Clinical Significance of Impaired Cerebrovascular Autoregulation After Severe Aneurysmal Subarachnoid Hemorrhage

Matthias Jaeger, FRACS; Martin Soehle, MD; Martin U. Schuhmann, MD; Jürgen Meixensberger, MD

Background and Purpose—The purpose of this study was to investigate the relationship between cerebrovascular autoregulation and outcome after aneurysmal subarachnoid hemorrhage.

Methods—In a prospective observational study, 80 patients after severe subarachnoid hemorrhage were continuously monitored for cerebral perfusion pressure and partial pressure of brain tissue oxygen for an average of 7.9 days (range, 1.9–14.9 days). Autoregulation was assessed using the index of brain tissue oxygen pressure reactivity (ORx), a moving correlation coefficient between cerebral perfusion pressure and partial pressure of brain tissue oxygen. High ORx indicates impaired autoregulation; low ORx signifies intact autoregulation. Outcome was determined at 6 months and dichotomized into favorable (Glasgow Outcome Scale 4–5) and unfavorable outcome (Glasgow Outcome Scale 1–3).

Results—Twenty-four patients had a favorable and 56 an unfavorable outcome. In a univariate analysis, there were significant differences in autoregulation (ORx 0.19±0.10 versus 0.37±0.11, P<0.001, for favorable versus unfavorable outcome, respectively), age (44.1±11.0 years versus 54.2±12.1 years, P=0.001), occurrence of delayed cerebral infarction (8% versus 46%, P<0.001), use of coiling (25% versus 54%, P=0.02), partial pressure of brain tissue oxygen (24.9±6.6 mm Hg versus 21.8±6.3 mm Hg, P=0.048), and Fisher grade (P=0.03). In a multivariate analysis, ORx (P<0.001) and age (P=0.003) retained an independent predictive value for outcome. ORx correlated with Glasgow Outcome Scale (r=-0.70, P<0.001).

Conclusions—The status of cerebrovascular autoregulation might be an important pathophysiological factor in the disease process after subarachnoid hemorrhage, because impaired autoregulation was independently associated with an unfavorable outcome. (Stroke. 2012;43:2097-2101.)

Key Words: autoregulation ■ brain tissue oxygen ■ cerebral perfusion pressure ■ intracranial pressure ■ outcome ■ subarachnoid hemorrhage

Cerebrovascular pressure autoregulation is the intrinsic protective ability of the brain’s vasculature to maintain adequate cerebral blood flow relatively independent of fluctuations of arterial blood pressure.1 After acute aneurysmal subarachnoid hemorrhage (SAH), autoregulation is frequently impaired, leaving the brain susceptible to secondary ischemic insults.2–5 Impaired autoregulation has been associated with delayed cerebral ischemia after SAH in clinical studies,5–8 but its impact on patient outcome after SAH has not been determined.

The purpose of this study was to investigate the relationship between the individual cerebrovascular autoregulatory status and outcome after severe SAH. We hypothesized that autoregulation impairment is associated with an unfavorable outcome and tested this hypothesis by continuous recordings of cerebrovascular autoregulation using the index of brain tissue oxygen pressure reactivity, ORx.

Patients and Methods

Patients and Management

Eighty patients with the diagnosis of acute aneurysmal SAH treated at Leipzig University Hospital over a 5.5-year period were included in this prospective observational study. Collected data included age, sex, neurological status according to the World Federation of Neurosurgical Societies,9 the amount of blood on CT according to Fisher et al,10 location of aneurysm, and treatment interventions (surgical clipping versus endovascular coiling).

After admission, the bleeding source was identified by early cerebral digital subtraction angiography. Aneurysm treatment, by craniotomy and surgical clipping or interventional endovascular coil occlusion, was determined by interdisciplinary consensus of the treating neurosurgeon and the interventional neuroradiologist after...
an analysis of the individual risks and chances of each therapeutic modality. After aneurysm occlusion, therapy aimed at avoiding secondary hypotensive episodes by maintaining euvoilema and mean arterial pressure (MAP) of 80 to 90 mm Hg. MAP was elevated as required using moderate volume expansion and vasopressors (noradrenaline, dobutamine, and/or dopamine).

