Cerebral Perfusion Pressure Thresholds for Brain Tissue Hypoxia and Metabolic Crisis After Poor-Grade Subarachnoid Hemorrhage

J. Michael Schmidt, PhD; Sang-Bae Ko, MD; Raimund Helbok, MD; Pedro Kurtz, MD; R. Morgan Stuart, MD; Mary Presciutti, BSN, RN; Luis Fernandez, MD; Kiwon Lee, MD; Neeraj Badjatia, MD, MSc; E. Sander Connolly, MD; Jan Claassen, MD; Stephan A. Mayer, MD

Background and Purpose—To identify a minimally acceptable cerebral perfusion pressure threshold above which the risks of brain tissue hypoxia (BTH) and oxidative metabolic crisis are reduced for patients with subarachnoid hemorrhage (SAH).

Methods—We studied 30 poor-grade SAH patients who underwent brain multimodality monitoring (3042 hours). Physiological measures were averaged over 60 minutes for each collected microdialysis sample. Metabolic crisis was defined as a lactate/pyruvate ratio \( \geq 40 \) with a brain glucose concentration \( \leq 0.7 \) mmol/L. BTH was defined as \( P_{btO2} < 20 \) mm Hg. Outcome was assessed at 3 months with the Modified Rankin Scale.

Results—Multivariable analyses adjusting for admission Hunt-Hess grade, intraventricular hemorrhage, systemic glucose, and end-tidal CO\(_2\) revealed that cerebral perfusion pressure \( 
\leq 70 \) mm Hg was significantly associated with an increased risk of BTH (OR, 2.0; 95% CI, 1.2–3.3; \( P = 0.007 \)) and metabolic crisis (OR, 2.1; 95% CI, 1.2–3.7; \( P = 0.007 \)). Death or severe disability at 3 months was significantly associated with metabolic crisis (OR, 5.4; 95% CI, 1.8–16; \( P = 0.002 \)) and BTH (OR, 5.1; 95% CI, 1.2–23; \( P = 0.03 \)) after adjusting for admission Hunt-Hess grade.

Conclusions—Metabolic crisis and BTH are associated with mortality and poor functional recovery after SAH. Cerebral perfusion pressure levels \( \leq 70 \) mm Hg was associated with metabolic crisis and BTH, and may increase the risk of secondary brain injury in poor-grade SAH patients. (Stroke. 2011;42:1351-1356.)

Key Words: brain tissue oxygen tension ■ cerebral microdialysis ■ cerebral perfusion pressure ■ subarachnoid hemorrhage

Brain tissue oxygen pressure (\( P_{btO2} \)) and microdialysis monitoring\(^2,3 \) are used to indicate impending ischemia from vasospasm, and findings are related to outcome\(^4,5 \) for patients with poor-grade subarachnoid hemorrhage (SAH). SAH patients with cerebral vasospasm are more vulnerable to infarction when brain oxygen tension is dependent on cerebral perfusion pressure (CPP), a phenomenon referred to as oxygen autoregulation failure.\(^6,7 \) Brain tissue hypoxia and elevation of the lactate/pyruvate ratio after SAH has been linked to an increased risk of symptomatic vasospasm, cerebral infarction, hospital mortality, and poor functional outcome after SAH.\(^4,8–10 \)

Blood pressure is often manipulated after SAH to improve cerebral perfusion and is a critical component of hypertensive hypervolemic therapy used to treat delayed cerebral ischemia from vasospasm.\(^1 \) However, in poor-grade SAH there is limited ability to detect delayed cerebral ischemia clinically.\(^11 \) Therefore, it would be of interest to know if there is an ideal maintenance CPP threshold above which the risk of cerebral ischemia is minimized. Guidelines exist that recommend maintaining CPP between 50 and 70 mm Hg after severe traumatic brain injury,\(^12 \) but it has been difficult to generate data to support specific CPP targets in postoperative SAH patients.\(^13 \) Using simultaneous \( P_{btO2} \) and microdialysis multimodality neuromonitoring, we sought to identify a CPP threshold that is associated with reduced risk of brain tissue hypoxia and oxidative metabolic crisis in comatose patients with SAH.

Materials and Methods

Study Population

Between May 2006 and December 2009, 106 poor-grade SAH patients were consecutively admitted to the neurological intensive care unit at Columbia University Medical Center. Thirty patients who underwent a minimum of 12 hours of simultaneous intracranial pressure, \( P_{btO2} \), and microdialysis monitoring as part of their clinical...
care were included in the present analysis. Of the 76 patients who were excluded, 57 did not undergo monitoring because of early death or decisions to limit aggressive care, 10 were excluded because they had $P_{br}O_2$ or microdialysis data but not both (because of technical problems), 5 had contraindications for the procedure to place the probes (coagulaopathy or platelet dysfunction), 4 were monitored for <12 hours, and 1 had the probes placed in infarcted tissue.

