<td>Hypertension</td>
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<td>Loss of consciousness at ictus</td>
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<tr>
<td><strong>Admission neurological and radiographic findings</strong></td>
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<td>Admission Hunt &amp; Hess grade</td>
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<td>1 and 2</td>
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<tr>
<td>Modified Fisher scale</td>
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<tr>
<td>0, no blood</td>
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<tr>
<td>1, focal or diffuse thin SAH</td>
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<tr>
<td>2, focal or diffuse thin SAH with bilateral IVH</td>
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<tr>
<td>3, focal or diffuse thick SAH</td>
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<td>4, focal or diffuse thick SAH with bilateral IVH</td>
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<td>SAH sum score</td>
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<td>IVH sum score</td>
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<tr>
<td>Global cerebral edema</td>
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<td>Infarction on admission CT scan</td>
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<td>Intracerebral hemorrhage on admission CT scan</td>
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<tr>
<td><strong>Admission physiological variables</strong></td>
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<tr>
<td>Systolic blood pressure, mm Hg</td>
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<td>Serum glucose, mmol/L</td>
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<td><strong>Neuromonitoring</strong></td>
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<td>Days from admission to neuromonitoring</td>
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<td>Days with neuromonitoring</td>
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<td><strong>Values are presented as mean (SD), median (interquartile), or no. (%)</strong></td>
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<td><strong>SAH indicates subarachnoid hemorrhage; IVH, intraventricular hemorrhage.</strong></td>
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and a tendency to brain hypoglycemia (<0.7 mmol/L, 33% versus 18%, P=0.1).

**Daily Variations in Neuromonitoring Parameters in Patients With and Without GCE**

Patients with GCE had higher overall LPR (P<0.05) and lower overall pyruvate levels (P<0.05). Brain glucose was higher in non-GCE patients during the first days of monitoring (P<0.01) and significantly decreased over time (P<0.001) to a nonsignificant difference by Day 7 (Figure 1B–D). There was a trend toward higher ICP in patients with GCE (P=0.05; Figure 2A). No difference was observed in CPP, flow velocity in the middle cerebral artery ipsilateral to the neuromonitoring probes (not shown), PbtO2, or pressure reactivity index (PRx; Figure 2B–D). To verify the association between presence of GCE and elevated levels of LPR and decreased pyruvate levels, generalized estimating equation models were calculated with day post-SAH and presence of GCE as factors, including important covariates (gender, admission GCS). These models confirmed that LPR was higher and brain-pyruvate was lower early after SAH (SAH day significant at P<0.01, respectively) and in those with GCE.
Our findings suggest that GCE after SAH is associated with brain metabolic distress. The present data are of potential importance because it is the first that allows a comprehensive assessment of brain metabolism, CPP, and brain oxygenation abnormalities seen in patients with GCE. Although a causative relationship cannot be proven using observational data alone, our findings may support blood flow augmentation in patients with GCE.

