Continuous Monitoring of Cerebrovascular Autoregulation After Subarachnoid Hemorrhage by Brain Tissue Oxygen Pressure Reactivity and Its Relation to Delayed Cerebral Infarction

Matthias Jaeger, MD; Martin U. Schuhmann, MD, PhD; Martin Soehle, MD; Christoph Nagel, MD; Jürgen Meixensberger, MD, PhD

Background and Purpose—Disturbances of cerebrovascular autoregulation are thought to be involved in delayed cerebral ischemia and infarction after aneurysmal subarachnoid hemorrhage (SAH). We hypothesized that the continuous monitoring of brain tissue oxygen (PtiO2) pressure reactivity enables the detection of impaired autoregulation after SAH and that impaired autoregulation is associated with delayed infarction.

Methods—In 67 patients after severe SAH, continuous monitoring of cerebral perfusion pressure (CPP) and PtiO2 was performed for an average of 7.4 days. For assessment of autoregulation, the index of PtiO2 pressure reactivity (ORx) was calculated as a moving correlation coefficient between values of CPP and PtiO2. Higher ORx values indicate disturbed autoregulation, whereas lower ORx values signify intact autoregulation.

Results—Twenty patients developed delayed cerebral infarction, and 47 did not. Mean ORx was significantly higher in the infarction group compared with the noninfarction group (0.43 ± 0.09 vs 0.23 ± 0.14, respectively; \( P < 0.0001 \)). In a day-by-day analysis, ORx did not differ between groups from days 1 to 4 after SAH but was significantly higher from day 5 onward in the infarction group, indicating a deficit of autoregulatory capacity. In a logistic-regression model, ORx values from days 5 and 6 after SAH carried predictive value for the occurrence of delayed infarction but before this event ultimately occurred (\( P = 0.003 \)).

Conclusions—ORx indicates impaired autoregulation in patients who develop delayed infarction after SAH. Furthermore, this index may distinguish between patients who finally develop delayed infarction and those who do not. (Stroke. 2007; 38:981-986.)

Key Words: autoregulation • brain tissue oxygen • delayed ischemia • subarachnoid hemorrhage

Patients after aneurysmal subarachnoid hemorrhage (SAH) carry a considerable risk for the development of delayed cerebral ischemia and subsequent cerebral infarction. These critical reductions of brain perfusion are typically attributed to posthemorrhagic vasospasm, but the traditional concept of progressive vessel narrowing as the sole cause for ischemia has been challenged.\(^1\)\(^-\)\(^3\) Other models suggest that disturbances of cerebrovascular autoregulation are involved in the development of delayed ischemia. After SAH, when autoregulation is frequently impaired,\(^4\)\(^-\)\(^6\) the risk of ischemia may increase as the disturbed autoregulatory function of the cerebral vasculature fails to compensate for reductions in vessel diameter caused by vasospasm. In contrast, patients with intact autoregulation appear not to experience delayed ischemia after SAH.\(^1\)\(^,\)\(^7\)

Assessment of the status of cerebrovascular autoregulation could thus play a role in the identification of patients with an increased risk for delayed ischemia and infarction. The continuous monitoring of brain tissue oxygen (PtiO2) pressure reactivity has been shown to allow for an assessment of autoregulation after head injury.\(^8\) In this study, we examine the hypothesis that the continuous monitoring of PtiO2 pressure reactivity enables the detection of autoregulatory disturbances after SAH and that these disturbances are related to the occurrence of delayed cerebral infarction.

Patients and Methods

Patients and Management

Sixty-seven patients with the diagnosis of acute SAH were included in this study. Collected data included age, sex, neurological status according to the World Federation of Neurosurgical Societies,\(^9\) the amount of blood on computed tomography (CT) scan according to Fisher et al,\(^10\) location of the aneurysm, and choice of treatment (surgical clipping versus endovascular coiling).
After admission, early cerebral angiography was done to identify the source of bleeding. The decision to treat the aneurysm by either craniotomy and surgical clipping or interventional endovascular coil occlusion was based on an 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 euovolemia (central venous pressure at 6 to 10 cm H2O) and mean arterial pressure (MAP) of 80 to 90 mm Hg. When necessary, MAP was elevated by moderate volume expansion and individually titrated vasopressors (noradrenaline, dobutamine, and/or dopamine).