This observational study was approved by the Columbia University Medical Center Institutional Review Board. The diagnosis of SAH was established on the basis of an admission CT in all cases. Delayed cerebral ischemia was defined as clinical deterioration, cerebral infarction, or both attributable to vasospasm after adjudication of all relevant clinical information in weekly meetings by the study team.14 Outcome was assessed at 3 months with the Modified Rankin Scale.

Clinical Management
All patients received mechanical ventilation, external ventricular drainage, daily interruption of sedation, prophylactic oral nimodipine, and intravenous hydration with 0.9% saline at 1 mL/kg/h and 250 mL of 5% albumin solution every 2 hours to maintain central venous pressure >5 cm H$_2$O according to a standardized management protocol.15 CPP was targeted to avoid levels <50 mm Hg at all times. Clinical deterioration from delayed cerebral ischemia was treated with hypertensive hypervolemic therapy to maintain systolic blood pressure between 160 and 220 mm Hg as required to reverse the neurological deficit. Strict normothermia was maintained with a surface (Arctic Sun; Medivance) or endovascular (Alsius Thermogard; Zoll Circulation) cooling device. Intracranial pressure was maintained <20 mm Hg using a stepwise management strategy (cerebrospinal fluid drainage, sedation, CPP optimization, hyperventilation to $PCO_2$ 30 to 34 mm Hg, osmotherapy with mannitol and hypertonic saline, and mild hypothermia [35°C]).17 The hemoglobin threshold for blood transfusion was 7 mg/dL in the absence of ongoing myocardial or cerebral ischemia and 10 mg/dL if either condition was present. All patients were ventilated to achieve an arterial oxygen saturation $\geq$95% and $P_{br}CO_2$ of 30 to 40 mm Hg. $P_{br}O_2$ measurements were excluded from this analysis when the fraction of inspired oxygen exceeded 50%.

Data Acquisition
A high-resolution data acquisition system (BedmasterEX; Excel Medical Electronics) was used to acquire digital data every 5 seconds from General Electric Solar 8000i monitors. Heart rate, arterial blood pressure, end-tidal $CO_2$, CPP, and intracranial pressure were continuously monitored in all patients. Intracranial pressure was measured using an intraparenchymal probe (Camino; Integra Neurosciences), $P_{br}O_2$ was measured with a flexible polarographic Licox Clark-type probe (Licox GMBH), and a CMA 70 microdialysis catheter with 10-mm membrane length (CMA Microdialysis) was used to monitor cerebral metabolism.18 Probes were placed via a single burr hole at the bedside using a triple-lumen bolt in the frontal lobe ipsilateral to lateralized aneurysms when possible, or in the right frontal lobe in the case of midline aneurysms.19 Two measures of the adequacy of autoregulation, the pressure reactivity index (PRx) and the oxygen ($P_{br}O_2$) pressure reactivity index (ORx), were calculated post hoc.

Statistical Analysis
Mean arterial pressure, CPP, intracranial pressure, end-tidal $CO_2$, and $P_{br}O_2$ measures were averaged over 60 minutes preceding each microdialysis measurement. Metabolic crisis was defined as a lactate/pyruvate ratio >40 and brain glucose <0.7 mmol/L.22 Brain tissue hypoxia was dichotomized as brain tissue oxygen tension <20 mm Hg based on data demonstrating a higher risk of poor outcome below this threshold.21–28 Univariate comparisons of pooled data were performed using a generalized linear model using a binomial distribution and logit link function and extended by generalized estimating equations (GEE) using the autoregressive process to handle repeated observations within subject. SPSS 17 software was used for data analysis. $P<0.05$ was considered statistically significant.

Results
Baseline Characteristics
Thirty patients were mechanically ventilated and comatose (Glasgow Coma Scale score <9) at the initiation of neuromonitoring. A total of 3042 hours of data were recorded and analyzed (Table 1). Twelve patients (40%) had delayed cerebral ischemia from vasospasm develop; 3 experienced clinical deterioration only, 5 had clinical deterioration with cerebral infarction, and 4 had only cerebral infarction develop.