Discussion

GCE is common in patients with poor-grade SAH and leads to a poor outcome.\(^1\) Despite advances in monitoring techniques, pathophysiological mechanisms are incompletely understood. Rapid increase of ICP and brain circulatory arrest in the initial minutes after onset of SAH are followed by a lasting reduction of cerebral blood flow and may result in cytotoxic cerebral edema.\(^{12,13}\) The combination of substrate deficiency and cellular (mitochondrial) dysfunction results in brain metabolic distress indicated by markers of anaerobic metabolism.\(^6\) Vasogenic edema may follow at the time when irreversible tissue damage and the breakdown of the blood–brain barrier occur.\(^{14}\) This irreversible neuronal cell loss occurs between the third and seventh days after bleeding,\(^{15,16}\) leaving a potential therapeutic window of 3 days after ictus. Therapeutic interventions restoring microcirculation after SAH in humans are limited. Raising mean arterial pressure targets can only be contemplated after clip or coil embolization of the aneurysm. Interventions should ideally start at an earlier time. Hypertonic solutions decrease brain water content and restore cerebral perfusion. Hypertonic saline is an effective osmotic agent with a high reflection coefficient at the blood–brain barrier resulting in brain shrinkage with ICP decrease.\(^{17}\) In prehospital resuscitation of patients with trauma and severe traumatic brain injury,\(^{18,19}\) hypertonic saline has been proven beneficial most likely due to its osmotic potency. Mobilization of parenchymal and intraendothelial water restores intravascular volume and improves regional cerebral blood flow,\(^{20}\) which enhances cerebral oxygen delivery in patients with traumatic brain injury and SAH with\(^{21,22}\) and without intracranial hypertension.\(^{23}\) Increase in cardiac output, increase in oxygen delivery, and reduction of oxygen extraction were also observed when hypertonic solutions were infused over a time of approximately 20 minutes in severely brain-injured patients.\(^{22}\) There are no trials of early brain resuscitation in patients with GCE after SAH; however, animal data suggest that early brain resuscitation with hypertonic saline improves neurological recovery and, when given in combination with dextran, exhibits survival benefit for neurons.\(^{16,24}\) Considering that the maximum brain water content is not seen until 24 hours and that morphological damage may not occur before 72 hours after ictus,\(^{15}\) early initiation of a such a therapeutic intervention may be of benefit. In our series, higher CPP was associated with improved brain metabolism.

The median CPP in our patients was 92 mm Hg, which may be higher than in other intensive care units. Current guidelines recommend a CPP >60 mm Hg.\(^8\) In general, blood pressure goals are liberalized after the aneurysm is secured. A European group investigating the effect of blood pressure variability on outcome report a median CPP >110 mm Hg in 105 patients with SAH.\(^{25}\) Another driving factor for a high CPP is the occurrence of cerebral vasospasm. Bijlenga and colleagues reported an optimized CPP in this group of 98±4 mm Hg.\(^{26}\) A high CPP may also reflect a physiological response in the setting of preserved cerebral autoregulation. In fact, PRx was lower in our patients with GCE, although not in the widely accepted range of preserved autoregulation. This has to be further investigated if a high CPP can serve as marker for severe injury in patients with SAH with GCE.
We did not find a difference in PbtO2 in patients with and without GCE. PbtO2 is a measure of oxygen diffusion more than delivery. Moreover, mitochondrial dysfunction may lead to failure in consumption of oxygen in patients with GCE and result in energy failure with increase in LPR despite normal PbtO2 values. There was no difference in occurrence of fever, seizures, or ICP crisis between our groups; however, all of these complications may be associated with brain metabolic distress. Based on the present findings alone, we cannot provide information whether brain MC is a treatable condition in these patients. However, a valid approach would be to try to optimize and treat MC in an attempt to improve GCE.

Our results are not in the line with a recently published observational trial including 52 patients with SAH. The authors observed a higher brain lactate and pyruvate but not LPR level in patients with admission GCE and interpreted their findings as cerebral hypermetabolism in the recovery phase after SAH. The most likely explanation is that our study included a group of more severe patients (19% World Federation of Neurological Surgeons V versus 33% Hunt & Hess 5 in our patients with GCE) supported by the higher LPR and lower interstitial glucose level in our patients with GCE. Additionally, only 64% of their patients had loss of consciousness in the GCE group compared with 100% in our study. Unfortunately, they did not report data on ICP, CPP, and hospital complications, which might have contributed to their findings. A higher ICP may minimize energy delivery and increase the demand leading to anaerobic metabolism. Moreover, hypermetabolism may be a result of fever, seizures, or cerebral ischemia.

In this study, we did not measure local brain perfusion. Although CPP and mean transcranial Doppler velocities did not differ between groups, a subgroup analysis of patients with GCE suggested a metabolic benefit of increased CPP. Based on the assumption of autoregulatory failure in patients with GCE, a higher CPP may directly translate to better energy supply for brain tissue with secondary improvement of cerebral metabolism. This finding was not reproducible in non-GCE patients. Pressure reactivity index (PRx) was high in both groups (PRx, refer to reference 28). Our analysis of PRx has some methodological limitations. Taking the daily averaged data on PRx may not represent autoregulatory status appropriately. We might have over- or underestimated PRx in each group. Moreover, this index is based on the correlation coefficient of ICP and mean arterial pressure and may therefore not properly represent local brain homeostasis.