The clinical condition of all patients included in this study was considered poor due to their neurological impairment or SAH-associated cardiac or pulmonary failure; therefore, they required continuous sedation and artificial ventilation. Midazolam (6 to 18 mg/h) and fentanyl (0.1 to 0.5 mg/h) were used for analgesia and sedation. Patients were ventilated to keep the partial pressure of arterial carbon dioxide (PaCO2) at 35 to 40 mm Hg and the partial pressure of arterial oxygen (PaO2) at 100 to 120 mm Hg. Arterial blood gas samples were obtained every 8 hours or as clinically indicated to adjust ventilation parameters (ABL 700, Radiometer A/S). In all patients, an external ventricular drain was placed for treatment of acute hydrocephalus. As a general policy in our department, external ventricular drains are inserted in SAH patients admitted with a Glasgow Coma Scale score <14 to rule out hydrocephalus as the underlying cause for the depressed consciousness. Nimodipine 6×60 mg was administered via nasogastric tube. None of the patients underwent postoperative/postinterventional angiography, endovascular angioplasty, or intra-arterial papaverine infusion. Treatment was performed according to previously published recommendations.11,12

Outcome was assessed at 6 months after the hemorrhage according to the Glasgow Outcome Scale (GOS) either by personal follow-up examination or by telephone interview with the patient, next relative, or caregiver.13

Neuromonitoring

All patients were included in our routine multimodal neuromonitoring protocol for patients with acute severe cerebral insults, comprising measurement of MAP, intracranial pressure (ICP), cerebral perfusion pressure (CPP), and PtiO2. 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 Systeme GmbH) during intensive care treatment. This was performed every 30 seconds, a new ORx value was calculated from 120 data points. ORx has been demonstrated to allow for a continuous assessment of cerebrovascular autoregulation at the patient’s bedside after head injury and is described in detail elsewhere.6 In brief, the physiological basis for determining autoregulation with PtiO2 monitoring is that PtiO2 is a surrogate marker of cerebral blood flow.14,15

Quantifying the relation between spontaneous fluctuations of CPP and PtiO2 thus enables an assessment of autoregulation. ORx, which may theoretically vary between −1 and +1, displays impaired autoregulation when PtiO2 passively follows CPP. In this situation, a good correlation between the 2 parameters exists and ORx is high. When autoregulation is intact, PtiO2 is relatively unaffected by changes in CPP, so that no correlation between CPP and PtiO2 can be observed, and ORx is thus near zero.

This study was approved by the local ethics committee. Because the invasive monitoring of MAP, ICP, CPP, and PtiO2 is standard clinical practice in our department in patients with severe SAH requiring continuous sedation and mechanical ventilation and the calculation of ORx did not require additional patient manipulation, the need for informed consent was waived.

Definition of Delayed Cerebral Infarction

Delayed cerebral infarction was defined as radiologically confirmed new hypodensities on the CT scan that were attributable only to posthemorrhagic cerebral vasospasm. New hypodensities due to factors such as brain retraction during surgery, edema around an intracerebral hematoma, and ischemic complications related to aneurysm treatment were noted but not considered for analysis.

Statistical Analysis

Artifacts caused by temporary disconnection of catheters or nursing interventions were manually eliminated from the data sets, and ORx was calculated after artifact elimination. In cases of progressive vasospastic cerebral infarction, data collection was terminated when PtiO2 readings reached 2 mm Hg.

Individual mean values of all neuromonitoring parameters during the whole monitoring period as well as for each single day after SAH were calculated. Patients were divided into 2 groups depending on the occurrence of delayed cerebral infarction as defined earlier. Comparison of clinical and neuromonitoring parameters between these 2 groups was done with the univariate Mann–Whitney U test and χ² test (SPSS 11.0.1, SPSS Inc). Independent predictors of delayed cerebral infarction were evaluated by fitting a step-down logistic-regression model after identification of candidate variables in the univariate analysis. A value of P<0.05 was considered statistically significant.

Results

Patient Characteristics

Of the 67 patients in this study, 20 developed delayed infarction. Table 1 shows the characteristics of both groups. No differences between the groups were seen with respect to clinical variables, except that in the infarction group, neuromonitoring ended significantly earlier, and the time of valid monitoring during which artifact-free data were obtained was significantly shorter.

Delayed cerebral infarction was diagnosed at an average of 9.0 days after SAH (range, 7 to 14 days) and was clinically detected by routine CT scan (n=9) or worsening neuromonitoring trends (n=11). Outcome was significantly worse in the infarction group, with all 20 patients having a poor outcome (GOS 1 to 3), compared with the noninfarction group.
TABLE 2. CPP, ICP, PtiO2, and ORx Obtained During the Entire
Neuromonitoring and
lost to follow-up. One patient was achieved a favorable outcome (GOS 4 to 5). One patient was

Variable
Infarction
Group
(n=20)
P

Noninfection
Group
(n=47)
Age, y
53.0 Higher in the infarction group compared with the
neuromonitoring parameters, CPP showed significantly

