Acute Focal Neurological Deficits in Aneurysmal Subarachnoid Hemorrhage
Relation of Clinical Course, CT Findings, and Metabolite Abnormalities Monitored With Bedside Microdialysis

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Background and Purpose—We sought (1) to identify early metabolic markers for the development of (ir)reversible neurological deficits and cerebral infarction in subarachnoid hemorrhage (SAH) patients by using the microdialysis technique and (2) to evaluate the influence of intracerebral hemorrhage (ICH) on microdialysis parameters.

Methods—We performed a prospective study of 44 SAH patients with acute focal neurological deficits (AFND) occurring acutely with SAH (due to ICH) or directly after surgery (due to clip stenosis, thromboembolism, or early edema). Fifty-one nonischemic SAH patients served as a control group. A microdialysis catheter was inserted into the vascular territory of the aneurysm after clipping. The microdialysates were analyzed hourly for extracellular glucose, lactate, lactate/pyruvate ratio, glutamate, and glycerol with a bedside analyzer. Microdialysis-related CT findings were evaluated for the presence of ICH and cerebral infarction. Reversibility of neurological symptoms after 4 weeks and 6- and 12-month outcomes were assessed.

Results—In patients with AFND, cerebral metabolism was severely disturbed when microdialysis started compared with controls (P<0.005). Infarction on CT was associated with pathological microdialysis parameters (P<0.002) and development of a fixed deficit (P<0.003), while the presence of ICH alone was not. A secondary neurological deterioration of AFND patients (n=11) was reflected by preceding (0 to 20 hours) changes of microdialysate concentrations.

Conclusions—In the presence of ICH, pathological microdialysis values may indicate reversible tissue damage. Extreme microdialysis values and pathological microdialysis concentrations that further deteriorate 2-fold are highly indicative of the development of cerebral infarction and permanent neurological deficits. Therefore, the analysis of relative changes of microdialysis parameters is crucial for the detection of ischemia in SAH patients. (Stroke. 2003;34:1382-1388.)

Key Words: cerebral metabolism ■ ischemia ■ microdialysis ■ neurological deficits ■ subarachnoid hemorrhage

Patients with aneurysmal subarachnoid hemorrhage (SAH) and acute focal neurological deficits (AFND) are at high risk of developing permanent neurological deficits. Their related Fisher score1 and outcome in most cases are worse compared with those of the general SAH population. The acute focal deficits occur with the onset of SAH in addition to the direct effect of the hemorrhage or develop as a new deficit directly after surgery. Major causes of AFND are primary brain damage due to space-occupying hematomas or immediate postsurgical complications such as vessel clip occlusion, thromboembolic events, or early brain swelling.

A visible infarction on CT is an adverse prognostic indicator that increases the risk of mortality and morbidity at 6 months.2 For characterization of cerebral metabolism and the development of ischemia in SAH patients, neurochemical monitoring by cerebral bedside microdialysis has been proposed as a useful tool.3 An experimental study of focal ischemia in primates showed that the extracellular changes of energy-related metabolites and glutamate differed depending on the ischemic state of the brain during middle cerebral artery occlusion.4 A microdialysis study in patients with large middle cerebral artery infarction revealed significantly higher values for glutamate, glycerol, and the lactate/pyruvate (L/P) ratio in the peri-infarct region and in the core of the infarct region than in the noninfarcted hemisphere.5 Whether the extracellular concentrations of microdialysis parameters indicate reversible damage of brain tissue or development of cerebral infarction is still unclear. Therefore, a detailed characterization of the primary brain damage, the secondary development of cerebral infarction, and possible markers of

Received November 4, 2002; final revision received January 17, 2003; accepted January 27, 2003.
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Stroke is available at http://www.strokeaha.org

DOI: 10.1161/01.STR.0000074036.97859.02

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neuronal viability may help to improve therapy, especially in critically ill SAH patients.

In this study we sought to determine the extracellular concentrations of metabolites in the affected brain tissue, as monitored by in vivo microdialysis, in relation to CT findings (presence of intracerebral hemorrhage [ICH]/infarction) of the monitored brain region in SAH patients presenting with AFND. Second, we wanted to clarify whether dialysate changes are the consequence of the initial brain damage or if they are predictors of subsequent neurological worsening in patients with AFND.

