Identification and Clinical Impact of Impaired Cerebrovascular Autoregulation in Patients With Malignant Middle Cerebral Artery Infarction

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Background and Purpose—To study cerebrovascular autoregulation and its impact on clinical course in patients with impending malignant middle cerebral artery infarction, we used invasive multimodal neuromonitoring, including measurement of cerebral perfusion pressure, tissue oxygen pressure, and microdialysis.

Methods—Fifteen patients with a stroke that involved >50% of the middle cerebral artery territory were included. Probes were placed into the ipsilateral frontal lobe. Autoregulation was assessed by calculation of the cerebral perfusion pressure–oxygen reactivity index (COR) and the correlation coefficient (R) of cerebral perfusion pressure and tissue oxygen pressure at 24 and 72 hours after stroke.

Results—COR and R at 24 hours after stroke were higher in the 8 patients with a malignant course (ie, massive edema formation) compared with the 7 patients with a benign course (COR, 1.99 ± 1.46 versus 0.68 ± 0.29; R, 0.49 ± 0.28 versus 0.06 ± 0.31; P < 0.05), indicating impaired autoregulation in the malignant course group. At 72 hours, further increases in COR and R were observed in the malignant course group in contrast to the benign course group with stable values over time (COR, 3.31 ± 2.38 versus 0.75 ± 0.31; R, 0.75 ± 0.11 versus 0.36 ± 0.27; P < 0.05). With a COR of 0.99, a cutoff value for prediction of a malignant course was found. The lactate-pyruvate ratio was higher in patients with a malignant compared with a benign course at both time points. COR, R, and the lactate-pyruvate ratio showed significant correlations with outcome parameters as a midline shift on cranial computed tomography and score on the modified Rankin scale after 3 months.

Conclusions—We found early impairment of cerebrovascular autoregulation in peri-infarct tissue of patients who developed malignant brain edema, whereas autoregulation was preserved in patients with a benign course. Impaired cerebral autoregulation seems to play a key role for development of a malignant course and might serve as a predictive marker. Impaired cerebral autoregulation also accentuates the need for consequent adjustment of cerebral perfusion pressure in patients with impaired autoregulation. (Stroke. 2007;38:56-61.)
hemorrhage, and such loss has been associated with poor outcome.7-10 Experimental studies of focal brain ischemia have similarly shown that loss of autoregulation promotes postischemic edema formation.11,12 We hypothesized that the loss of cerebrovascular autoregulation is a relevant mechanism involved in the sequelae of malignant stroke. Clinical studies on the status of autoregulation and its impact on secondary deterioration and outcome in patients with severe ischemic stroke are lacking. We therefore used CPP and ptO2 measurements in combination with microdialysis to study autoregulation and its impact on secondary deterioration and outcome in patients with an impending malignant MCA infarction.

Patients and Methods

Patients

The study was approved by the ethics committee of the medical faculty of the University of Cologne, Cologne, Germany. We included 15 patients who had experienced a severe MCA stroke with dense hemiparesis, conjugate gaze palsy, and infarction >50% of the MCA territory on early (<12 hours) CT or MRI scans. Patients were excluded from the study if they had initial involvement of additional vascular territories or chronic obstructive pulmonary disease or if they underwent hemicraniectomy. Neurological deficit was assessed by the National Institutes of Health Stroke Scale at admission and by the modified Rankin Scale (mRS) after 3 months. According to their clinical course and the appearance of brain swelling on the CT scans, patients were categorized into a malignant group or a benign group. The clinical course was regarded as malignant when the patients had clinical signs of uncal herniation and when space-occupying brain edema occurred with a midline shift (MSh) >5 mm (in situ) at the level of the septum pellucidum.

