Extracellular Concentrations of Non–Transmitter Amino Acids in Peri-Infarct Tissue of Patients Predict Malignant Middle Cerebral Artery Infarction

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Background and Purpose—Space-occupying brain edema is a life-threatening complication in patients with large middle cerebral artery (MCA) infarction. To determine predictors of this detrimental process, we investigated alterations of extracellular non–transmitter amino acid concentrations in peri-infarct tissue.

Methods—Thirty-one patients with infarctions covering >50% of the MCA territory in early cranial CT scans were included in the study. Probes for microdialysis, intracranial pressure, and tissue oxygen pressure were placed into the noninfarcted ipsilateral frontal lobe. Positron emission tomography imaging was performed in 16 of these patients to measure cerebral blood flow in the tissue around the neuromonitoring probes.

Results—Fourteen of the 31 patients developed a malignant MCA infarction, and 17 did not. The patients in the malignant group had significantly lower extracellular concentrations of non–transmitter amino acids than those in the benign group in the first 12 hours of neuromonitoring. At this time, CBF values determined in regions of interest around the probes by positron emission tomography and tissue oxygen pressure showed that the monitored tissues were not yet infarcted, and no differences in transmitter amino acids concentrations were found between the 2 groups. Furthermore, extracellular concentrations of non–transmitter amino acids were negatively correlated with size of infarction.

Conclusions—We assume that reduction of non–transmitter amino acid concentrations reflects an expansion of the extracellular space by vasogenic edema formation in peri-infarct tissue of patients with malignant MCA infarction. Our findings facilitate early prediction of malignant edema formation and may help to increase knowledge of the pathophysiology of the peri-infarct zone of large MCA infarction. (Stroke. 2003;34:2908-2915.)

Key Words: amino acids ▪ brain edema ▪ cerebral infarction ▪ middle cerebral artery

Space-occupying brain edema is a life-threatening complication in patients with large middle cerebral artery (MCA) infarction. Therefore, early identification is essential for timely application of invasive therapies such as hemi-craniectomy. We implemented invasive neuromonitoring comprising measurements of extracellular substrate concentrations by microdialysis, intracranial pressure (ICP), and tissue oxygen partial pressure (Pto2). In recent studies we have focused on neuromonitoring of neuroactive substances such as transmitter amino acids (TAAs), lactate, pyruvate, and purines in peri-infarct tissue in patients at risk for malignant MCA infarction. These investigations were based on the hypothesis that early elevation of neuroactive substances (eg, glutamate) could predict malignant MCA infarction, as had been suggested by other authors. It was shown, however, that these substances rise only during the later course of malignant infarction at time points that might be too late for implementation of hemicraniectomy. To determine other predictors of malignant MCA infarction, we enlarged the spectrum of the detected substances. Shimada et al reported alterations of extracellular concentrations of non–transmitter amino acids (non-TAAs) using a cat ischemia model. In the present study we systemically investigated alterations of non-TAAs in patients with large MCA infarction with special emphasis on changes in the first 12 hours after the start of neuromonitoring. Furthermore, positron emission tomography (PET) imaging was performed to measure cerebral blood flow (CBF) in the tissue around neuromonitoring probes. This is the first report on non-TAAs in human stroke.

Subjects and Methods

Patients

We included 31 patients in this study. Neumonitoring was performed in 34 patients (see Dohmen et al), but in 3 cases the volume...
of microdialysates was insufficient for further high-performance liquid chromatography (HPLC) analysis. All patients suffered from ischemic infarction that covered >50% of the MCA territory on early cranial CT scans. They showed clinical signs of a severe ischemic MCA syndrome with dense hemiparesis and conjugate gaze palsy. Patients were categorized post hoc into a malignant group or a benign group according to the clinical course. Courses were regarded as malignant when the patients had signs of uncal herniation with a unilaterally fixed and dilated pupil. All patients with malignant course under conservative treatment showed clinical signs of herniation: space-occupying brain edema with a midline shift >2 mm at the level of the septum pellucidum on CT corresponds to >5.54 mm in situ. All patients were admitted to the neurological intensive care unit and treated with antiedematous therapy, including 30° elevation of the upper body and osmotic therapy with mannitol; mean arterial blood pressure was controlled with the use of urapidil or catecholamines. Twenty-seven patients were sedated with fentanyl plus midazolam, intubated, and mechanically ventilated during the neuromonitoring. Four patients were sedated only for probe implantation; thereafter they were conscious and breathed spontaneously. This study was approved by the ethics committee of the medical faculty of the University of Cologne (approval No. 99182).