Subjects and Methods
This study was performed in accordance with the local medical ethics policies for the study of human subjects, and written informed consent was obtained from the patient or nearest family relative.

Patient Characteristics and Management
During the study period (June 1997 to May 2002), 44 patients with aneurysmal SAH and symptoms of AFND were enrolled in a prospective study on cerebral metabolism monitored by bedside microdialysis.

The inclusion criteria were as follows: (1) SAH was confirmed by cranial CT; (2) cerebral angiogram demonstrated intracranial aneurysms; (3) patients had undergone surgical therapy; and (4) AFND was present. Patients were not included in the study if (1) they initially were asymptomatic and developed delayed ischemic neurological deficits (DIND) (symptomatic vasospasm); (2) they presented clinical and/or microbiological signs of meningitis during microdialysis monitoring; or (3) the microdialysis probe was not located within the vascular territory of the affected brain tissue.

The diagnosis of AFND was determined on a clinical basis, with the use of the following criteria: (1) symptoms of neurological deficits with onset of SAH related to the initial hemorrhage or directly after surgery (vessel clip occlusion, thromboembolic events, or early edema); (2) symptoms developing immediately after the insult or after surgery within a few hours; (3) CT findings to rule out a preexisting neurological disorder or hydrocephalus as cause of the acute neurological deterioration; and (4) no other identifiable cause of neurological deterioration such as electrolyte disturbance, hypoxia, seizure, or cardiopulmonary dysfunction. SAH patients with only minor or completely reversible neurological symptoms (eg, a seizure due to SAH) and no secondary complications (especially no occurrence of DIND, no meningitis, no cerebral infarction) served as a control group (n = 51).

Initially asymptomatic patients who developed symptomatic vasospasm (DIND) were a priori not included in this study to avoid a combination of 2 distinct complications of SAH: the acute focal deficits and the delayed ischemic deficits due to vasospasm and treatable with hypervolemic hypertensive hemodilutive therapy. However, AFND patients who possibly developed symptomatic vasospasm as a secondary complication were not excluded from this study.

Clinical presentation was graded according to the World Federation of Neurological Surgeons (WFNS) scale and the modified Glasgow Coma Scale. Patient follow-up was performed prospectively. The neurological deficits were classified into 2 groups on the basis of the degree of recovery: (1) reversible neurological deficits (symptoms improved within the first 4 weeks after SAH) and (2) irreversible deficits (no improvement within 4 weeks after SAH). Additionally, patients were followed up at 6 and 12 months with the Glasgow Outcome Scale (GOS).

Determination of CT Pathology
Admission and follow-up CT scans (CT Somatom Plus 4, Siemens) were independently evaluated by a study radiologist for amount and location of blood, presence of hydrocephalus, focal or global cerebral edema, and presence of cerebral infarction. At least 3 consecutive CT scans were performed in each patient with acute ischemic deficits: (1) CT 1 on admission; (2) CT 2 postoperatively on day 1 to 3 after surgery; and (3) CT 3 on day 4 to 8 after surgery. If possible, a fourth CT (late CT) was performed on day 10 to 3 months after surgery. Since AFND occurred within the time window between day of SAH and 24 hours after surgery, infarction development should be depicted.

A localized hypodense area surrounding a thick clot was categorized as focal edema. Cerebral infarction was diagnosed when the following were present: (1) focal hypodensity not surrounding an ICH on the admission CT and/or early postoperative CT that did not resolve on the later CT scans and (2) focal hypodensity surrounding an ICH on the admission CT and/or early postoperative CT that did not resolve on the late CT (10 days to 3 months after surgery).

CT pathology was classified into 4 categories: (1) signs of cerebral infarction without ICH present; (2) ICH without infarction present; (3) signs of cerebral infarction and ICH present; (4) neither ICH nor hypodensity present.