All patients were admitted to the neurological intensive care unit and received antedematous therapy with mannitol and 30° elevation of the upper body. Patients were sedated with fentanyl plus midazolam, intubated, and ventilated because of a decrease in consciousness to somnolence or stupor. Arterial O2 pressure, CO2 pressure, hemoglobin, serum glucose, pH, base excess, serum sodium, and potassium levels were measured at least every 6 hours. Capillary O2 saturation was monitored continuously. A CT or MRI scan was performed on admission; a follow-up cranial CT scan was performed on days 1, 2, and 5 after stroke; and additional scans were performed during, and after the measurement period. A period of 30 minutes that fulfilled these criteria was selected for each patient at an early time point (COR I, 24±4 hours after stroke), ie, before maximal edema formation occurred and within a time window during which invasive therapies like hemicraniectomy could be performed effectively, and at a late time point (COR II, 72±4 hours after stroke) when maximal edema formation was expected. To quantify the relation between CPP and ptO2, COR was calculated according to Menzel et al10 as COR=ΔptO2/ΔCPP, where ΔptO2 is the mean percentage variation in ptO2 (mean deviation×100/mean ptO2), and ΔCPP is the mean percentage variation in CPP (mean deviation×100/mean CPP) during the 30-minute period. As an additional parameter to quantify the relation between CPP and ptO2, we calculated the linear correlation coefficient between CPP and ptO2 (at the early time point R I and the late time point R II).

Invasive Multimodal Neuronomonitoring

Probes for intracranial pressure (Codman) and ptO2 (Licox, Integra NeuroSciences) as well as a microdialysis probe (CMA 70 Bolt) were inserted into the frontal lobe of the infarcted hemisphere with use of a 3-channel bolt kit (Licox). Microdialysis catheters were perfused continuously with artificial cerebrospinal fluid (CMA) at a rate of 0.3 μL/min. Microdialysate was collected for 120 minutes, and microdialysates were continuously analyzed at the bedside for extracellular concentrations of glutamate, lactate, pyruvate, and glyceral with the CMA 600 microdialysis analyzer. Microdialysates collected before, during, and after the time episodes analyzed for COR (see later section) were selected, and data on these dialysates were averaged for presentation. Intracranial pressure, ptO2, and mean arterial blood pressure were continuously monitored. CPP was calculated as mean arterial blood pressure minus intracranial pressure. All data were added to the database on the mainframe computer and were calculated and depicted on a bedside monitor with software for data navigation (ICU-Pilot, CMA). Other datasets for microdialysis, CPP, and ptO2, presented in earlier publications were derived partially from those of the patients included herein.

Assessment of Cerebrovascular Autoregulation

For assessment of autoregulation, the relation between CPP and ptO2 was analyzed. When autoregulation is intact, the level of ptO2 stays approximately constant when CPP changes within the physiological range of 70 to 110 mm Hg. In contrast, when autoregulation is lost, fluctuations of CPP within this physiological range cause changes in ptO2 that parallel the changes in CPP.13,14 Because ptO2 is proportional to regional cerebral blood flow (CBF), when arterial O2 pressure and cerebral O2 metabolism are constant,15,16 the following criteria had to be fulfilled for data analysis: (1) CPP was within the range for physiological cerebrovascular autoregulation, ie, >70 mm Hg and <110 mm Hg; (2) CPP was not manipulated during the selected period; (3) blood gases, O2 saturation, and ventilator settings were stable; and (4) markers of energy metabolism and ischemia as detected by microdialysis remained stable before, during, and after the measurement period. A period of 30 minutes that fulfilled these criteria was selected for each patient at an early time point (COR I, 24±4 hours after stroke), ie, before maximal edema formation occurred and within a time window during which invasive therapies like hemicraniectomy could be performed effectively, and at a late time point (COR II, 72±4 hours after stroke) when maximal edema formation was expected. To quantify the relation between fluctuations in CPP and ptO2, COR was calculated according to Menzel et al10 as COR=ΔptO2/ΔCPP, where ΔptO2 is the mean percentage variation in ptO2 (mean deviation×100/mean ptO2), and ΔCPP is the mean percentage variation in CPP (mean deviation×100/mean CPP) during the 30-minute period. As an additional parameter to quantify the relation between CPP and ptO2, we calculated the linear correlation coefficient between CPP and ptO2 (at the early time point R I and the late time point R II).