### Neuromonitoring

Probes for microdialysis (CMA 70 custom probe, Axel Semrau GmbH), for ICP measurement (Codman Microsensor, Ethicon Medical GmbH), and for PtO₂ (Licox CCI SB, Integra Neurosciences) were placed into the noninfarcted frontal lobe of the affected hemisphere by standardized implantation via a 3-channel bolt kit (Licox IM3.S, Integra Neurosciences). Probe locations were evaluated on follow-up CT scans. The mean distance between probes and infarcted tissue was 9±4 mm (malignant group, 8±3; benign group, 10±5; P=NS). The implantation did not harm the patients, and no symptomatic bleeding occurred. ICP and PtO₂ were continuously monitored. The microdialysis probe was perfused continuously at a rate of 0.3 μL/min with a sterile isotonic solution, and samples were collected every 120 minutes. Microdialysates were analyzed for extracellular concentrations of non-TAAs (arginine, asparagine, isoleucine, leucine, methionine, phenylalanine, serine, threonine, valine) and TAAAs (glutamate, aspartate, γ-aminobutyric acid [GABA]) in a post hoc analysis on a HPLC system.

### PET and CT Studies

PET studies were performed on an ECAT EXACT HR scanner (Siemens/CTI) in 16 of the 31 patients. A total of 20 mCi (740 MBq) [11C]flumazenil was injected intravenously, and the distribution and accumulation of this tracer were followed by serial scanning. Tracer distribution within 2 minutes after injection allows a semiquantitative measurement of regional CBF, which can be quantified by a reference method described earlier. In PET images we formed a 0.51-cm³ volume of interest around the probes, which was identified on coregistered cranial CT scans. Cranial CT scans were performed on admission, at 6 to 12 hours, and at day 5. Scans were scrutinized for probe localization, presence of mass effect, secondary hemor-

### Statistical Analysis

Results are expressed as mean±SD if not otherwise noted. Comparisons between the patient groups were analyzed by Student t test for quantitative variables, by Mann-Whitney U test for ordinal variables, and by χ² test for categorical variables. The Spearman coefficient was used to analyze correlations between size of infarction and extracellular non-TAA concentrations. A significance level of P<0.05 was chosen. Discriminatory power and the optimal cutoff values of non-TAAs for differentiation among the patient groups were determined by analysis of the receiver operating characteristic curves. Statistical analysis was performed with the use of SPSS for Windows version 10 (SPSS).

### Results

#### Patients

Fourteen of the 31 patients included in the study had a malignant course, and 17 had a benign clinical course. On admission there were no significant differences in clinical parameters, ie, sex, affected hemisphere, age, National Institutes of Health Stroke Scale score, leukocyte count, temperature, and mean arterial blood pressure between the 2 groups. The portion of patients treated with intravenous recombinant tissue plasminogen activator thrombolysis did not differ significantly between the malignant and the benign group (Table 1). Values of the modified Rankin Scale, as an indicator of patient’s outcome 3 months after stroke, were significantly lower in the malignant group than in the benign group (malignant group, median score 6; benign group, median score 4; P<0.01; mean scores were 5.5 and 4.2, respectively).

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trations of TAAs (glutamate, aspartate, and GABA) did not differ significantly between the 2 groups. At this time, we did not find hypoxic values of the PtO₂ in peri-infarct tissue in either group (malignant group, 18.9±11.7 mm Hg; benign group, 19.2±5.9 mm Hg; P=NS). ICP tended to be higher in the malignant group, but this difference did not reach statistical significance (malignant group, 13.3±7.8 mm Hg; benign group, 8.5±4.0 mm Hg).