Sex, female/male
29/18
0.13†

WFNS grade
4 (4, 5)
4 (4, 4)
0.47*

Fisher grade
4 (3, 4)
3.5 (3, 4)
0.88*

Aneurysm location
ACoA
18 (38%)
5 (25%)
0.25†

ACA
2 (4%)
0 (0%)

Pericallosal artery
2 (4%)
2 (10%)

ICA
11 (23%)
9 (45%)

MCA
11 (23%)
2 (10%)

VB
3 (6%)
2 (10%)

Clipping/coiling
31/16
11/9
0.50†

Hypodensities not attributable to delayed infarction
16 (34%)
6 (30%)
0.75†

Start of monitoring after SAH, h
55.1
3.9
0.50*

End of monitoring after SAH, h
247.9 ± 55.2
205.1 ± 64.8
0.01*

Time of valid monitoring, h
165.3 ± 56.6
129.6 ± 53.3
0.02*

GOS score
3 (2, 5, 4)
1 (1, 2)
0.0000001*

Values are given as mean ± SD, median (25th and 75th percentiles), or
absolute numbers (%). WFNS indicates World Federation of Neurological
Surgeons; ACoA, anterior communicating artery; ACA, anterior cerebral artery;
ICA, internal carotid artery; MCA, middle cerebral artery; VB, vertebrobasilar
system.

* P for Mann–Whitney U test; † P for \chi^2 likelihood ratio.

wherein 29 patients had a poor outcome and 17 patients achieved a favorable outcome (GOS 4 to 5). One patient was lost to follow-up.

Neuromonitoring and Autoregulation Characteristics
Values of CPP, ICP, PtiO2, and ORx for the entire period of monitoring are given in Table 2. No significant differences between groups were observed for the standard neuromonitoring parameters CPP, ICP, and PtiO2. In contrast, ORx was significantly higher in the infarction group compared with the noninfarction group. Mean daily values of ORx, CPP, ICP, and PtiO2 from days 1 to 12 after SAH are presented in the Figure. ORx did not differ between groups from days 1 to 4, but from day 5 onward, it was significantly lower in the noninfarction group than in the infarction group. Whereas mean ORx gradually decreased to values <0.2 in the noninfarction group, it remained >0.4 in patients who developed delayed infarction, indicating a persistent deficit in cerebrovascular autoregulatory capacity. Regarding the standard neuromonitoring parameters, CPP showed significantly higher values on days 4 and 5 in the infarction group, ICP showed significantly higher values in the infarction group on days 9 and 10, and PtiO2 showed significantly lower values in the infarction group on day 8. These higher ICP and lower PtiO2 readings at the beginning of the second week of monitoring appear to be related to the occurrence of cerebral infarctions with the associated elevations in ICP and deficits in cerebral perfusion. Owing to the heterogeneous start and end of monitoring, patient numbers per day varied in both groups.

Maximum mean blood flow velocity in the middle cerebral artery was 160 ± 46 cm/s in the noninfarction group and 172 ± 46 cm/s in the infarction group (P = 0.32). In 2 patients of the infarction group and 2 patients of the noninfarction group, however, no reliable TCD data could be obtained through the trans-temporal window during intensive care unit treatment.

Early Predictors of Delayed Cerebral Infarction
Because ORx displayed significant differences between the noninfarction and infarction group from day 5 onward but delayed cerebral infarction was detected at the earliest on day 7 after SAH, this suggested a "diagnostic window" at days 5 and 6 that might allow for the early identification of patients with an increased risk for delayed infarction but before this event ultimately occurs.

In the univariate analysis, mean values at days 5 and 6 of ORx, PtiO2, and CPP were identified as candidate variables for a logistic-regression model, because they displayed significant differences between the noninfarction and infarction group (ORx, 0.25 ± 0.16 vs 0.41 ± 0.15, P = 0.0007; PtiO2, 26.3 ± 7.6 vs 19.9 ± 8.7 mm Hg, P = 0.02; CPP, 78.1 ± 12.7 vs 85.8 ± 13.2 mm Hg, P = 0.04, for the noninfarction and infarction groups, respectively). Thus, ORx and PtiO2 values from days 5 and 6 were entered into the analysis; however, CPP was not considered, because higher CPP levels are not related to symptomatic vasospasm according to our current understanding of the pathophysiological mechanisms of the disease. In the final model, ORx carried a predictive value on the occurrence of delayed cerebral infarction after SAH (P = 0.003), whereas PtiO2 did not (P = 0.08). Table 3 displays the probability of infarction for ORx thresholds of <0.25 and >0.4. These values were chosen after data analysis, with the intention to provide thresholds for easy clinical interpretation. Only 42 patients from the noninfarction group and 19 patients from the infarction group could be entered into the logistic-regression analysis, as they were monitored during the time interval of days 5 and 6.