Due to their poor neurological condition, all patients in this study required continuous sedation and artificial ventilation. Midazolam (6–18 mg/hour) and fentanyl (0.1–0.5 mg/hour) were used for analgesia and sedation. Ventilation aimed at a partial pressure of arterial carbon dioxide at 35 to 45 mm Hg and the partial pressure of arterial oxygen at 100 to 120 mm Hg. Arterial blood gas samples were obtained every 8 hours or as clinically indicated to adjust ventilation parameters. Seventy-six patients received an external ventricular drain for treatment of acute hydrocephalus. Nimodipine 6×60 mg was administered through a nasogastric tube in all patients. None of the patients received statins or erythropoietin during intensive care unit stay. Treatment was performed according to previously published recommendations.11

Outcome was assessed 6 months after the hemorrhage by the first author (M.J.) using the Glasgow Outcome Scale (GOS) by either personal follow-up examination or telephone interview with the patient, next of kin, or caregiver.12

**Neuromonitoring**

All patients underwent continuous measurement of MAP, intracranial pressure (ICP), and the partial pressure of brain tissue oxygen (PbrO2). MAP was monitored by a catheter inserted into the radial or femoral artery with the transducer referenced to the foramen of Monro (DTXPlus; Becton Dickinson Infusion Therapy Systems Inc). ICP (Codman Microsensors ICP Transducer; Codman & Shurtleff Inc) and PbrO2 (Licox CC1.SB; Integra NeuroSciences Inc) were monitored using flexible catheters inserted through a double-lumen skull bolt kit (Licox IM2; Integra NeuroSciences Inc) into the frontal white matter of the hemisphere supplied by the aneurysm-carrying artery. In case of anterior communicating artery aneurysms or posterior circulation aneurysms, the right frontal region was chosen. Probes were inserted in the intensive care unit after occlusion of the aneurysm and a CT scan obtained within 24 hours after aneurysm occlusion to rule out intervention related infarction to avoid placing the probes in infarcted tissue. Correct positioning of the PbrO2 probe in CT-normal tissue at a depth of approximately 25 mm subdurally was confirmed by routine CT. Neuromonitoring continued while clinically indicated.

Analog data of MAP, ICP, and PbrO2 were sampled at 50 Hz, processed through an analog-to-digital converter (Licox MMM; Integra NeuroSciences Inc), and recorded by a bedside portable computer. Cerebral perfusion pressure (CPP) was calculated as the difference between MAP and ICP. Time averaged means for MAP, ICP, CPP, and PbrO2 were calculated and stored every 30 seconds.

Transcranial Doppler mean blood flow velocities in both middle cerebral arteries were obtained every second to fourth day as part of the diagnostic routine using a handheld 2-MHz probe (DWL Multidop X; DWL Elektronische Systeme GmbH). Maximum flow velocities were recorded for further analysis.

**Index of Brain Tissue Oxygen Pressure Reactivity (ORx) for Assessment of Autoregulation**

The index of brain tissue oxygen pressure reactivity ORx was calculated as the moving linear (Pearson) correlation coefficient between values of CPP and PbrO2 from the previous 60 minutes of monitoring, that is, every 30 seconds a new ORx value was calculated from 120 data points. ORx has been previously validated to allow for a continuous assessment of cerebrovascular autoregulation at the patient’s bedside and is described in detail elsewhere.13 In brief, PbrO2 is a surrogate of cerebral blood flow.14,15 ORx quantifies the relationship between spontaneous fluctuations of CPP and PbrO2 and thus quantifies the cerebrovascular autoregulatory status. ORx may vary on a scale between -1 and +1 and displays impaired autoregulation when PbrO2 passively follows CPP, meaning a good correlation between the 2 parameters exists and ORx is high. When autoregulation is intact, PbrO2 is relatively unaffected by changes in CPP so that no correlation between CPP and PbrO2 can be observed and ORx is near 0.

Artsfacts, resulting from temporary disconnection of catheters or nursing interventions, were manually eliminated from the data sets and not included in ORx calculations. In case of progressive delayed cerebral infarction or terminal decrease of PbrO2, data collection was terminated when PbrO2 readings reached 2 mm Hg, because PbrO2 becomes unreactive to CPP changes around this level.

The ethics committee of Leipzig University approved this study. The invasive monitoring of MAP, ICP, and PbrO2 is standard clinical practice at Leipzig University Hospital in patients with severe SAH requiring continuous sedation and mechanical ventilation. Because the calculation of ORx did not require additional patient manipulation, the need for informed consent was waived.