To analyze the discriminatory power of non-TAA concentrations in the first 12 hours of measurement for early differentiation among the patient groups, we created receiver operating characteristic curves (Figure 2). Receiver operating characteristic curves demonstrated optimal cutoff values as well as percentage of subjects who had true-positive (sensitivity) and false-positive (100—specificity) results. Cutoff values found for the individual non-TAA concentrations are designated by an arrow in Figure 2. The areas under the curves indicated diagnostic accuracy (1, optimal test assertion; 0.5, test assertion equal to random). Sensitivity and specificity as well as the area under the curve varied only slightly among analyzed non-TAAs.

Figure 3 shows time courses of non-TAA concentrations related to stroke onset. For better display, only 6 non-TAAs are presented as mean values of the several patients of each group (Figure 3, top). Non-TAA concentrations in the malignant group were lower than in the benign group throughout the whole analyzing period. The order of substance concentrations (with valine highest, leucine second, and asparagine lowest) was the same in both groups. It did not vary over time in either the benign or the malignant group. In the benign group, the concentrations of the several non-TAAs showed a similar pattern of changes over time; this was also valid for the malignant group (Figure 3a and 3b). To demonstrate the uniformity of extracellular non-TAA alterations within 1 group over time, ratios for all pairs of non-TAAs (eg, valine/leucine; the reciprocal values, ie, leucine/valine are not shown) were calculated for corresponding time points (Figure 3c and 3d; ratios were calculated for 15 possible pairs of the 6 non-TAAs in each group). These ratios remained almost constant throughout the observation period, documenting that substrate concentrations changed homogeneously. Thus, only absolute but not relative values of non-TAA concentrations

Figure 1. Extracellular concentrations of non-TAAs and TAAs expressed as mean±SD of the first 12 hours of microdialysis measurement. Measurements were performed in peri-infarct tissue of patients with large MCA infarction. Patients in the malignant group developed life-threatening edema formation, whereas patients in the benign group did not.

Figure 2. Receiver operating characteristic curves analyze the discriminatory power of non-TAA concentrations in the first 12 hours of measurement for prediction of patients with life-threatening edema formation. Curves demonstrate the optimal cutoff values as well as the percentage of true-positive (sensitivity) and false-positive (100—specificity) results in tested individuals. The areas under the curves indicate diagnostic accuracy.
changed over time, and it becomes clear that common mechanisms must be responsible for the observed changes.

PET and CT Studies
The mean time from stroke onset to PET imaging was 15.9 ± 6.4 hours (malignant group, 15.2 ± 7.1 hours; benign group, 16.4 ± 6.3 hours; P=NS). PET measurements demonstrated that CBF within the volume of interest around the probes was not at ischemic levels in both groups but was significantly lower in the malignant group than in the benign group (59.5 ± 6.4% versus 89.1 ± 20.5% of mean CBF of contralateral hemisphere \(P<0.01\), which corresponds to approximately 18 versus 25 mL/100 g per minute; see also Thiel et al\(^7\)).

Negative correlations were found between size of infarction on follow-up CT scan and non-TAA concentrations (Table 2). These correlations reached statistical significance for extracellular concentrations of arginine, asparagine, isoleucine, leucine, methionine, phenylalanine, serine, and valine. Threonine showed the same tendency, but this did not reach statistical significance \(P=0.064\).