Statistical Analysis

Results are expressed as mean±SD. Comparisons between patient groups were analyzed by Student t test for quantitative variables, by the Mann-Whitney U test for ordinal variables, and by the χ² test for categorical variables. Comparisons between 2 different time points within 1 group were analyzed by the Wilcoxon test. Results from the microdialysis data are expressed as medians and quartiles. Correlation analysis was performed with Spearman correlation coefficient. A value of P<0.05 was chosen as the significance level. To define
a threshold (cutoff value) with optimal diagnostic accuracy for differentiation between groups, we determined the receiver operating characteristic curve. Statistical analysis was performed with SPSS for Windows, v. 11 (SPSS).

Results

Patients

Fifteen patients were included: 8 had a malignant course and developed space-occupying brain edema. Of the 8 patients with a malignant course, 5 died as a result of transtentorial herniation, and 3 survived with moderate to severe neurological defects. The remaining 7 patients did not develop malignant brain edema and were categorized as the benign group. Patients with a benign course survived with mild to moderate handicap; 1 of these patients died from a nonneurological cause. On admission, clinical characteristics like age, sex, affected hemisphere, and comorbidity, as well as mean arterial blood pressure, body temperature, leukocyte count, and National Institutes of Health Stroke Scale score, showed no significant differences between patients with a malignant and those with a benign clinical course (Table).

Arterial O₂ pressure, capillary O₂ saturation, and arterial CO₂ pressure were stable during the recording periods and microdialysis was started at a mean time of 19.4 hours after stroke. Patients were monitored at least until 84 hours after stroke onset. The dependence of ptiO₂ on CPP alterations in impaired cerebrovascular autoregulation in contrast to its relative independence when autoregulation is intact is illustrated in Figure 2 (original registrations). In patients with a benign course and intact autoregulation, the level of ptiO₂ remained nearly constant despite large, spontaneous fluctuations in CPP, whereas in patients with a malignant course and impaired autoregulation, fluctuations in CPP caused changes in ptiO₂ that paralleled those of CPP. At the early time point, COR and R showed marked differences between patients with a malignant and a benign course (Figure 3a): COR I was significantly higher in the malignant (1.99±1.46) than in the benign (0.68±0.29, P<0.05) group. Also, the linear correlation coefficient (R I) was significantly higher in the malignant (0.49±0.28) than in the benign (0.06±0.31, P<0.05) group. In the late time period (Figure 3b), an additional significant increase in COR compared with the early time period was seen in the malignant group (COR II, 3.31±2.38). In the benign group, in contrast, COR II was 0.75±0.31, which was not significantly different from COR I in this group, indicating preserved autoregulation over time. The same tendency of increasing values over time in the malignant group and of stable values in the benign group was found for the linear correlation coefficient, which was 0.75±0.011 (malignant group) compared with 0.36±0.27 (benign group; P<0.05) for R II. At the early time period, microdialysis data showed a significantly higher lactate-pyruvate ratio in the malignant compared with the benign group (Figure 4). Glutamate and glycerol concentrations did not differ significantly between the 2 groups at this time point. At the later time period, the lactate-pyruvate ratio and glycerol concentrations were significantly higher in the malignant compared with the benign group, whereas glutamate tended to show lower concen-