**Delayed Cerebral Infarction on CT**

Delayed cerebral infarction was defined as new hypodensities on CT scan attributable only to posthemorrhagic cerebral vasospasm. A CT scan was obtained within 12 to 24 hours of aneurysm occlusion in each patient to assess for baseline hypodensities. New hypodensities were evaluated on follow-up CT scans thereafter. Hypodensities due to factors such as brain retraction during surgery, edema around an intracerebral hematoma, or ischemic complications related to aneurysm treatment were separately recorded and entered into the analysis.

**Statistical Analysis**

Individual mean neuromonitoring values were calculated for each patient’s entire monitoring period as well as for each day after SAH. Clinical and neuromonitoring parameters were compared between outcome groups using univariate Mann-Whitney U test, χ² test, and Kruskal-Wallis-test (SPSS 11.0.1; SPSS Inc). For the purpose of the main statistical analysis, patients were dichotomized into favorable (GOS 4–5) and unfavorable (GOS 1–3) outcome. Independent predictors of outcome were evaluated in a stepdown binary logistic regression model after identification of candidate variables in the univariate analysis. Interaction variables were considered between variables as part of the logistic regression model building. Correlation was analyzed using Spearman coefficient. The probability of a Type 1 error (α) of <5% was accepted as being statistically significant.

**Results**

**Patient Characteristics**

Of the 80 patients in this study, 24 had a favorable outcome and 56 had an unfavorable outcome. Table 1 shows the characteristics of both groups. Patients with an unfavorable outcome had a significantly higher age, higher Fisher grade, higher proportion of endovascular coil occlusion, and higher incidence of delayed cerebral infarction.

**Neuromonitoring and Autoregulation Characteristics**

Average values of ORx, CPP, PbrO2, and ICP for patients with favorable and unfavorable outcomes are given in Table 2. Patients with an unfavorable outcome had impaired cerebrovascular autoregulation, as indicated by high ORx, whereas the autoregulatory status was better in those with a favorable outcome. PbrO2 was lower in the unfavorable outcome group, whereas CPP and ICP were not different between outcome groups.

Daily values of ORx, CPP, PbrO2, and ICP from Days 1 to 12 after SAH are presented in Figure 1. ORx did not differ between groups on Days 1 and 2 but was significantly higher...
Table 1. Clinical Characteristics of Favorable (GOS 4–5) and Unfavorable (GOS 1–3) Outcome Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Favorable (n=24)</th>
<th>Unfavorable (n=56)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>44.1 (±11.0)</td>
<td>54.2 (±12.1)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Sex, female/male</td>
<td>14/10</td>
<td>39/17</td>
<td>0.33†</td>
</tr>
<tr>
<td>WFNS grade</td>
<td>(4, 4)</td>
<td>(4, 5)</td>
<td>0.08*</td>
</tr>
<tr>
<td>Fisher grade</td>
<td>(3, 4)</td>
<td>(3, 4)</td>
<td>0.03*</td>
</tr>
<tr>
<td>Aneurysm location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACoA</td>
<td>5 (21%)</td>
<td>23 (41%)</td>
<td>0.52†</td>
</tr>
<tr>
<td>ACA</td>
<td>1 (4%)</td>
<td>4 (7%)</td>
<td></td>
</tr>
<tr>
<td>Pericallosal artery</td>
<td>1 (4%)</td>
<td>4 (7%)</td>
<td></td>
</tr>
<tr>
<td>ICA</td>
<td>9 (38%)</td>
<td>14 (25%)</td>
<td></td>
</tr>
<tr>
<td>MCA</td>
<td>5 (21%)</td>
<td>10 (18%)</td>
<td></td>
</tr>
<tr>
<td>VB</td>
<td>3 (13%)</td>
<td>4 (7%)</td>
<td></td>
</tr>
<tr>
<td>Clipping/coiling</td>
<td>18/6</td>
<td>26/30</td>
<td>0.02†</td>
</tr>
<tr>
<td>Delayed cerebral infarction</td>
<td>2 (8%)</td>
<td>26 (46%)</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Hypodensities not attributable to delayed infarction</td>
<td>8 (33%)</td>
<td>20 (36%)</td>
<td>0.84†</td>
</tr>
</tbody>
</table>

Values given as mean (±SD), median (25th, 75th percentile), or absolute numbers (% values).
GOS indicate Glasgow Outcome Scale; WFNS, World Federation of Neurosurgical Societies; ACoA, anterior communicating artery; ACA, anterior cerebral artery; ICA, internal carotid artery; MCA, middle cerebral artery; VB, vertebro-basilar system.
*P for Mann-Whitney U test.
†P for χ² likelihood ratio.

in patients with an unfavorable outcome thereafter. While ORx gradually decreased to values of approximately 0.1 in the favorable outcome group, it remained at 0.3 to 0.4 in patients with an unfavorable outcome, demonstrating a persistent deficit in cerebrovascular autoregulatory capacity. PbrO₂ was significantly higher in patients with a favorable outcome on Days 4 and 5, whereas CPP and ICP did not differ between groups at individual days post-SAH.