**TABLE 2. Correlation Between Size of Infarction on Follow-Up CT and Extracellular Non–Transmitter Amino Acid Concentrations in the First 12 Hours of Measurement (n=31)**

<table>
<thead>
<tr>
<th>Non–Transmitter Amino Acid</th>
<th>Spearman’s (\rho)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arginine</td>
<td>-0.536</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Asparagine</td>
<td>-0.407</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Isoleucine</td>
<td>-0.718</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Leucine</td>
<td>-0.622</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Methionine</td>
<td>-0.604</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>-0.632</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Serine</td>
<td>-0.376</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Threonine</td>
<td>-0.361</td>
<td>NS</td>
</tr>
<tr>
<td>Valine</td>
<td>-0.585</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

**Discussion**
In animal experiments and clinical studies, elevated extracellular concentrations of TAAs such as glutamate indicate not only primary but also secondary ischemic tissue damage.\(^9\)–\(^11\) We have recently shown that TAAs increase in peri-infarct regions if cerebral perfusion pressure drops below approximately 60 mm Hg.\(^4\) The time point of this increase, however, is too late for successful intervention with invasive strategies such as hemicraniectomy. To determine other markers and predictors of malignant MCA infarction, we enlarged the spectrum of analyzed substances and systematically investigated non-TAA concentrations, with a special focus on early detection (within 12 hours after the onset of neuromonitoring). In this early time period, differences of TAA concentrations, ie, glutamate, aspartate, and GABA, were small and did not differ significantly between benign and malignant patient groups. These findings can be explained by the fact that \(\text{PtO}_2\) values in peri-infarct tissue in the malignant as well as in the benign group were at levels of noninfarcted tissue\(^6,12\), and \(\text{PtO}_2\) did not differ significantly between groups. We therefore assume that microdialysis determinations were performed in both groups in not-yet-infarcted tissue. This assumption is underscored by the PET findings, which revealed normal CBF values in probe regions of all studied patients. One must consider, however, that PET measurements were performed before the onset of neuromonitoring. Since, under the described conditions, release and reuptake mechanisms of TAAs were presumably intact in the investigated peri-infarct tissue, we suppose that TAA concentrations were well controlled, and changes were therefore not detectable.

In contrast to the TAAs, we found lower concentrations of non-TAAs in the first 12 hours of measurement in patients...
who developed malignant brain edema during the later clinical course compared with the patients who did not. Furthermore, we observed that the proportional composition of the extracellular pool of non-TAAs as well as the concentration ratios among the several non-TAAs did not change over time. From this result, we conclude that decreases of extracellular concentrations of non-TAAs reflect a passive alteration of all non-TAA concentrations, possibly by dilution due to edema formation.

Ischemic brain edema results from cytotoxic edema due to ionic pump failure and from vasogenic edema as a consequence of increased blood vessel permeability.13 These 2 types of ischemic brain edema follow a different time course. Cytotoxic edema begins minutes after stroke onset; diffusion-weighted MRI takes advantage of this phenomenon in hyperacute stroke diagnosis.14 Vasogenic edema appears later than cytotoxic edema in severe ischemic injury.15,16 It leads to a rise in net water content of the ischemic brain tissue. However, vasogenic edema formation is not restricted to the infarcted tissue but spreads into the extracellular space of the peri-infarct tissue.13,15,17,18 Such spread has been reported to occur in particular along nerve fibers by bulk flow and diffusion.17,19 Since our measurements were performed in subcortical white matter of the peri-infarct zone and at a time when vasogenic edema formation predominantly occurs,20,21 an expansion of the extracellular space and a subsequent dilution effect may not be surprising. In general, the volume of the extracellular space influences substance concentrations detected by microdialysis/HPLC.22 One possible explanation for our findings is that non-TAAs are diluted in the malignant group due to vasogenic edema formation in the infarcted tissue that spreads out into the extracellular space of peri-infarct tissue. The predominantly passive character of the decrease of non-TAA concentrations is supported by the observation that the order of magnitude of individual non-TAA concentrations was exactly the same in patients in the malignant and benign groups (with valine highest, leucine second, and asparagine lowest, as shown in Figure 3). The same order has been found experimentally in cat brain under nonischemic conditions,6 and this order remained unaltered through all patients. Even though concentrations changed over time, the order never varied (Figure 3a and 3b), and ratios between concentrations of the all pairs of non-TAAs remained approximately constant (Figure 3c and 3d).