Other potential weaknesses of this study deserve mention. The sample size is relatively small and no causative association between GCE and brain metabolism can be made based on observational data. These results are primarily hypothesis-generating and should be considered as preliminary data. Secondarily, we did not monitor the first day after SAH. Metabolic changes may differ from the following monitoring days. Third, changes in brain and systemic variables cannot be attributed solely to GCE. To minimize this risk, we carefully tried to control for confounders. Fourth, inclusion criteria were based on the institutional criteria for multimodal neuromonitoring. This may have introduced a selection bias, although patients with GCE clinically rarely present without an altered level of consciousness and were therefore likely selected for neuromonitoring. On the other hand, critically ill patients not included in our monitoring based on early withdrawal of care might have aggravated the observed differences in brain metabolism.

Conclusions

In conclusion, our findings suggest that in patients with poor-grade SAH, GCE is associated with brain metabolic distress and increasing energy delivery to the brain may improve brain metabolism. Furthermore, investigations elucidating pathomechanisms underlying the development of GCE after SAH should combine animal models, advanced imaging, and invasive multimodality neuromonitoring techniques. Invasive neuromonitoring may verify findings from animal models such as the observation that the glial water channel protein aquaporin-4 is fundamental in the development of GCE in the mouse model of SAH. Intervention trials studying the ability to modulate the development of GCE for example by activation or upregulation of aquaporin-4 could be powered to neuromonitoring or imaging end points.

Acknowledgments

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Disclosures

None.

References


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http://stroke.ahajournals.org/content/suppl/2016/03/31/STROKEAHA.110.604488.DC2