Figure 2 shows the distribution of ORx among the 5-tier GOS outcome scale, which was statistically uneven (P<0.001). Figure 2 also shows patient numbers in each 5-tier GOS category. The correlation between GOS and ORx was r=−0.70 (P<0.001).

Table 2. Neuromonitoring Characteristics of Favorable (GOS 4–5) and Unfavorable (GOS 1–3) Outcome Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Favorable (n=24)</th>
<th>Unfavorable (n=56)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORx</td>
<td>0.19 (±0.10)</td>
<td>0.37 (±0.11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CPP, mm Hg</td>
<td>83.5 (±13.8)</td>
<td>80.4 (±11.6)</td>
<td>0.70</td>
</tr>
<tr>
<td>PbrO₂, mm Hg</td>
<td>24.9 (±6.6)</td>
<td>21.8 (±6.3)</td>
<td>0.048</td>
</tr>
<tr>
<td>ICP, mm Hg</td>
<td>12.7 (±3.6)</td>
<td>13.6 (±6.0)</td>
<td>0.98</td>
</tr>
<tr>
<td>Start of monitoring after SAH, h</td>
<td>50.8 (±40.9)</td>
<td>47.8 (±36.5)</td>
<td>0.55</td>
</tr>
<tr>
<td>End of monitoring after SAH, h</td>
<td>240.8 (±68.9)</td>
<td>236.0 (±64.4)</td>
<td>0.62</td>
</tr>
<tr>
<td>Time of valid monitoring, h</td>
<td>164.8 (±55.5)</td>
<td>164.8 (±61.9)</td>
<td>0.90</td>
</tr>
</tbody>
</table>

Values are mean ±SD; P for Mann-Whitney U test.
ORx indicates index of brain tissue oxygen pressure reactivity; CPP, cerebral perfusion pressure; PbrO₂, partial pressure of brain tissue oxygen; ICP, intracranial pressure; SAH, subarachnoid hemorrhage.
*Neuromonitoring parameters are from the entire period of neuromonitoring, including the period of delayed cerebral infarction.

Delayed Cerebral Infarction
The incidence of delayed cerebral infarction was higher in patients with an unfavorable outcome as compared with those with a favorable outcome (46% versus 8%, respectively, P<0.001; Table 1). Delayed cerebral infarction occurred on average 9 days after SAH (range, 5–14 days) and was clinically detected by routine CT in 14 patients and by worsening neuromonitoring trends in 14 patients. The correlation between GOS and delayed cerebral infarction was r=0.57 (P<0.001).

Predictors of Outcome
In the final binary logistic regression model, with outcome dichotomized into favorable (GOS 4–5) and unfavorable (GOS 1–3), only ORx (P<0.001) and age (P=0.003) remained independently associated with outcome. Other candidate variables identified in the univariate analysis, that is, Fisher grade (P=0.47), use of coiling (P=0.17), occurrence of delayed cerebral infarction on CT (P=0.22), and PbrO₂ (P=0.61), did not carry predictive value. No significant interactions between considered variables were identified.

Discussion
This study demonstrated differences in cerebrovascular autoregulation, as measured by the index of brain tissue oxygen pressure reactivity ORx, between patients with a favorable and unfavorable outcome after severe SAH. This intrinsic cerebral mechanism to control blood flow relatively independent of CPP was significantly diminished in those with an unfavorable outcome. We also found an almost linear relationship between the degree of autoregulation impairment and outcome, as demonstrated in Figure 2. Impaired autoregulation was furthermore statistically independently associated with an unfavorable outcome, suggesting that impaired autoregulation might be an important pathophysiological factor in the disease process leading to an unfavorable outcome after aneurysm rupture.