The integrity of neuronal tissue, especially astrocytes, is essential for the function of the blood-brain barrier.23–25 Consequently, damage of neuronal tissue results in increased blood-brain barrier permeability. Direct ischemic damage of brain vessels26 may add to the problem, and reperfusion, eg, after thrombolysis, may also exacerbate blood-brain barrier damage.26 The greater the brain tissue and vessel damage, the greater is the water increase in extracellular space of infarction, and because of bulk flow, secondarily of peri-infarct tissue.17 Accordingly, we expected a negative correlation between size of infarction and non-TAA concentrations. The observation that size of infarction on follow-up CT scans and concentrations of non-TAAs in the peri-infarct tissue were negatively correlated (Table 2) may prove the hypothesis that decreased non-TAA concentrations in patients with malignant infarction result from excessive vasogenic edema formation due to primary or secondary brain vessel damage.

Next to H2O shifts from intracellular or vascular compartments to the extracellular compartment, other mechanisms that could alter extracellular concentrations of non-TAAs in the peri-infarct tissue must be taken into consideration. It has been suggested that suppression of protein synthesis is already induced at approximately 80% of normal CBF.27,28 Accordingly, one might expect protein synthesis to be inhibited in peri-infarct tissue of patients with large MCA infarction and extracellular concentrations of non-TAAs to be increased because of continuous protein degradation. One would therefore expect concentrations of non-TAAs in peri-infarct tissue of malignant patients to be higher rather than lower if compared with the same site in benign patients because CBF in the probe region was shown to be lower in the malignant group. In consideration of our findings and the fact that half-life values of brain proteins vary between 3 and 9 days,29 the influence of protein synthesis inhibition on alteration of extracellular non-TAAs, however, may have played a minor role.

Other mechanisms by which extracellular substrate concentrations may be altered include transmembrane transport mechanisms for individual substances. Various transport systems are known for selected non-TAAs in brain cells, predominantly in gray matter regions.30 Several of these transport mechanisms are coupled to ion gradients across cell membranes. Since our measurements were performed in not-yet-ischemic peri-infarct tissue in subcortical white matter, we assume that ion homeostasis was not affected in this compartment, and transport systems should have still worked in physiological conditions. Therefore, changes in transmembrane transport are unlikely to explain the differences found in extracellular concentrations of non-TAAs between malignant and benign patients.

Regarding the usefulness of our findings for prediction of malignant edema formation, the acquired cutoff values permitted good diagnostic accuracy, with sensitivities and specificities of approximately 80% in the first 12 hours of neuromonitoring. The presented data have been acquired by post hoc HPLC analysis. We are currently implementing bedside HPLC to test whether online monitoring of non-TAAs is feasible. The method is not much slower than enzymatic detection by semiautomated commercial analyzers such as those used in the preceding studies3,4 but is more elaborate and therefore is not suitable for routine use in intensive care stroke units, and it is questionable whether the method can be implemented in more diffused non–intensive care stroke units. Hence, the search for more easily detectable markers of edema formation should be continued. Other approaches for detection of extracellular space alterations should also be considered in this context. First, diffusion-weighted MRI is capable of providing good estimates of extracellular space alterations that derive from cytotoxic or vasogenic edema.14,31 To provide longitudinal information, however, sequential imaging would be needed, perhaps in combination with neuromonitoring. Other, more quantitative assessments of diffusion conditions in the extracellular space, by using tetramethylammonium ions, for example, have been
described, but these methods have not been adapted to clinical conditions.

**Conclusion**

We found significantly lower concentrations of non-TAAs in peri-infarct tissue of patients who developed malignant brain edema than in patients with a benign clinical course. This decrease of non-TAAs may be attributed to a dilution of substances in an expanded extracellular space resulting from vasogenic edema of infarcted tissue. This edema may proceed into the peri-infarct region when the tissue is not yet secondarily ischemic. Our findings may help to predict the malignant progression of edema formation in patients suffering from hemispheric stroke. These results emphasize the relevance of vasogenic edema in the pathophysiology of the peri-infarct zone of malignant MCA infarction.

**Acknowledgments**

This work was supported by a grant from the Bundesministerium für Bildung und Forschung (Kompetenznetz Schlaganfall) to Dr Graf and Dr Heiss. The authors thank Paula Gabel, Andreas Beyrau, and the staff of the neurological intensive care unit for valuable technical assistance.