Relation Between Location of PtiO2 Probe and Territory of Delayed Infarction
The position of the PtiO2 probe in relation to the location of delayed cerebral infarction is shown in Table 4. No signifi-
cant differences in ORx were seen between probes located in a later-infarcted area and probes not so located.

Discussion
This study demonstrated differences in cerebrovascular autoregulation, as measured by the index of PtiO2 pressure reactivity ORx between patients who developed delayed cerebral infarction after SAH and those who did not. The intrinsic capacity of the brain to control cerebral blood flow relatively independently of CPP was significantly diminished in infarcted patients. This finding confirms the pathophysiological model that impairment of autoregulation plays a role in the development of critical ischemia after SAH. ORx was equally high, \( \approx 0.4 \), during the first days after the ictus,
irrespective of future infarction, indicating the immediate impact of the bleeding on the cerebral vasculature. In the further course of the disease, patients with improving autoregulation rarely experienced delayed infarction, whereas a continuing loss of autoregulation was closely associated with this devastating event.

The results of the study showed that continuous monitoring of ORx provides early information on the patient’s individual risk for delayed infarction. This is of major interest, because in our cohort of predominantly poor-grade SAH patients, this information was unavailable from other methods, either clinically or from monitoring. Also, TCD did not differentiate between the groups, but the limited frequency of TCD examinations (only every 2 to 4 days) might have attenuated the significance of this finding. However, especially in ventilated and sedated patients, the diagnosis of symptomatic delayed ischemia remains challenging, because a reliable neurological assessment is impossible and appropriate timing of invasive therapeutic measures that are not risk-free, such as aggressive hypertensive/hypervolemic/hemodilutional therapy or angioplasty, cannot be made. Monitoring of ORx at the bedside of ventilated and sedated patients may thus allow clinicians to identify those with a high probability of infarction, for whom such invasive therapeutic measures may appear justified. On the other hand, when ORx is low, therapy can be maintained at a more restrained level.

Despite the promising results of the logistic-regression analysis in predicting the occurrence of delayed infarction, we have been unable to establish a certain threshold for ORx above which infarction definitely occurred or below which infarction could be ruled out. It appeared that with deteriorating ORx, the risk of infarction greatly increased, but high ORx values did not fully explain all of the observed new hypodensities. As demonstrated in Table 3, a subset of patients still experienced new infarctions, although their ORx values did not fully explain all of the observed new infarction. Whereas a continuing loss of autoregulation was closely associated with this devastating event.

Despite the promising results of the logistic-regression analysis in predicting the occurrence of delayed infarction, we have been unable to establish a certain threshold for ORx above which infarction definitely occurred or below which infarction could be ruled out. It appeared that with deteriorating ORx, the risk of infarction greatly increased, but high ORx values did not fully explain all of the observed new hypodensities. As demonstrated in Table 3, a subset of patients still experienced new infarctions, although their ORx values did not fully explain all of the observed new infarction. Whereas a continuing loss of autoregulation was closely associated with this devastating event.

### TABLE 3. Likelihood of Delayed Infarction Among Suggested Thresholds of ORx From Days 5 and 6

<table>
<thead>
<tr>
<th>Variable</th>
<th>Noninfarction Group (n = 42)</th>
<th>Infarction Group (n = 19)</th>
<th>Percentage With Delayed Infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORx &lt;0.25</td>
<td>21</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>0.25 &lt; ORx &lt;0.40</td>
<td>14</td>
<td>6</td>
<td>30</td>
</tr>
<tr>
<td>ORx &gt;0.40</td>
<td>7</td>
<td>11</td>
<td>61</td>
</tr>
</tbody>
</table>

### TABLE 4. ORx Obtained From PiTO2 Probes Not Located in the Territory of Delayed Cerebral Infarction vs PiTO2 Probes Located in the Territory of Delayed Cerebral Infarction

<table>
<thead>
<tr>
<th>Variable</th>
<th>Probe Not in Infarction (n = 11)</th>
<th>Probe in Infarction (n = 9)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORx</td>
<td>0.42 ± 0.06</td>
<td>0.45 ± 0.12</td>
<td>0.79</td>
</tr>
</tbody>
</table>

Values are mean ± SD. 
P for Mann–Whitney U test.
Continuous Monitoring of Cerebrovascular Autoregulation After Subarachnoid Hemorrhage by Brain Tissue Oxygen Pressure Reactivity and Its Relation to Delayed Cerebral Infarction

Matthias Jaeger, Martin U. Schuhmann, Martin Soehle, Christoph Nagel and Jürgen Meixensberger

*Stroke*. 2007;38:981-986; originally published online February 1, 2007; doi: 10.1161/01.STR.0000257964.65743.99

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/38/3/981

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

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

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