Bedside Microdialysis
A microdialysis catheter (CMA 70; length, 10 mm; molecular weight limit, 20 000 Da) was inserted immediately after clipping of the aneurysm into brain parenchyma of the respective vascular territory of the aneurysm, eg, the right frontal lobe in patients with an anterior communicating artery aneurysm. Care was taken to avoid insertion of the catheter directly into macroscopically lesioned brain tissue or directly into an ICH. Catheters were perfused with sterile Ringer’s solution at a flow rate of 0.3 μL/min. On the outlet tube, perfusates were collected in microvials, exchanged hourly, and immediately

### TABLE 1. Demographic Characteristics of SAH Patients

<table>
<thead>
<tr>
<th></th>
<th>AFND (n = 44)</th>
<th>Asymptomatic (n = 51)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>53.1±11.6</td>
<td>49.9±15.0</td>
<td>0.608 NS</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>15/29</td>
<td>23/28</td>
<td>0.539 NS</td>
</tr>
<tr>
<td>Fisher score</td>
<td>3.5±0.8</td>
<td>2.2±0.9</td>
<td>0.001</td>
</tr>
<tr>
<td>ICH</td>
<td>15</td>
<td>15</td>
<td>0.001</td>
</tr>
<tr>
<td>Location of aneurysm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACM</td>
<td>13</td>
<td>13</td>
<td>0.001</td>
</tr>
<tr>
<td>ACT</td>
<td>15</td>
<td>15</td>
<td>0.001</td>
</tr>
<tr>
<td>ACI</td>
<td>15</td>
<td>15</td>
<td>0.001</td>
</tr>
<tr>
<td>ACM/Pcom/Other</td>
<td>1/—</td>
<td>2/5</td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD. AFND indicates Abnormalities Monitored With Bedside Microdialysis; ACM, anterior cerebral artery; ACI, internal carotid artery; ACT, anterior communicating artery; ACM/Pcom, anterior/posterior communicating artery; ACI, intracerebral hemorrhage.

*Mortality in the control group is related to nonsurgical complications.*
analyzed at bedside in a mobile photometric, enzyme-kinetic analyzer (CMA 600). Human microdialysis baseline values at a perfusion rate of 0.3 μL/min represent approximately 70% of actual values (estimated recovery for the system, 0.65 to 0.72). Baseline human microdialysis values, obtained from normal frontal cerebral cortex in patients, are as follows: glucose, 1.7±0.9 mmol/L; lactate, 2.9±0.9 mmol/L; pyruvate, 166±47 μmol/L; L/P ratio, 23±4; glycerol, 82±44 μmol/L; glutamate, 16±16 mmol/L. Extracellular microdialysis concentrations determined in this study are given as microdialysate concentrations; results were not corrected for recovery.

Definition of Microdialysis Courses

To evaluate the possible importance of relative changes, the course of the microdialysis parameters after insertion was classified into 4 categories: course 0, decrease of microdialysate concentrations of glutamate, lactate, and L/P ratio to normal values after insertion; course 1, decrease of extracellular glutamate, lactate, and L/P ratio to abnormal values after insertion; course 2, further secondary increase of 2 of the parameters glutamate, lactate, and L/P ratio to >2 times individual baseline values; and course 3, extremely pathological values from the beginning (glutamate >100 mmol/L, lactate >10 mmol/L, L/P ratio >50).

Data Analysis

Between-group comparisons were performed with 24-hour median values for each microdialysis variable recorded for each patient. Nonparametric tests were used to test the relation of CT pathology, the courses of microdialysis parameters, and the neurological deficit (classified as [ir-reversible deficit]). Differences were considered statistically significant at P<0.05 (SPSS 11.0, SPSS Inc).

Results

Demographic data of the patients and CT pathology are given in Table 1. Patient groups were comparable for age and sex. Three patients (1 asymptomatic, 2 AFND patients) with concomitant ventricular drainage who developed meningitis during or after microdialysis monitoring were excluded from the analysis to avoid a putative masking effect of infection on microdialysis parameters. In none of these 3 patients was there a relevant increase of the dialysate concentrations (when day 2 and the last day of microdialysis monitoring were compared). Figure 1 shows CT and angiographic findings and microdialysis parameters in a patient with AFND.

