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;42:1534-1539.)

Key Words: global cerebral edema ■ microdialysis ■ subarachnoid hemorrhage

Global cerebral edema is common after aneurysmal subarachnoid hemorrhage (SAH) and significantly impacts outcome. Pathophysiological mechanisms are incompletely understood. The initial bleeding is associated with a rapid increase in intracranial pressure (ICP) and reduction in cerebral blood flow, 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. 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. Recently, global cerebral edema (GCE) after SAH was associated with increased cerebral energy metabolism indicated by increased cerebral extracellular levels of lactate and pyruvate. There was no association with GCE and lactate–pyruvate ratio (LPR) and data on cerebral perfusion and brain tissue oxygenation (PbtO2) are not reported.

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
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 SAH. 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<0.001). 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),
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 \( (P=0.05; \text{Figure 2A}) \). 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.

![Figure 1. Differences in mean (SEM) percent of metabolic distress (LPR > 40, A) and daily mean (SEM) values of lactate-pyruvate ratio (LPR, B), pyruvate (C), and cerebral glucose (D) at 2 to 10 days after subarachnoid hemorrhage in patients with (■) and without (□) global cerebral edema (GCE).](image)

![Figure 2. Differences in daily mean (SEM) values of intracerebral pressure (ICP, A), cerebral perfusion pressure (CPP, B), brain tissue oxygen tension (PbtO2, C), and pressure reactivity index (PRx, D) at 2 to 10 days after subarachnoid hemorrhage in patients with (■) and without (□) global cerebral edema (GCE). Comparisons between the 2 groups were nonsignificant.](image)
GCE (P<0.03 and <0.001, respectively). No significant interactions were identified (Figure 1B).

CPP and Brain Metabolism
To investigate a possible effect of CPP on brain metabolism in patients with and without GCE, 2 CPP groups were formed separated at the median (94 mm Hg). In patients with admission GCE, a higher CPP was associated with lower LPR (Figure 3); GEE analysis identified significant effects of high CPP (P=0.003) and days post-SAH (P=0.03) but not of their interaction (P=0.06). CPP did not have an effect on LPR in patients without admission GCE (P=0.6; graph not shown). There was no difference in ICP between these groups.

GCE and Metabolic Distress: Relationship With Outcome
Outcome at hospital discharge was assessed using modified Rankin Scale. Patients with modified Rankin Scale 5 and 6 were considered to have a poor outcome. Hunt & Hess grade, age, and modified Fisher grade did not differ significantly between groups. Patients with poor outcome (N=24, 62%) had higher percentage of monitored time in MC (17%±25% versus 5%±11%, P<0.05) and LPR >40 (35±38 versus 12±25, P<0.05) compared with those with a good outcome (N=15, 38%). Mode of death was almost exclusively withdrawal of care.

Discussion
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.

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 intracerebrothelial water restores intravascular volume and improves regional cerebral blood flow,20 which enhances cerebral oxygen delivery in patients with traumatic brain injury and SAH with21,22 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 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

We thank the attendings, fellows, and nurses of the Neuroscience Intensive Care Unit for their overall support of this project.

Disclosures

None.

References


Supplemental Table S1

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

<table>
<thead>
<tr>
<th><strong>Intervention</strong></th>
<th><strong>GCE</strong></th>
<th><strong>No GCE</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hospital Complications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aneurysm clipping</td>
<td>13 (54)</td>
<td>9 (60)</td>
</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>
</tr>
<tr>
<td><strong>Radiographic complications</strong></td>
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<td></td>
</tr>
<tr>
<td>Intracerebral hematoma</td>
<td>12 (50)</td>
<td>8 (53)</td>
</tr>
<tr>
<td>Ischemia</td>
<td>19 (79)</td>
<td>8 (53)</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td></td>
<td></td>
</tr>
<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>
</tr>
<tr>
<td>3months modified Rankin Scale</td>
<td>5 (4-6)</td>
<td>5 (3-6)</td>
</tr>
<tr>
<td>1-3</td>
<td>4 (17)</td>
<td>5 (33)</td>
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<tr>
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<td>5 (21)</td>
<td>1 (7)</td>
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<tr>
<td>5</td>
<td>5 (21)</td>
<td>4 (27)</td>
</tr>
<tr>
<td>6</td>
<td>10 (42)</td>
<td>5 (33)</td>
</tr>
</tbody>
</table>

Values are presented as median (IQR) or number (%); GCE = global cerebral edema, ICU = intensive care unit, LOS = length of stay.
背景和目的：全脑水肿常见于分级不良的蛛网膜下腔出血患者，且与不良预后相关。目前没有靶向治疗，主要是由于对其机制的了解不全面。

方法：本研究是一项前瞻性观察性研究，纳入了连续收治的39例多模式神经监测的分级不良的蛛网膜下腔出血患者。分析了微透析液中乳酸/丙酮酸比值、脑代谢危机（乳酸/丙酮酸比值>40和脑葡萄糖<0.7 mmol/L）发作、脑组织氧张力、脑灌注压及经颅多普勒超声血流速度。