To our knowledge, this is the largest series of continuous PbrO₂ monitoring after SAH. PbrO₂ was lower in patients with unfavorable outcomes, indicating the perfusion deficits associated with impaired autoregulation. However, we consider the difference of 3.1 mm Hg between average PbrO₂ values, as shown in Table 2, to be of only limited clinical significance and the discriminating value was even less at the individual days post-SAH. Despite these concerns, PbrO₂ can serve as an indicator of the adequacy of brain perfusion and deserves further evaluation to optimize CPP and brain oxygenation after SAH, because it has been demonstrated for head injury management.56–18 Continuous bedside calculation and display of ORx will provide valuable prognostic information not available from other parameters, neither clinical nor from...
monitoring. ORx can be readily determined and its clinical use would assist bedside decision-making in patients with poor-grade SAH. Although our single-center experience with calculation of ORx in patients with SAH using the Licox system has been very encouraging, another report, using different methodology and PbrO2 system, found limited value of ORx for assessing autoregulation after head injury and our results need to be tested in larger, ideally prospective multicenter, cohorts.

Delayed cerebral infarction was not an independent predictor of outcome in the investigated cohort, although it is generally considered to be an important factor contributing to an unfavorable outcome. However, previous studies have suggested that delayed cerebral infarction may be mediated by underlying impaired autoregulation, when the vasculature’s disturbed autoregulatory function fails to compensate for progressive reductions in vessel diameter caused by vasospasm. This causative relationship might have been reflected in the results of the logistic regression model, accounting for the statistically dependent character of delayed cerebral infarction. However, it needs to be kept in mind that the moderate size of the patient cohort and possible dilution of outcome information by dichotomization of the 5-tier GOS outcome data for the purpose of the binary logistic regression analysis could have obscured the statistical results. Furthermore, outcome assessment at 6 months was nonblinded, because the first author was part of the treating team with continuous computerized bedside display of individual ORx values, leaving a source for potential bias.

In the recent Clazosentan to Overcome Neurological Ischemia and Infarction Occurring After Subarachnoid Hemorrhage (CONSCIOUS) trials, the significant pharmacological reduction of angiographic vessel narrowing after SAH was not associated with improved outcome or a clear reduction in delayed ischemic events. The results from these prospective trials, together with other observations, have raised issues for the traditional paradigm of vessel narrowing as the main or sole cause of neurological deterioration and poor outcome after SAH and the need for improved pathophysiological understanding and models of the disease process has been emphasized. The results of our study point toward the pathophysiological significance of impaired cerebrovascular autoregulation and improvement of autoregulation might thus

Figure 1. Time course of the index of brain tissue oxygen pressure reactivity ORx, cerebral perfusion pressure (CPP), partial pressure of brain tissue oxygen (PbrO2), and intracranial pressure (ICP) after SAH. Black line indicates the unfavorable outcome group; gray line is the favorable outcome group. Given values are the mean; error bars represent 95% CIs of the mean. One asterisk indicates $P<0.05$; 2 asterisks indicate $P<0.001$ from Mann-Whitney $U$ test. The number of patients at each day of monitoring after SAH are given at the bottom left of the figure. ORx indicates index of brain tissue oxygen pressure reactivity; SAH, subarachnoid hemorrhage.

Figure 2. Index of brain tissue oxygen pressure reactivity ORx among the 5-tier Glasgow Outcome Scale (GOS) grades. Given values are the mean; error bars represent 95% CIs of the mean. The distribution of ORx was statistically uneven; $P<0.001$ from Kruskal-Wallis test. The Spearman correlation coefficient between GOS and ORx was $r=−0.70$ ($P<0.001$). The number of patients in each GOS category is given at the bottom of the figure.
be a promising therapeutic and scientific strategy to improve outcome. However, despite the statistical results indicating the pathophysiological significance of impaired autoregulation, it needs to be considered that our statistical model cannot differentiate whether impaired autoregulation is truly a causative factor of unfavorable outcome or merely an independent marker of the severity of SAH-induced brain injury, in which case improving autoregulation would not affect outcome. Nonetheless, previous studies have indicated that administration of statins and erythropoietin can effectively improve autoregulation and might consequently improve outcome.18,30 The results of the currently ongoing Simvastatin in Aneurysmal Subarachnoid Hemorrhage (STASH) trial are awaited, in which simvastatin is tested in a prospective randomized fashion after SAH.29 In addition to these pharmacological interventions, managing blood pressure at individually required optimal CPP levels has been suggested as a therapeutic hemodynamic target with the potential to improve both autoregulation and outcome.18,30

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Disclosures
None.

References
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