Acute Focal Neurological Deficits

In 33 patients the AFND occurred with onset of SAH as a consequence of the initial brain damage. Twenty-nine patients had a space-occupying ICH, and in 4 patients malignant brain swelling was diagnosed on the day of SAH, proven by CT and high intracranial pressure (>25 mm Hg).

In 11 patients (25% of the AFND group), the acute focal deficit developed after surgery and was caused by clip

Table 2. Course of Microdialysis Parameters After Surgery

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Day 1</th>
<th>Day 3</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (controls)</td>
<td>2.8 (2.2, 3.6)</td>
<td>2.4 (1.7, 3.0)</td>
<td>1.9 (1.1, 1.9)</td>
</tr>
<tr>
<td>Glucose (AFND)</td>
<td>1.5 (0.1, 3.5)</td>
<td>2.1 (1.1, 2.8)</td>
<td>1.0 (0.2, 2.3)</td>
</tr>
<tr>
<td>Lactate (controls)</td>
<td>0.019</td>
<td>0.346</td>
<td>0.140</td>
</tr>
<tr>
<td>Lactate (AFND)</td>
<td>2.3 (1.4, 2.9)</td>
<td>2.4 (1.7, 3.0)</td>
<td>2.7 (1.9, 3.4)</td>
</tr>
<tr>
<td>L/P ratio (controls)</td>
<td>6.0 (3.3, 12.9)</td>
<td>5.0 (3.0, 12.1)</td>
<td>6.0 (3.8, 10.0)</td>
</tr>
<tr>
<td>L/P ratio (AFND)</td>
<td>0.0005</td>
<td>0.0005</td>
<td>0.0005</td>
</tr>
<tr>
<td>Glutamate (controls)</td>
<td>4.4 (2.3, 7.4)</td>
<td>1.8 (1.2, 1.7)</td>
<td>1.2 (0.8, 1.7)</td>
</tr>
<tr>
<td>Glutamate (AFND)</td>
<td>25.2 (3.2, 152.2)</td>
<td>22.6 (1.3, 133.7)</td>
<td>23.6 (1.7-140.2)</td>
</tr>
<tr>
<td>Glycerol (controls)</td>
<td>69.2 (39.6, 126.4)</td>
<td>65.4 (40.2, 101.2)</td>
<td>44.0 (25.1, 94.3)</td>
</tr>
<tr>
<td>Glycerol (AFND)</td>
<td>275.7 (89.6, 570.8)</td>
<td>127.6 (66.7, 346.6)</td>
<td>73.8 (29.5, 272.9)</td>
</tr>
</tbody>
</table>

Data are expressed as median values of daily medians (with 25, 75 quartiles). In patients with acute focal neurological deficits (AFND), anaerobic metabolism (increased lactate and L/P ratio, low glucose) and high glutamate and glycerol concentrations were measured compared with controls.
stenosis (n=6), thromboembolic complication (n=3), or early edema with intracranial hypertension (n=2). These patients experienced AFND symptoms on the day of surgery, within 6 hours after clipping. Symptoms were hemiparesis not present before surgery (n=9) and development of intracranial hypertension (intracranial pressure >20 mm Hg).

In all patients except 1, angiography was performed for diagnosis of the acute focal deficit. In all of these patients, angiographic vasospasm as a possible cause for the focal deficit after surgery was excluded.

Cerebral Metabolism in AFND Patients and Controls
The AFND occurred with SAH or directly after surgery. Mean time from SAH to start of microdialysis monitoring was 33.7±49.3 hours in AFND patients and 48.9±43.2 hours in controls (P=0.125 [NS]). Earliest microdialysis data were available after surgery, within 2 days after the stroke. The median values of microdialysate concentrations on days 1, 3, and 7 after surgery in AFND patients and the control group are given in Table 2. The microdialysate concentrations (lactate, glutamate, L/P ratio, and glycerol) of AFND patients were significantly higher than those of controls (P<0.005). The excitotoxic amino acid glutamate correlated highly with the L/P ratio, a marker of anaerobic metabolism (24-hour median values; n=126; Pearson’s r=0.899, P<0.01).