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## Table S1 Hospital Complications and Outcome in Relation to Global Cerebral Edema (N = 39)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>GCE</th>
<th>No GCE</th>
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<tbody>
<tr>
<td>Hospital Complications</td>
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</tr>
<tr>
<td>Fever &gt;38.6 °C</td>
<td>18 (75)</td>
<td>8 (53)</td>
</tr>
<tr>
<td>Anemia treated with blood transfusion</td>
<td>13 (54)</td>
<td>10 (67)</td>
</tr>
<tr>
<td>Aneurysm rebleeding</td>
<td>5 (21)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Herniation</td>
<td>12 (50)</td>
<td>6 (40)</td>
</tr>
<tr>
<td>Hydrocephalus treated with CSF diversion</td>
<td>21 (88)</td>
<td>11 (73)</td>
</tr>
<tr>
<td>Hyperglycemia (&gt; 11 mmol/L)</td>
<td>23 (96)</td>
<td>12 (80)</td>
</tr>
<tr>
<td>Hypernatremia (&gt;150 mmol/L)</td>
<td>18 (75)</td>
<td>8 (53)</td>
</tr>
<tr>
<td>Hyponatremia (&lt; 130 mmol/L)</td>
<td>4 (17)</td>
<td>5 (33)</td>
</tr>
<tr>
<td>Hypotension requiring vasopressors</td>
<td>11 (46)</td>
<td>4 (27)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>20 (83)</td>
<td>11 (73)</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>11 (46)</td>
<td>7 (47)</td>
</tr>
<tr>
<td>Seizure</td>
<td>8 (33)</td>
<td>3 (20)</td>
</tr>
<tr>
<td>Triple-H therapy</td>
<td>15 (63)</td>
<td>7 (47)</td>
</tr>
<tr>
<td>Clinical delayed cerebral ischemia</td>
<td>3 (13)</td>
<td>5 (33)</td>
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<tr>
<td>Radiographic complications</td>
<td></td>
<td></td>
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<tr>
<td>Intracerebral hematoma</td>
<td>12 (50)</td>
<td>8 (53)</td>
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<tr>
<td>Ischemia</td>
<td>19 (79)</td>
<td>8 (53)</td>
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<tr>
<td>Outcome</td>
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<tr>
<td>ICU LOS</td>
<td>18 (14-25)</td>
<td>13 (10-20)</td>
</tr>
<tr>
<td>Hospital LOS</td>
<td>25 (15-37)</td>
<td>17 (14-25)</td>
</tr>
<tr>
<td>Hospital mortality</td>
<td>5 (21)</td>
<td>4 (27)</td>
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<tr>
<td>3 months modified Rankin Scale</td>
<td>5 (4-6)</td>
<td>5 (3-6)</td>
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<tr>
<td>1-3</td>
<td>4 (17)</td>
<td>5 (33)</td>
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<td>4</td>
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<td>6</td>
<td>10 (42)</td>
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Values are presented as median (IQR) or number (%); GCE = global cerebral edema, ICU = intensive care unit, LOS = length of stay
全脑水肿在动脉瘤性蛛网膜下腔出血 (subarachnoid hemorrhage, SAH) 之后是常见的，可显著影响预后。人们尚未完全认识其病理生理机制 [1]。初期出血可引起快速的颅内压 (intracranial pressure, ICP) 增高和脑血流下降 [2,3]，导致输送到脑的代谢底物在其需求量增加时下降。动物实验数据提示，细胞内钙离子 (Ca+) 增加、兴奋性毒性以及线粒体功能障碍可引起细胞危象，从而导致细胞毒性脑水肿 [4]。然而，现有动物模型不能令人信服地复制出发生在人类自发性动脉瘤性 SAH 的病理生理。这就是为什么人的生理数据可能是更好地认识 SAH 后早期所见病理生理机制的关键。有创性脑监测可以评估脑代谢，并且可以根据能量供应缺乏 (葡萄糖、氧气)、线粒体功能异常或细胞需求增加而在发生不可逆脑损害之前数小时提示处在代谢危象的脑组织 [5,6]。最近，SAH 后全脑水肿 (global cerebral edema, GCE) 被发现与由脑细胞外乳酸和丙酮酸水平升高所提示的脑能量代谢增加相关 [7]。GCE 与乳酸 / 丙酮酸比值 (lactate-pyruvate ratio, LPR) 没有相关性，而有关脑灌注和脑组织氧合 (brain tissue oxygenation, PbtO2) 的数据未曾被报道过 [7]。

我们将 SAH 后有 GCE 患者的脑代谢类型与 PbtO2 和脑灌注结合起来进行观察。我们检验了脑低灌注情况下 GCE 与脑代谢危象有关这一假设。

### 材料与方法

**患者**

2006 年 6 月至 2008 年 12 月，39 例被收治到哥伦比亚大学医学中心神经科重症监护单元的分级不良的 SAH 患者根据我们机构的研究方案接受了脑多
模式监测。将数据作为经本地机构审查委员会批准的一个正在进行中的前瞻性数据库的一部分进行采集。

全脑水肿

由高级研究人员（J.C., N.B., K.L., S.A.M.）基于首次脑CT扫描诊断GCE，正如以前所描述的那样；(1) 半球脑沟和基底池完全或几乎完全消失；以及(2) 在半卵圆中心层面上呈两侧或广泛的大脑半球灰-白质界限的破坏，这是由于灰质和白质之间正常界限变模糊或向周围弥漫性“指样”（finger-like）扩展所致[1]。

一般处理

针对SAH患者的治疗符合指南[8]。血液动力学和液体管理的目标是维持脑灌注压（cerebral perfusion pressure, CPP）>60 mmHg 和 ICP<20 mmHg[9]。