**References**

Large infarctions of the middle cerebral artery (MCA) territory still represent a challenge for neuro-intensive care. Some patients may develop a space-occupying brain edema leading to raised intracranial pressure, midline shift, and, in the worst case, herniation with subsequent death. Clinical deterioration with decreasing levels of consciousness and evolvement of brain stem signs usually occurs within 2 to 5 days following symptom onset. Prognosis of these so-called malignant MCA infarctions (MMI) is poor: In prospective case series, 80% died from herniation despite maximum conservative therapy.

In order to prevent or reverse edema formation, to lower increased intracranial pressure, to improve cerebral perfusion, and to attenuate deleterious ischemic processes, more drastic rescue therapies such as craniectomy or therapeutic hypothermia have been applied. Moderate hypothermia initiated within 14 hours after stroke onset resulted in a mortality rate of 44% in an open case series. Decompressive surgery at a mean time of 39 hours after stroke onset reduced mortality to <35% in another case series, while earlier craniectomy at a mean time of 21 hours between stroke onset and surgery was associated with a further reduced mortality rate of 16% and improved clinical outcome. Early enough commencement of these strategies seems crucial for the prevention of a malignant stroke course. However, these therapeutic strategies are invasive, they may involve long-term sedation and ventilation on intensive care units, and they are associated with various serious side-effects.

Therefore, reliable data predicting MMI are required as early as possible in the course of stroke to make a decision on which patients may develop malignant brain edema and, thus, may benefit from more aggressive therapeutic measures. One diagnostic tool predicting MMI beside stroke syndrome severity is brain imaging. A prospective study of 99m-technetium-ethyl-cysteinate-dimer single-photon emission CT within 6 hours of symptom onset predicted mortality with 82% sensitivity and 98% specificity. Conventional CCT scan showing hypodensity covering >50% of the MCA territory within the first 6 hours predicted fatal outcome in another prospective study. In a recent study on 37 patients with acute MCA infarction and proximal vessel occlusion, quantitative analysis of early (within 6 hours) diffusion- and perfusion-weighted MRI predicted MMI with high sensitivity and specificity.

Neurochemical monitoring with cerebral microdialysis may be another tool potentially predicting the future course of severe stroke. So far, cerebral microdialysis in stroke patients has been used to monitor ongoing neurochemical changes in infarcted or noninfarcted brain tissue: Increasing extracellular glutamate concentrations measured in brain areas adjacent to infarcted tissue reflect pending or developing brain edema with subsequent secondary neuronal ischemia. Decreasing concentrations of glutamate and glycerol are observed in peri-infarct tissue under hypothermic conditions. However, standard microdialysate analyses for glutamate, glycerol, lactate, and pyruvate are not sensitive to predict MMI early enough for successful implementation of invasive therapies.

Bosche et al included 31 patients with infarctions covering >50% of the MCA territory on initial CCT scans in their currently published study. Fourteen of them developed MMI. Concentrations of non-transmitter amino acids as measured by microdialysis in the non-infarcted ipsilateral frontal lobe within the first 12 hours after stroke onset were significantly lower in MMI patients. Additionally, they correlated negatively with final infarct size. The authors assumed that the expansion of the extracellular space by vasogenic edema reduced the concentrations of these structural non-transmitter amino acids. The predictive value of their determination had a sensitivity and specificity of about 80%.

These data are unique in that they provide evidence that early neurochemical monitoring of non-transmitter amino acids within 12 hours of stroke onset may help to predict MMI. However, the method is currently limited by the use of a non-routine HPLC analysis system, which is not widely commercially available as an easily implemented bedside test. Therefore, before these parameters can be used in clinical practice, they will need to show robust validity in multiple stroke centers as well as in larger prospective studies.

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References


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*Stroke*. 2003;34:2908-2913; originally published online November 20, 2003;
doi: 10.1161/01.STR.0000100158.51986.EB

*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

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