<table>
<thead>
<tr>
<th>Physiological Variables</th>
<th>Malignant, n=8</th>
<th>Benign, n=7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial Po₂ mm Hg</td>
<td>Early Period</td>
<td>93.4±8.0</td>
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<tr>
<td>Capillary O₂ saturation %</td>
<td>99.3±1.1</td>
<td>99.3±0.8</td>
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<tr>
<td>Arterial Pco₂ mm Hg</td>
<td>39.7±2.1</td>
<td>40.3±2.4</td>
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<td>Clinical Characteristics</td>
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<td>Age, mean±SD, years</td>
<td>55±6</td>
<td>61±8</td>
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<tr>
<td>Sex, female/male, n (%)</td>
<td>3/5 (38%)</td>
<td>2/5 (29%)</td>
</tr>
<tr>
<td>Affect ed hemisphere, left/right, n (%)</td>
<td>5/3 (63%)</td>
<td>3/4 (43%)</td>
</tr>
<tr>
<td>NIHSS on admission</td>
<td>20</td>
<td>16</td>
</tr>
<tr>
<td>Mean arterial blood pressure on admission, mm Hg</td>
<td>135.7±16.4</td>
<td>121.7±13.8</td>
</tr>
<tr>
<td>History of hypertension, yes/no, n (%)</td>
<td>7/1 (88%)</td>
<td>7/0 (100%)</td>
</tr>
<tr>
<td>History of diabetes mellitus, yes/no, n (%)</td>
<td>3/5 (38%)</td>
<td>3/4 (43%)</td>
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<tr>
<td>History of nicotine abuse, yes/no, n (%)</td>
<td>5/3 (63%)</td>
<td>4/3 (57%)</td>
</tr>
<tr>
<td>History of dyslipoproteinemia, yes/no, n (%)</td>
<td>4/4 (50%)</td>
<td>1/6 (14%)</td>
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<tr>
<td>History of hyperuricemia, yes/no, n (%)</td>
<td>2/6 (25%)</td>
<td>1/6 (14%)</td>
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<td>Temperature on admission, °C</td>
<td>36.67±0.35</td>
<td>36.82±0.71</td>
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<tr>
<td>Leucocytes on admission, µL</td>
<td>10650±1733 per µL</td>
<td>9213±4870 per µL</td>
</tr>
</tbody>
</table>

NIHSS indicates National Institutes of Health Stroke Scale; ns, nonsignificant.
tations in the benign group, but this difference was not statistically significant (Figure 4). The lactate-pyruvate ratio increased over time in the malignant but not in the benign group. On the contrary, glutamate and glycerol concentrations decreased in the benign group over time, with glycerol reaching significantly lower levels in the late period.

The follow-up cranial CT scans showed the size of definite infarctions in the MCA territory. The mean volume of infarction was significantly larger in the malignant group than in the benign group (90.62±10.15% versus 71.57±18.13% of the MCA territory; \( P<0.05 \)). The maximal MSh on the cranial CT images ranged from 0.0 to 25.0 mm and was significantly larger in the malignant than in the benign group (15.3±7.6 versus 2.8±2.4 mm; \( P<0.05 \)). Three months after stroke, the mRS score ranged from 2 to 6 and was significantly high for all calculated parameters (COR I–mRS \( r=0.55, P=0.052 \); COR I–mRS \( r=0.44, P=0.157 \); R I–MSh \( r=0.52, P=0.084 \)). At the late time point, correlations were significantly high for all calculated parameters (COR II–mRS \( r=0.62, P<0.05 \); COR II–MSh \( r=0.86, P=0.01 \); R II–mRS \( r=0.85, P<0.01 \); R II–MSh \( r=0.82, P<0.01 \)). Correlations between the microdialysis data and COR were significant even in the early clinical course for lactate-pyruvate ratio and COR I (\( r=0.95, P<0.01 \)). In the late period, significant correlations were found for lactate-pyruvate ratio and COR II (\( r=0.98, P<0.01 \)) and for glycerol–COR II (\( r=0.91, P<0.01 \)). With COR I=0.99, we found a cutoff value for the prediction of a malignant clinical course with a sensitivity of 85.7% and a specificity of 83.3%.

**Discussion**

Cerebrovascular autoregulation and its pathophysiology have been investigated and described in numerous experimental studies, in most of which CBF was measured directly. However, in critically ill patients, direct CBF measurement is difficult to achieve. Furthermore, continuous monitoring of cerebrovascular autoregulation is desirable, which allows prompt estimation of autoregulation whenever needed. Therefore, several bedside methods for clinical practice have been developed, which monitor a surrogate marker considered to be proportional to CBF. The indirect character of these approaches is emphasized by the fact that these techniques do not yield any information on the status of brain tissue itself. In our study, we analyzed the relation between CPP and ptiO2 for assessment of autoregulation by continuous multimodal neuromonitoring, including microdialysis. Such monitoring provides direct information on the tissue compartment being monitored; however, these techniques are invasive, and microdialysis requires expertise that, to date, is available only in specialized centers. Menzel et al. have recently introduced the
COR as a marker for cerebrovascular autoregulation, suggesting it to be intact when COR is $<1$ and impaired when $>1$.