Predictors of Brain Tissue Hypoxia
Univariate analysis logistic regression (GEE) revealed that patients were 22% more likely to experience brain tissue hypoxia for every 10-mm Hg decline in CPP (OR, 1.22; 95% CI, 1.07–1.39; $P=0.002$). Mean arterial pressure and end-tidal $CO_2$ were significantly associated with brain tissue hypoxia in a univariate analysis (Table 2). In a multivariable generalized linear model (GEE), CPP was the strongest predictor of brain tissue hypoxia after adjusting for end-tidal $CO_2$ (Table 3).

Predictors of Brain Metabolic Crisis
There was a threshold effect of CPP on the likelihood of metabolic crisis, occurring 10% of the time when mean hourly CPP was >70 mm Hg compared to 24% when CPP was $\leq$70 mm Hg ($P<0.001$). In univariate analysis, metabolic crisis was significantly associated with an admission Hunt-Hess grade of 5, CT evidence of intraventricular or intraparenchymal clot, hydrocephalus, and low systemic glucose concentrations (Table 2). After adjusting for other significant factors, a multivariable logistic regression (GEE) analysis revealed that CPP was the strongest predictor of metabolic crisis, but only when CPP was $\leq$70 mm Hg (Table 3).

Relationship of CPP to Brain Tissue Oxygenation and Energy Metabolism
The probability of brain tissue hypoxia increased steadily and significantly from 19% to 47% as CPP declined from 110 to 50 mm Hg. In contrast, the probability of metabolic crisis remained <10% when CPP was between 70 and 110 mm Hg, but it doubled significantly to 24% when CPP was between 60 and 70 mm Hg, and continued to increase to $>80$% when CPP was <50 mm Hg (Figure). Compared to CPP >90 mm Hg, the CPP threshold associated with significant increases in the risk of both brain tissue hypoxia, and metabolic crisis was $\approx$70 mm Hg (Table 3).

3-Month Outcome
Seven patients (23%) had died by day 90. Among the survivors, 7 patients (23%) had mild or moderate disability (Modified Rankin Scale score 2 or 3, able to ambulate but unable to perform all activities independently), 9 (30%) had moderate-to-severe disability (Modified Rankin Scale score 4, unable to ambulate independently), and 7 (23%) had severe disability (Modified Rankin Scale score 5, bed-bound;
In this study of 30 poor-grade SAH patients, we found that death or severe disability at 3 months was significantly associated with brain metabolic crisis and tissue hypoxia, which confirm what has been observed previously. Abnormalities of $P_{bto}$, brain glucose, and lactate/pyruvate ratio were all more likely with lower CPP, with a statistically significant threshold effect occurring with levels ≤70 mm Hg. These findings suggest that maintaining CPP above this level might minimize the risk of secondary ischemic injury in comatose SAH patients.

Studies have shown that brain oxygen tension and cerebral metabolism do not always tightly correlate despite the capacity for both methods to identify tissue hypoperfusion. Brain oxygen tension is a complicated multidimensional parameter that, under specific circumstances, is a useful surrogate marker for regional cerebral blood flow. $P_{br}$ is best-characterized as an interaction between oxygen delivery, diffusion, and demand at the capillary, tissue, and cellular levels. This can make changes in $P_{br}$ difficult to interpret in isolation.

In contrast to the linear reduction in $P_{br}$ that occurred with declining CPP, an ischemic pattern of cerebral metabolism occurred when CPP decreased to ≤70 mm Hg.
cerebral autoregulation mechanisms are intact, the arterial response to a reduction in CPP is vasodilation. Small arterioles $< 100 \mu m$ in diameter begin to dilate when mean arterial pressure is $< 90 \, mm \, Hg$ and can expand to $140\%$ to $170\%$ of their original diameter$^{36}$ to maintain adequate cerebral blood flow and protect against ischemia.$^{37}$

The sharp increase in the frequency of metabolic crisis of CPP levels $< 70 \, mm \, Hg$ that we observed, combined with the gradual reduction in $P_{CO_2}$ that occurred across the entire range of CPP, suggests that both blunting and a rightward shift of pressure autoregulation can occur in poor-grade SAH patients. Our data also suggest that brain oxygen metabolism behaves differently from glucose metabolism, such that mild reductions in cerebral blood flow and substrate delivery result in a graded decrease in $P_{tot}O_2$, as opposed to having more of a threshold effect in terms of triggering anaerobic glucose metabolism. Brain oxygen tension monitoring may be best-suited to determine autoregulation status and to identify patients that are particularly vulnerable to hypoperfusion events, whereas cerebral metabolism monitoring may be better-suited to detect a safe lower limit of CPP on a patient-specific basis.$^{38}$ Further studies are needed to confirm these observations.