Course of Microdialysis Parameters
The course of microdialysis parameters was significantly different between the 2 groups (P<0.0005). In the majority (88.5%) of the controls, microdialysis concentrations decreased after insertion and remained within a normal range throughout the monitoring time (course 0). Pathological microdialysate concentrations were measured in only 4 patients of the control group. These patients exhibited symptoms such as headache and slight lethargy without evidence of cerebral vasospasm; they recovered quickly without hypodynamic therapy.

In AFND patients (n=44), 4 different courses of relative microdialysate changes were observed (Figure 2). In course 0, 5 AFND patients (11%) had normal values after insertion, which was comparable to controls. In these cases, microdialysis did not detect ischemia, although the probe was close to the hypodense region on CT scan. In course 1, in 11 AFND patients, a secondary deterioration of microdialysis parameters occurred in 17
AFND patients (39%). In course 3, 11 AFND patients (25%) had extremely pathological concentrations initially, which remained relatively unchanged during the monitoring time.

**Secondary Neurological Deterioration of AFND Patients**

To clarify whether microdialysis changes are the consequence of primary brain damage or if they are predictors of subsequent neurological worsening, the clinical courses of AFND patients in relation to the microdialysis courses were analyzed. In AFND patients who improved clinically during microdialysis monitoring, microdialysis values were normal (course 0; n=4) or decreased over time (course 1; n=11), and in only 4 cases were microdialysate concentrations extremely high (course 3). AFND patients who neither improved nor deteriorated during microdialysis monitoring (no change in grade of paresis, stable intracranial hypertension) had some brain swelling (course 0). AFND patients who deteriorated (course 1) had pathological microdialysate concentrations (n=5; course 2) or a secondary deterioration of microdialysis values (n=9).

In patients who clinically deteriorated further (n=11), the clinical deterioration was reflected in changes of microdialysates, as shown in Table 3.

**Cerebral Metabolic Changes in Infarction**

Cerebral infarction developed in 26 AFND patients. Of these, 15 patients had no evidence of ICH or hypodensity on admission CT. In patients with ICH, infarction was diagnosed on the latest CT, which was performed on day 24 (range, 14 to 79 days) after surgery.

The presence of infarction on CT (with or without additional ICH) was significantly associated with pathological microdialysate concentrations of glutamate and lactate and/or the L/P ratio (P<0.002) and with a fixed neurological deficit (P<0.003), while the presence of an ICH alone (without infarction) was not.

**Correlation With Outcome**

According to the GOS, the 6-month outcome (GOS6) and 12-month outcome (GOS12) were comparable. GOS6 data were available in 91 patients (AFND group, n=42; control group, n=49) and GOS12 data in 77 patients (AFND group, n=35; control group, n=42). The mean±SD GOS score of the AFND patients was significantly lower than that of the control group, as follows: GOS6: AFND group, 3.3±1.3; control group, 4.4±1.0 (P=0.001); GOS12: AFND group, 3.0±1.4; control group, 4.5±0.9 (P=0.001). The majority (60%) of the AFND patients (n=21) had an unfavorable outcome (GOS12 score 1 to 3), and 40% (n=14) had a favorable outcome (GOS12 score 4 to 5). This relatively poor outcome reflects the severity of the strokes included. In the control group, 91% (n=38) of the patients had a favorable outcome (GOS12 score 4 to 5), and 9% (n=4) of the patients had an unfavorable outcome (GOS12 score 1 to 3). The causes for an unfavorable outcome in the control group were not related to surgery.

**Discussion**

The microdialysate concentrations (lactate, glutamate, L/P ratio, and glycerol) of SAH patients with AFND were