颅内监测

在监测开始时，所有患者的格拉斯哥昏迷评分（Glasgow Coma Scale，GCS）≤8 分。如果(1) 患者在随后48 小时内不太可能恢复意识；和(2) 患者在接下去的48 小时存活的可能性大，则开始多模式监测。这一决定是由神经重症监护单元主治医师和神经外科医师组长做出的。采用额部入路（接受动脉瘤夹闭手术患者的开颅的对侧[n=22; 56%]; 血管内治疗后有弥漫性SAH患者的非优势半球额部或有偏侧SAH患者的同侧）, 将一个三腔螺栓固定在颅骨钻孔处。将一个CMA-70 微透析导管（CMA/Microdialysis, Stockholm, Sweden）插入脑实质并分析每小时的取样（CMA-600; CMA/Microdialysis）。探头插入和取样开始之后至少历经1 小时才能使探头插入所致改变的正常化。采用Licox Clark-type 探头（Licox GMBHMT, Kiel-Germany; Integra Neurosciences, Plainsborgough, NJ）测定PbtO2。用一个脑实质探头(Integra Neurosciences) 监测ICP。操作后即刻行脑CT 扫描确定监测导管在脑白质的位置。代谢危象（metabolic crisis, MC）被定义为微透析液中葡萄糖<0.7 mmol/L 和LPR>40[10,11]。

统计分析

将微透析、PbtO2 以及脑灌注压的测定值进行日平均和锁定距 SAH 起病的时间。组间比较酌情采用Mann-Whitney U 检验（Bonferroni 校正）、Student t 检验、卡方检验以及Fisher 精确检验。计算每位患者处在代谢危机（LPR>40）和MC 状态的时间占总的神经监测时间的比例。如无特别指出，数据表达为均值±标准差、中位数（四分位数）或例数（%）。计算多变量一般线性模型以确定GCE 与脑代谢、PbtO2 以及脑灌注随时间推移的关系。采用带自动回归工作相关矩阵的广义估计方程处理每个受试者的多项观察指标。采用对数转换对非正态分布的连续变量进行正态化。

结果

患者特征及临床经过

患者的基线特征见表。共分析了来自39 例SAH患者的3402 份微透析标本。两组间入院时 GCS 评分无差异（P=0.2）。所有入院时 Hunt &Hess 分级 1-3 级的9 例患者均因脑积水、再出血以及脑缺血 (各3 例患者) 而在住院期间恶化至 Hunt & Hess 分级 4-5 级。有 GCE 的患者 (n=24[62%]) 年龄较小 (49±13 和61±14 岁，P<0.01) 且起病时都有意识丧失 (对33%,
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图 1 伴（■）和不伴（□）全脑水肿（GCE）患者蛛网膜下腔出血后第 2 至 10 天代谢应激（LPR>40，A）的平均（标准误）百分比和乳酸/丙酮酸比值（LPR，B）、丙酮酸（C）、脑葡萄糖（D）的日均值（标准误）的差异。

两组间入院时其他变量和治疗选择（开颅夹闭和血管内栓塞）没有差异。首次 CT 扫描显示偏侧 SAH 的 12 例患者在两组的分布相等（有 GCE/无 GCE：n=7/5（29%/33%），P=0.8）。导管头远端皮层区域插入血肿（<1 cm）见于 2 例患者。距神经监测的平均时间在两组中均为 2 天（P=0.9）。两组间住院期间并发症的发生率没有显著差异（补充表 1：http://stroke.ahajournals.org）。

GCE 和脑代谢

在神经系统监测的最初 12 小时内，入院时 GCE 与可引起 MC 发作比例增高（15% 和 2%，P<0.05）的脑丙酮酸（102±48 µmol/L 和 137±38 µmol/L，P<0.05）和葡萄糖（1.3±0.7 mmol/L 和 1.8±1.1 mmol/L，
可能影响，以中位数 (94 mmHg) 为界分为 2 个CPP 组。在伴 GCE 患者中，CPP 增高与 LPR 降低相关 (图 3)；GEE 分析发现有显著性影响的是高 CPP (P=0.003) 和 SAH 后天数 (P=0.03) 而非它们之间的相互作用 (P=0.06)。在不伴 GCE 患者中，CPP 对 LPR 没有影响 (P=0.6，数据未提供)。这些组之间的ICP 的差异无显著性。