Patients who had a poor outcome (death or severe disability) at 3 months were significantly more likely to have a greater burden of brain tissue hypoxia and metabolic crisis during monitoring, even after adjusting for admission Hunt and Hess grade. However, this association does not prove causality; although it is feasible that low CPP exacerbates tissue ischemic injury and directly contributes to poor outcome, it is also possible that other factors, such as patient comorbidities or the severity of SAH, may play a role in determining outcome.

### Table 3. Multivariable Predictors of Brain Tissue Hypoxia and Metabolic Crisis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Metabolic Crisis</th>
<th></th>
<th>Brain Tissue Hypoxia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>$P$</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Admission Hunt and Hess grade 5</td>
<td>5.1 (1.6–16)</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>IVH on admission CT</td>
<td>5.4 (1.5–20)</td>
<td>0.009</td>
<td></td>
</tr>
<tr>
<td>Hourly systemic glucose $&lt; 6.6 , mmol/L$</td>
<td>1.4 (1.1–1.8)</td>
<td>0.016</td>
<td></td>
</tr>
<tr>
<td>End–tidal $CO_2$ $\leq 35$</td>
<td></td>
<td></td>
<td>1.2 (0.9–1.5)</td>
</tr>
<tr>
<td>CPP $&gt; 90 , mm , Hg$</td>
<td>CPP OR Reference Group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPP $80–90 , mm , Hg$</td>
<td>1.1 (0.8–1.5)</td>
<td>0.406</td>
<td>1.2 (1.0–1.5)</td>
</tr>
<tr>
<td>CPP $70–80 , mm , Hg$</td>
<td>1.4 (0.9–2.1)</td>
<td>0.159</td>
<td>1.6 (1.1–2.3)</td>
</tr>
<tr>
<td>CPP $60–70 , mm , Hg$</td>
<td>2.1 (1.2–3.7)</td>
<td>0.007</td>
<td>2.0 (1.2–3.3)</td>
</tr>
<tr>
<td>CPP $50–60 , mm , Hg$</td>
<td>2.8 (1.5–5.0)</td>
<td>0.001</td>
<td>2.8 (1.4–5.3)</td>
</tr>
<tr>
<td>CPP $&lt; 50 , mm , Hg$</td>
<td>6.7 (2.6–17)</td>
<td>0.000</td>
<td>3.5 (1.5–7.9)</td>
</tr>
</tbody>
</table>

Multivariable logistic regression model (GEE) adjusted for the variables listed. Metabolic crisis indicates lactate/pyruvate ratio $> 40$ and brain glucose concentration $< 0.7 \, mmol/L$. Brain tissue hypoxia $P_{tot}O_2 < 20 \, mm \, Hg$; CPP indicates cerebral perfusion pressure modeled as 6-level factor using a CPP $> 90$ as the reference group.

CI indicates confidence interval; CPP, cerebral perfusion pressure; CT, computed tomography; IVH, intraventricular hemorrhage; OR, odds ratio; GEE, generalized estimating equation.
This study has a number of important limitations. We did not have access to direct measurements of cerebral blood flow, which can be measured with thermodilution tissue probes (Hemedex). This would have allowed us to gain a better understanding of the state of pressure autoregulation in our patients. We could not incorporate detailed FiO2 or PaO2/FiO2 measurements, all of which may influence brain oxygenation, into the regression model for predicting PbtO2 because of technical limitations. To minimize this problem, however, we excluded hourly data collected when FiO2 was ≥50%. We recorded an hourly average CPP of ≤70 mm Hg for 217 hours (7%) of the observed monitoring. At the time of this study, our clinical practice was to maintain CPP >50 mm Hg and intracranial pressure <20 mm Hg, in accordance with Brain Trauma Foundation guidelines. In the case of symptomatic vasospasm, which occurred in 27% of patients, we directed further increases in CPP at reversal of the clinical deficit to levels ranging between 90 and 120 mm Hg. Wide variances in blood pressure are common in poor-grade SAH patients. Individual physiological responses to cerebral perfusion decreases to ≤70 mm Hg were not analyzed and it is unknown from this study if these fluctuations are harmful and should also be avoided. Patient-specific responses of PbtO2 and cerebral metabolism also are not analyzed in this study and might lead to different conclusions. Confirmation of the importance of maintaining CPP >70 mm Hg in a larger validation cohort is needed. If confirmed, then a randomized controlled trial of PbtO2-targeted CPP management strategy might be justified.

Advanced multimodality neuromonitoring provides a platform to devise strategies to identify personalized clinical thresholds for physiological variables that can influence brain perfusion such as CPP and end-tidal CO2. Our findings have purely prognostic value or represent modifiable factors that can be manipulated to improve patient outcome.

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Disclosure
None.