**TABLE 3. Patients With Acute Focal Neurological Deficits and Secondary Neurological Deterioration**

<table>
<thead>
<tr>
<th>No.</th>
<th>AFND</th>
<th>Secondary Deterioration</th>
<th>MD Initially Pathological</th>
<th>Cause</th>
<th>Onset†</th>
<th>Angiography/TCD</th>
<th>Secondary MD Deterioration Time, h‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Edema 2 No</td>
<td>Malignant brain swelling</td>
<td>3</td>
<td>No VSP present</td>
<td>Yes</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Edema 1 Yes</td>
<td>Increased ICP</td>
<td>4</td>
<td>NA</td>
<td>Yes</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>ICH 1 Yes</td>
<td>VSP</td>
<td>5</td>
<td>TCD +</td>
<td>No§</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Edema 1 Yes</td>
<td>Malignant brain swelling</td>
<td>6</td>
<td>NA</td>
<td>Yes</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>ICH 1 Yes</td>
<td>Malignant brain swelling</td>
<td>4</td>
<td>Retrograde filled MCA</td>
<td>Yes</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>ICH 1 Yes</td>
<td>VSP</td>
<td>7</td>
<td>VSP</td>
<td>Yes</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>ICH 1 Yes</td>
<td>VSP</td>
<td>6</td>
<td>TCD +</td>
<td>Yes</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Clip stenosis 1 Yes</td>
<td>Malignant MCA infarction</td>
<td>3</td>
<td>Missing MCA branch</td>
<td>Yes</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>ICH 1 No</td>
<td>Infarction</td>
<td>3</td>
<td>NA</td>
<td>No</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>ICH 1 Yes</td>
<td>VSP</td>
<td>2</td>
<td>TCD +</td>
<td>Yes</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>ICH 1 Yes</td>
<td>VSP</td>
<td>2</td>
<td>TCD +</td>
<td>No§</td>
<td>...</td>
<td></td>
</tr>
</tbody>
</table>

In almost all AFND patients, microdialysis (MD) concentrations were initially pathological, reflecting the initial brain damage. In average 4 days after the acute focal neurological deficit (AFND), patients secondarily deteriorated, which was reflected in preceding and parallel changes of microdialysate concentrations.

TCD + indicates mean flow >120 cm/s in transcranial Doppler ultrasound; VSP, vasospasm; ICH, intracerebral hemorrhage; MCA, middle cerebral artery; NA, not available.

*Day 1 indicates day of SAH; †day of onset of secondary neurological deterioration after AFND; ‡time of MD changes preceding onset of secondary neurological deterioration; §MD concentrations in these patients were initially extremely high and showed no further deterioration.

**Discussion**

The presence of infarction on CT (with or without additional ICH) was significantly associated with pathological microdialysate concentrations of glutamate and lactate and/or the L/P ratio (P<0.002) and with a fixed neurological deficit (P<0.003), while the presence of an ICH alone (without infarction) was not.
significantly higher than those of controls (P<0.005). The presence of infarction on CT was associated with pathological microdialysis values, while the presence of ICH alone was not. In AFND patients, glutamate, lactate, and the L/P ratio were equivalent markers of acute ischemia. Microdialysate concentrations of glutamate, lactate, and/or the L/P ratio that deteriorated further were predictors of subsequent neurological worsening, eg, as a result of brain swelling or cerebral vasospasm, and were highly indicative of the development of cerebral infarction (P<0.002) and permanent neurological deficits (P<0.003).

In patient studies and experimental positron emission tomography (PET) studies, the L/P ratio is discussed as the most robust marker of acute ischemia, with a high sensitivity and specificity,

while in transient ischemia without development of infarction or permanent deficits, elevated lactate levels without a concomitant high L/P ratio are described. These recent clinical studies suggest that lactate and glutamate may be the most sensitive and early markers for impending ischemia in SAH, followed by the L/P ratio and glycerol during manifest ischemia and cell degeneration, 12, 13

Results obtained from a middle cerebral artery occlusion study interpret the reversible increases of the L/P ratio as a transient penumbra situation. 4 In this study lactate and L/P ratio changes occurred, in most cases, in parallel with glutamate changes, which, in our view, reflect the severity of the symptoms observed in AFND patients. 14 In clinical practice, a sudden elevation of lactate and/or L/P ratio and glutamate might serve as a warning signal. In contrast to stroke patients with defined ischemic lesions, the causes responsible for the acute ischemic deficit are heterogeneous. Since this subgroup of SAH patients has the worst neurological outcome, an improved analysis of cerebral metabolic changes may lead to therapeutic options and a better outcome in these patients. 15