GCE 和代谢应激：与预后的关系

采用改良 Rankin 量表评估出院时的预后。改良 Rankin 量表 5 和 6 分的患者被认为有预后不良。各组间 Hunt & Hess 分级、年龄以及改良 Fisher 分级无显著性差异。与预后良好患者 (N=15, 38%) 相比，预后不良的患者 (N=24, 62%) MC (17%±25% 和 5%±11%, P=0.05) 和 LPR>40 (35±38 和 12±25, P<0.05) 占监测时间的百分比较高。死亡方式几乎全部是停止医疗。

讨论

我们的研究结果提示 SAH 后 GCE 与脑代谢性应激有关。本研究数据使得对见于 GCE 患者的脑代谢、CPP 以及脑氧代谢方面的异常进行全面评价首次成为可能，因此具有潜在的重要性。尽管单纯采用观察性研究数据也许不会证实因果关系，但是我们的研究结果可能支持 GCE 患者有脑血流量的增加。

GCE 常见于分级不良的 SAH 患者且可导致不良预后 [1]。尽管监测技术有诸多进展，但其病理生理机制仍没有被完全了解。SAH 起病后最初数分钟之内出现 ICP 的快速增高和脑循环的停止，继之持续性脑血流量减少，并可导致细胞毒性脑水肿 [12,13]。代谢底物缺乏与细胞 (线粒体) 功能障碍一起可导致以无氧代谢为标志的脑代谢应激。发生不可逆性组织损害和血脑屏障破坏之后会出现血管源性水肿 [14]。不可逆神经元丧失发生在出血后第 3 至 7 天之间 [15,16]，因此起病后有一个为期 3 天的潜在治疗时间窗。在人类 SAH 之后，能恢复微循环的治疗干预措施受到限制。只有在开颅夹闭或血管内栓塞动脉瘤之后，才可考虑升高平均动脉压的控制范围。如有可能，应尽早开始干预。高张溶液可减少脑组织中水的含量并恢复脑灌注。高张盐水是一种血脑屏障反射系数高的有效渗透剂，可引起脑组织脱水和 ICP 降低 [17]。在创伤和严重创伤性脑损伤患者的院前复苏中 [18,19]，高张盐水的益处已得到证实，而这种益处最可能来
自其渗透压。脑实质和血管内皮内水的流动可恢复血管内容量并改善局部脑血流量 [20]，从而使伴 [21,22]和不伴 [23]颅高压的创伤性脑损伤和 SAH 患者的脑组织氧的输送得到提高。有研究也曾观察到脑外伤患者经过大约 20 分钟的高张盐水输注后出现氧输出量增加、氧输送增加以及氧摄取减少 [23]。还没有关于 SAH 之后伴 GCE 患者早期脑复苏的临床试验。然而，动物实验数据提示，早期高张盐水脑复苏可促进神经功能恢复，而当与右旋糖酐合用时，可提高神经元的存活率 [16,24]。鉴于在起病后 24 小时内脑组织水含量不会达到高峰而在 72 小时之前可能不会发生形态学损伤，早期开始这种治疗干预可能是有益的。在我们的病例系列中，高 CPP 可改善脑代谢。本组患者 CPP 中位数是 92 mmHg，可能高于其它重症监护单元的数值。目前指南建议 CPP>60 mmHg [8]。通常，在处理好动脉瘤之后，血压控制范围被放宽。欧洲一个研究组研究了血压变异对预后的影响，105 例 SAH 患者 CPP 的中位数>110 mmHg [25]。CPP 增高的另一个驱动因素是脑血管痉挛的发生。Bijlenga 和其同事报告的 SAH 患者最佳 CPP 是 98±4 mmHg [26]。CPP 增高可能也反映出在未破坏脑自动调节情况下的一种生理反应。事实上，本组中有 GCE 患者的 PRx 虽然在未已得到广泛认可的未破坏脑自动调节范围之内，但却是较低的。