References


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重症くも膜下出血後の脳組織低酸素およびメタボリック・クライシスに対する脳灌流圧の関値

Cerebral Perfusion Pressure Thresholds for Brain Tissue Hypoxia and Metabolic Crisis After Poor-Grade Subarachnoid Hemorrhage

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Abstract

背景および目的：くも膜下出血（SAH）患者において脳組織低酸素（BTH）および酸化的メタボリック・クライシスのリスクを低減させる基準となる最低限の脳灌流圧の閾値を同定する。

方法：脳のマルチモリティモニタリング（3,042時間）を受けた30例の重症SAH患者を検討した。採取した各微小透析サンプルについて、60分間の生理学的測定値の平均をとった。メタボリック・クライシスは、乳酸/ビルピン酸の比が40を超え、脳内グルコース濃度が0.7 mmol/L以下であることと定義した。BTHはPbtO2が20 mmHg未満であることと定義した。3カ月後に改変Rankin尺度（mRS）により転帰を評価した。

結果：入院時のHunt-Hessグレード、脳室内出血、血清グルコース、呼気終末CO2について補正した多変量解析の結果、70 mmHg以下の脳灌流圧はBTH（OR = 2.0, 95% CI: 1.2 〜 3.3, p = 0.007）およびメタボリック・クライシス（OR = 2.1, 95% CI: 1.2 〜 3.7, p = 0.007）のリスクの上昇と関連することが明らかになった。3カ月後の死亡または重度の障害は、入院時のHunt-Hessグレードについて補正した後、メタボリック・クライシス（OR = 5.4, 95% CI: 1.8 〜 16, p = 0.002）およびBTH（OR = 5.1, 95% CI: 1.2 〜 23, p = 0.03）と有意に関連していた。

結論：メタボリック・クライシスおよびBTHはSAH後の死亡および機能回復不良に関連している。70 mmHg未満の脳灌流圧レベルはメタボリック・クライシスおよびBTHと関連しており、重症SAH患者において二次的脳損傷のリスクを増加させる可能性がある。

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表3 脳組織低酸素およびメタボリック・クライシスの多変量予測因子

<table>
<thead>
<tr>
<th>変数</th>
<th>メタボリック・クライシス OR (95% CI) p 値</th>
<th>脳組織低酸素 OR (95% CI) p 値</th>
</tr>
</thead>
<tbody>
<tr>
<td>入院時のHunt-Hess grade 5</td>
<td>5.1 (1.6 〜 16) 0.006</td>
<td>1.2 (0.9 〜 1.5) 0.071</td>
</tr>
<tr>
<td>入院時CT時 IVH</td>
<td>5.4 (1.5 〜 20) 0.009</td>
<td></td>
</tr>
<tr>
<td>1時間の血清グルコース&lt;6.6 mmol/L</td>
<td>1.4 (1.1 〜 1.8) 0.016</td>
<td></td>
</tr>
<tr>
<td>呼気終末CO2&lt;35</td>
<td>1.0 (0.8 〜 1.5) 0.406</td>
<td></td>
</tr>
<tr>
<td>CPP＞90 mmHg</td>
<td>1.1 (0.9 〜 2.1) 0.159</td>
<td>1.2 (1.0 〜 1.5) 0.023</td>
</tr>
<tr>
<td>CPP 70 〜 80 mmHg</td>
<td>2.1 (1.2 〜 3.7) 0.007</td>
<td>2.0 (1.2 〜 3.3) 0.007</td>
</tr>
<tr>
<td>CPP 50 〜 60 mmHg</td>
<td>2.8 (1.5 〜 5.0) 0.001</td>
<td>2.8 (1.4 〜 5.3) 0.003</td>
</tr>
<tr>
<td>CPP&lt;50 mmHg</td>
<td>6.7 (2.6 〜 17) 0.000</td>
<td>3.5 (1.5 〜 7.9) 0.003</td>
</tr>
</tbody>
</table>

一覧の変数について補正した多変量ロジスティック回帰モデル（GEE）を示す。メタボリック・クライシスとは、乳酸/ビルピン酸の比が40を超え、脳内グルコース濃度が0.7 mmol/L以下である場合を指す。脳組織低酸素はPbtO2が20 mmHg未満である場合を指す。CPH OR（95% CI）は、各群におけるリスク比を示す。CPI OR（95% CI）は、各群におけるリスク比を示す。

CI: 信頼区間，CPP: 脳灌流圧，CT: コンピュータ断層撮影，IVH: 脳室内出血，OR: オッズ比，GEE: 一般化推定方程式。

（Stroke 誌の表を一部変更して記載）