The main finding of our study was that patients who developed a malignant course with massive brain edema had significantly higher values of COR when compared with patients with a benign course. In contrast to patients with a malignant course, who showed COR values well above 1, patients with a benign course had stable COR values $<1$. These data suggest that cerebrovascular autoregulation is abolished early in patients who eventually develop massive brain edema, whereas in patients with a benign outcome, autoregulation is preserved. This difference was already distinct at 24 hours after stroke onset; ie, at a time when maximum edema formation was still expected to occur, and it became even more pronounced 72 hours after stroke. In addition, we found that impairment of autoregulation was correlated with the extent of edema formation and poor outcome. A malignant course could be predicted by a COR $>0.99$ as the cutoff value, which corresponds well to the value of 1 found by Menzel et al in neurocritical care patients.

There are 2 main mechanisms that may explain the pathophysiological impact of impaired autoregulation in stroke patients. First, in the case of an abolished autoregulation, even elevations of CPP to values that are not harmful under physiological conditions will lead to a rise in regional CBF, followed by increased extravasation of fluid into the brain tissue. This process might be enhanced when the blood-brain barrier is disrupted, as is expected to occur in the core regions of infarcts of patients with malignant stroke. Subsequently, interstitial edema formation might further worsen tissue diffusion conditions between the vascular and cellular compartments. As an additional consequence of interstitial edema formation, the regional microcirculation would decrease, with the risk of additional regional ischemia and cell death.

Second, when CPP decreases in patients with lost autoregulation, regional CBF drops as well, and secondary ischemia is the consequence that promotes enlargement of the volume of tissue damage. This ischemia of the primarily surviving peri-infarct tissue with enlargement of the infarct and an increase in edema have been demonstrated in patients with malignant MCA infarction.5

In our study, probes were implanted into peri-infarct tissue, a compartment most sensitive to secondary brain damage. The fact that we found impaired autoregulation in such nonischemic tissue neighboring an infarct is in accord with findings of other authors, who showed that autoregulation can also be disturbed in the boundary zone of the ischemic lesion and even in areas more remote from such a lesion.11 It was suggested that brain edema, spreading from the primary lesion along white matter fiber tracts, and tissue acidosis are factors responsible for the loss of autoregulation in these remote compartments. In fact, edematous expansion of the extracellular space not detectable on CT scan seems to take place in the peri-infarct tissue of patients with malignant infarction.5 We found the lactate-pyruvate ratio to be higher in patients with malignant infarction as early as 24 hours after stroke, and it was closely correlated with COR, supporting the assumption that tissue acidosis might be involved in the impairment of autoregulation in peri-infarct tissue. From our findings, we hypothesize a cascade-like, self-energizing sequela in patients with malignant MCA infarction: lactate and extracellular fluid from the vasogenic edema of the infarct core spread into peri-infarct tissue and impair autoregulation in this compartment. Consequently, this tissue also becomes edematous, and expansion of the edema with a space-occupying effect is accelerated and/or secondary ischemia occurs when CPP is not adequately controlled. Such a vicious circle leads to further infarction of primarily surviving tissue and finally ends with transtentorial herniation and death. The ongoing cellular damage of this fatal progress is documented by the increase in glycerol as an indicator of cell membrane degradation in patients with a malignant course in contrast to patients with a benign course, in whom glycerol concentrations become normalized over time. Our data suggest that impaired autoregulation in patients with large MCA infarc-
tions should be identified as early as possible to avoid secondary brain damage by adjustment of CPP and to yield a predictive marker for a malignant clinical course.

Conclusions
In the present study, early impairment of cerebrovascular autoregulation could be detected in peri-infarct tissue of patients who developed malignant brain edema, as indicated by a higher COR, whereas autoregulation was preserved in patients with a benign course. The extent of edema formation and clinical outcome were closely correlated with COR. These results suggest that a malignant course in patients with large MCA infarctions is promoted by impaired cerebral autoregulation. We hypothesize that tissue lactate acidosis plays a key role in the pathophysiology of impaired autoregulation. Early identification of patients with impaired autoregulation will help clinicians to individually adjust CPP management and may serve as a predictive marker for a malignant clinical course.

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Disclosures
None.

References
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