结果：平均年龄54岁（45-61岁），62%为女性。与没有全脑水肿的患者相比，入院时有全脑水肿的患者（n=24[62%]）脑代谢危机的发生率在监测的最初12小时内（n=15[15%]和2%；P<0.05）和整个神经监测期间（20%和3%；P<0.001）较高。两组之间脑组织氧张力及脑灌注压没有差异；然而，在有全脑水肿的患者中，脑灌注压增高与乳酸/丙酮酸比值降低相关（P<0.05）。脑代谢危机发作与不良预后（改良Rankin量表评分5或6，P<0.05）相关。

结论：在分级不良的蛛网膜下腔出血患者中，全脑水肿与早期代谢危机相关。

关键词：全脑水肿，微透析，蛛网膜下腔出血

(Stroke. 2011;42:1534-1539. 北京天坛医院神经内科 史楠 李欣 译 曹亦宾 王拥军 校)
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双侧的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散性“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) 患者在接下来的 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 GMBH, Kiel-Germany; Integra Neurosciences, Plainsborough, 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 校正的)、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象 (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 (%)

结果

患者特征及临床经过

表 基线特征 (N=39 例)

<table>
<thead>
<tr>
<th></th>
<th>年龄, 岁</th>
<th>性别 ( 女性 )</th>
<th>高血压</th>
<th>起病时意识丧失</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>54(45-61)</td>
<td>24(62)</td>
<td>15(39)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>29(74)</td>
</tr>
</tbody>
</table>

SAH 总评分 18(12-24)
IVH 总评分 4(2-6)
全脑水肿 3(8)
入院时 CT 扫描上有脑梗死 3(8)
入院时 CT 扫描上有脑出血 16(41)
入院时生理指标
收缩压, mmHg 160(132-180)
血糖, mmol/L 9.7(8.2-11.3)

数值表达为均数 ( 标准差 )，中位数 ( 四分位数 ) 或例数 (%)

SAH, 蛛网膜下腔出血；IVH, 脑室内出血。

患者处在代谢危象 (LPR >40) 和 MC 状况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 ± 标准差或中位数 ( 四分位数 )。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。所有统计学比较均使用 SPSS 18(SPSS Inc, Chicago, IL)。P <0.05 时，差异被认为有显著性。

结果

表 基线特征 (N=39 例)
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 天内代谢激活（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）的日平均值（标准误）的差异。

图 2 伴（■）和不伴（□）全脑水肿（GCE）患者蛛网膜下腔出血后第 2 至 10 天内颅内压（ICP，A）、脑灌注压（CPP，B）、脑组织氧张力（PbtO2，C）以及压力反应指数（PRx，D）数值的日均数（标准误）的差异。两组之间的比较无显著性差异。
P=0.07) 浓度的降低有关。SAH 后监测的第2至10天期间，伴 GCE 患者 MC 发作（20%和3%，P<0.001）、LPR>40（42%和9%，P=0.001；图1A）的比例较高且有脑低糖症倾向（<0.7 mmol/L，33%和18%。P=0.1）。

伴和不伴 GCE 患者每天神经系统监测参数的变化

伴 GCE 患者的总体 LPR 值较高（P<0.05），而总体丙酮酸浓度较低（P<0.05）。不伴 GCE 患者的脑葡萄糖浓度在监测的最初几天较高（P<0.01），并随着时间的推移显著下降（P<0.001）至第7天时差异没有显著性（图1B-D）。伴 GCE 患者倾向于有较高的 ICP（P=0.05；图2A）。两组间 CPP、神经系统监测探头同侧大脑中动脉流速（数据未提供）、PbtO2或压力反应指数（PRx；图2B-D）的差异没有显著性。为了证实 GCE 的存在与 LPR 值增高和丙酮酸浓度降低之间的相关性，广义估计方程模型的计算利用 SAH 后的天数和 GCE 的存在作为系数，包括重要的共变量（性别、入院时 GCS 值）。这些模型证实，LPR 升高和脑丙酮酸水平降低见于 SAH 后的早期（SAH 当天的显著性分别为 P<0.01）和那些有 GCE 患者（分别为 P<0.03和P<0.001）。未发现显著性的相互作用（图1B）。

CPP和脑代谢

为了研究 CPP 对伴和不伴 GCE 患者脑代谢的影响，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 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分的患者被认为是预后不良。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液 [20]，从而促使 [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。有研究也曾观察到严重脑外伤患者经过大约 20 分钟的高张盐水输注后出现心输出量增加、氧输送增加以及氧摄取减少 [21]。还没有关于 SAH 之后伴 GCE 患者早期脑复苏的临床试验。然而，动物实验数据显示，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，动脉压力监测对预后的影响 [105]。105 例 SAH 患者 CPP 的中位数>110 mmHg [25]。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 虽然不在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。值得注意的是，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随后几天所监测到的情况不同。第三，脑部指标和全身指标的改变不能单纯归咎于 GCE。为了降低这种风险，我们谨慎地对干扰因素进行了控制。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 患者在临床中较少没有意识水平的改变而因此容易被选择为做神经监测。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
鼠 SAH 模型发生 GCE 的关键这一发现 [30]。神经监测或影像学终点应该能使研究某种干预措施对 GCE 发生发展的调控能力（例如通过激活或上调水通道蛋白 -4）的干预性试验更有说服力。

参考文献