The location of the microdialysis probe is crucial, and care should be taken to avoid insertion directly into a clot. In this study the majority of patients with ICH had initial pathological concentrations of lactate and glutamate levels in the tissue surrounding the ICH compared with asymptomatic patients. They progressed to cerebral infarction only if extracellular glutamate and lactate and/or L/P ratio secondarily deteriorated or were initially extremely elevated. These highly pathological concentrations of microdialysis parameters were comparable to concentration levels obtained from stroke patients within the infarct core. 5

The correlation of metabolic microdialysis parameters and radiological findings on CT observed in this study has certain pitfalls. Early signs of presumed infarction can be detected on CT within the first 6 hours only in up to 50% of patients. 16 Therefore, in some AFND patients it is possible that the initial CT scan did not detect ischemic regions; this may explain the extremely high concentrations of microdialysis parameters seen in 11 of our patients directly after insertion. The sensitivity in detecting an ischemic region is described as identical in PET and CT only within 2 to 6 days of the ictus. 17 Later, in the second and third weeks after stroke, an initially hypodense region on CT may become isodense (“fogging effect”), 18 and thus infarcts may be missed as well. Second, in a PET-CT correlation, patients with early CT signs had a significantly larger area of critical hypoperfusion on PET than suggested on CT. This emphasizes that the presumably infarcted tissue visible on CT is the “tip of the iceberg” in terms of tissue at risk of irreversible damage. 19 Even if the correlation of microdialysis parameters in respect to the visible lesion on CT for detection of ischemia is very promising, advanced methods using fluorodeoxyglucose PET and cerebral blood flow measurements in combination with microdialysis are desirable. Third, lesions on CT scan might not be related to the symptoms presented by the patients, 20 while hypometabolism seen on PET was often related to the character of the neurological syndromes. 17 In this study a high correlation between the reversibility of symptoms 4 weeks after the ictus and the course of microdialysate concentrations was observed. In some symptomatic patients, however, the microdialysis probe did not indicate a disturbed metabolism, although CT control confirmed that the microdialysis probe was close to infarcted brain tissue and ICH. Therefore, future studies may focus on optimizing the location of the microdialysis probe in respect to the cerebral lesion.

A series of studies have proposed that glutamate is an excellent marker of ischemia in SAH patients. 12, 13, 21 In regard to the long-term effect, however, there was only a weak association between abnormal glutamate level and unfavorable outcome in a small SAH patient group (n=40). 22 In this study a high correlation between glutamate and L/P ratio as a marker of energy metabolism was found, which confirms that glutamate is not an energy-dependent marker of ischemia in SAH.

Increased extracellular glycerol concentrations are observed in SAH patients with clinical vasospasm and ischemic events. 23 These probably originate from phospholipid breakdown of disintegrating cell membranes, eg, they are caused by ischemia leading to energy failure. After occlusion of the middle cerebral artery, a marked elevation of glycerol levels was observed, indicating severe irreversible ischemia, while in penumbral regions glycerol returned to baseline levels. 4 This is also confirmed by our own data, which showed high glycerol levels that did not normalize in patients who developed cerebral infarction, while an initial and reversible increase of glycerol might reflect local tissue damage after ICH.

Conclusion
In summary, our data demonstrate that bedside cerebral microdialysis is a safe technique to indicate cerebral ischemia in SAH patients with acute ischemic deficits when the probe is inserted into the affected region. In the presence of ICH, pathological microdialysis values may indicate only local damage, but in case of a further deterioration, they are highly indicative of the development of cerebral infarction and permanent neurological deficits. Therefore, study of relative microdialysis changes is mandatory. A better understanding of cerebral metabolism in SAH may lead to therapeutic options to minimize infarct development and may help to improve prognosis in the future.
References


Acute Focal Neurological Deficits in Aneurysmal Subarachnoid Hemorrhage: Relation of Clinical Course, CT Findings, and Metabolite Abnormalities Monitored With Bedside Microdialysis

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*Stroke*. 2003;34:1382-1388; originally published online May 15, 2003;
doi: 10.1161/01.STR.0000074036.97859.02

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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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/34/6/1382

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