需要进一步研究探讨是否 CPP 增高可以作为伴 GCE 的 SAH 患者的严重损伤的标记。我们并没有发现 PbtO2 在伴和不伴 GCE 患者之间有差异。PbtO2 是氧弥散而非氧输送的一个测定指标 [27]。而且，线粒体功能异常可以导致有 GCE 患者的氧消耗衰竭，并且可以在 PbtO2 数值正常的情况下引起能量衰竭和 LPR 增高 [8]。发热、抽搐发作或 ICP 危象的发生率在我们的病例组之间没有差异，然而，所有这些并发症都与脑代谢应激有关。仅凭本研究结果，我们还不能提供关于这类患者的脑 MC 是否可治疗方面的信息。然而，一个可信的途径将是设法减轻和治疗 MC 以试图改善 GCE。我们的结果与最近发表的一项对 52 例 SAH 患者的观察性试验不一致 [7]。此研究的作者发现脑乳酸和丙酮酸而非 LPR 的浓度在入院时有 GCE 的患者中是增高的，并将其结果解释为 SAH 后恢复期的脑高代谢。最可能的解释是，我们的研究纳入了一组更严重的患者（我们的伴 GCE 患者中 19% 为世界神经外科医师分级 IV 级，33% 为 Hunt&Hess 分级 5 级），支持这一解释的是在我们的 GCE 患者中 LPR 较高而间质葡萄糖浓度较低。此外，与在我们研究中占 100% 相比，有意识丧失者在他们的 GCE 组患者中仅占 64% [7]。不幸的是，他们没有报告关于 ICP、CPP 以及住院期间并发症的数据，这些数据或许会对他们的结果有帮助 [7]。ICP 增高可减少能量输送，并且增加对无氧代谢的需求。此外，高代谢可能是发热、抽搐发作或脑缺血的结果。本研究中，我们没有测定局部脑灌注。虽然 CPP 和平均经颅多普勒血流速度在两组间无差异，但是对 GCE 患者的亚组分析提示 CPP 增高对脑代谢有益。基于 GCE 患者有脑自动调节衰竭的假设，CPP 增高可直接转化成更好的脑组织能量供应，从而改善脑代谢。这一结果在伴 GCE 的患者中是不能复制的。PRx 在两组中均增高（PRx，见参考文献 28）。我们对 PRx 的分析有一些方法学上的局限性。采集每天 PRx 的平均数据或许不能合理地代表脑自动调节的状态 [28]。我们很可能高估或低估每组的 PRx。而且，此指数是以 ICP 和平均动脉血压的相关系数为依据，因此也许不能正确地体现局部脑自身平衡状态。值得一提的是，本研究还有其它潜在缺陷。样本量相对较小，而且基于观察性数据不能得出 GCE 与脑代谢之间有因果关系。这些结果旨在产生假说，而且应被视为初步数据。其次，我们对患者 SAH 后第 1 天没有进行监测，而第 1 天的代谢改变可能与此后几天所监测到的情况不同。第三，脑部指标和全身指征的改变不能单纯归咎于 GCE。为了降低这种风险，我们谨慎地对于扰因素进行了控制。第四，病例纳入标准以本研究机构多模式神经监护的标准为依据，这可能造成了选择性偏倚，尽管伴 GCE 患者在临床上很少没有意识水平的改变而因此容易被选择作神经监测。另一方面，因早期停止医疗而未被纳入监测的重症患者或许会使观察到的脑代谢差异加大。结论总之，我们的研究结果提示，在分级不良的 SAH 患者中，GCE 与脑代谢应激有关，而增加脑代谢能量的输送可改善脑代谢。此外，阐明 SAH 后发生 GCE 的病理机制的研究应将动物模型、先进的影像学以及有创性多模式神经监测技术结合在一起。有创性神经监测可以证实来自于动物模型的研究结果，诸如胶质细胞水通道蛋白 -4(aquaporin-4) 是小
Global Cerebral Edema After SAH


