Predictive Value of Neurochemical Monitoring in Large Middle Cerebral Artery Infarction

Susanne Schneweis, MD; Martin Grond, MD; Frank Staub, MD; Gerit Brinker, MD; Michael Neveling, MD; Christian Dohmen, MD; Rudolf Graf, PhD; Wolf-Dieter Heiss, MD

Background and Purpose—Space-occupying brain edema is a life-threatening complication in patients with large hemispheric stroke. Early identification of patients at risk is necessary to decide on invasive therapies such as decompressive hemicraniectomy or hypothermia. To assess potential predictors of malignant brain edema by measurement of intracranial pressure (ICP) and microdialysis in patients with large hemispheric stroke and different clinical course.

Methods—In an ongoing prospective clinical study, an ICP and microdialysis probe were placed into the parenchyma of the ipsilateral frontal lobe of 10 patients. Extracellular concentrations of glutamate, lactate, pyruvate, and glycerol were measured continuously. Repeated cranial CT scans were scrutinized for size of infarction and presence of mass effect.

Results—The dynamics of the different substances varied in accordance with the clinical course, size of infarction, and local brain edema: Increase in ICP and in glutamate concentration and lactate-pyruvate ratio was followed by massive edema and large infarcts; generally low and stable ICP and substrate concentrations were found in patients without progressive space-occupying infarcts.

Conclusions—In patients with large hemispheric infarction, bedside monitoring with microdialysis is feasible and might be helpful together with ICP recording to follow the development of malignant brain edema. (Stroke. 2001;32:1863-1867.)

Key Words: cerebral infarction ■ intensive care ■ microdialysis ■ middle cerebral artery

Patients with large hemispheric infarcts, especially with those involving the whole middle cerebral artery (MCA) territory, have a poor prognosis because of the development of space-occupying brain edema after the acute stage of ischemia. The early identification of the patients at risk of such as “malignant” infarction is necessary if live-saving, but invasive therapeutic strategies such as decompressive hemicraniectomy or hypothermia should be used. Because clinical data and early cranial CT (CCT) do not yield reliable prognostic criteria,1–3 invasive monitoring with measurement of intracranial pressure (ICP) and with microdialysis was evaluated for predicting malignant brain edema in patients with large hemispheric stroke.

Subjects and Methods

In an ongoing prospective clinical investigation, 10 patients with large MCA infarction were studied with invasive neuromonitoring. This study was approved by the Ethics Committee of the medical faculty of the University of Cologne (approval number 99182). The main inclusion criterion was presence of hypoattenuated tissue on early CCT covering >than 50% of the MCA territory. Eighteen to 36 hours after stroke onset, a microdialysis probe (CMA 70 probe) was placed into the parenchyma of the ipsilateral frontal lobe, together with an intracranial pressure measuring device (Codmann). The microdialysis probe was perfused at a rate of 0.3 μL/min with a sterile solution containing 147 mmol/L NaCl, 2.7 mmol/L KCl, 1.2 mmol/L CaCl₂, and 0.85 mmol/L MgCl₂. Dialysate samples were collected at 2-hour intervals and immediately analyzed for extracellular concentrations of glutamate, lactate, pyruvate, and glycerol. A second microdialysis probe (CMA/60) was placed into the abdominal subcutaneous tissue and served as a reference. A CCT scan was performed on admission, at 6 to 12 hours, and at day 5. Scans were scrutinized for presence of mass effect and size of infarction. Neurologic deficit was assessed by use of the National Institutes of Health Stroke Scale (NIHSS). Antiedema therapy included general treatment strategies such as elevation of the head and osmotic therapy with mannitol. Decompressive hemicraniectomy was additionally performed in 2 patients.

Results

Between March and October 2000, 10 patients with large stroke covering more than two thirds of the MCA territory were included in the study (Table). CT scans were performed 50 to 600 minutes after symptom onset, with a median time interval of 120 minutes. Four patients had a nonmalignant course; their condition did not deteriorate, and after 5 to 7 days, they could be transferred to the regular ward. In 1
patient, early decompressive surgery was performed; the follow-up CT disclosed a complete MCA infarction, but space-occupying edema did not develop. Malignant space-occupying brain edema occurred in 4 of the conservatively treated patients and in 1 patient treated with decompressive hemicraniectomy (patient 2). The dynamics of the different substances as assessed by microdialysis varied in accordance with the clinical course, increase in size of infarction, and development of local brain edema; patients without local brain edema in later CCT generally had low and stable concentrations of glutamate as well as a low lactate-pyruvate ratio (L/P ratio) over time, whereas in patients with occurrence of a massive edema in later CCT, an increase of these substances was found.

Illustrative Cases

Patient 1
A 51-year-old woman was admitted with a right-sided hemiparesis and a global aphasia. Follow-up CCT at 12 hours and at day 5 demonstrated an infarction covering more than two thirds of the MCA territory without mass effect. The levels of glutamate and lactate as well as the L/P ratio did not significantly increase over time and varied within the normal range (<2 μmol/L for glutamate, 2 mmol/L for the lactate concentration, and 25 for L/P ratio). ICP did not increase during the observation period and remained below a critical value of 20 mm Hg (Figure 1A). Similar results could be obtained from the other 3 patients without severe space-occupying edema (patients 4, 5, and 8).

Patient 6
The patient had a sudden right-sided hemiparesis and global aphasia. CCT 60 minutes after symptom onset was normal. Because of global aphasia and no next of kin, the patient was excluded from thrombolysis. Follow-up CCT 10 hours later disclosed a large left-sided MCA infarction covering almost the entire territory of the MCA. The patient’s condition rapidly deteriorated, signs of brain herniation occurred, and the patient died of malignant brain edema 32 hours after stroke onset. Immediately after insertion, the ICP probe revealed increased values. Despite antiedema therapy, ICP further increased. Concentrations of glutamate increased, with peak levels of 328 μmol/L, which means a 150-fold increase of normal values. The L/P ratio was only slightly elevated initially, then increased up to a ratio of 680, which means a >25-fold increase compared with normal brain (Figure 1B).

Patient 9
A 55-year-old man had a sudden right-sided hemiparesis and global aphasia. CCT 12 hours after symptom onset disclosed a large infarction covering more than two thirds of the MCA territory. After 48 hours, the patient’s consciousness slightly deteriorated; his pupils became nonresponsive to light first, then dilated. Follow-up CCT revealed an infarction of the MCA and anterior cerebral artery territory with midline shift. The patient died of brain herniation 98 hours after stroke. The results of ICP monitoring and microdialysis are shown in Figure 1C.

Patient 2
Figure 1D represents the results of ICP monitoring and microdialysis of a 59-year-old man who underwent a decompressive hemicraniectomy for a large MCA infarction. The patient was admitted to the hospital with a left-sided hemiparesis. CCT on admission revealed a hypoattenuation exceeding one third of the MCA territory. Follow-up CCT disclosed a large incomplete MCA infarction. Decompressive surgery was performed within the next hours, including the insertion of the microdialysis and ICP probes. After an initial peak, glutamate and the L/P ratio gradually declined but did not return to values usually found within normal brain tissue. Despite decompressive surgery, ICP increased slowly over time. Follow-up CT revealed a space-occupying MCA infarction. Approximately 94 hours after symptom onset, the pupils became dilated. Concomitantly, ICP increased dramatically up to peak values of 80 mm Hg preceding a rise of glutamate, lactate, and the L/P ratio. The patient died of space-occupying hemispheric infarction 117 hours after the onset of stroke.

Discussion

Because early decompressive hemicraniectomy and induced moderate hypothermia are applied as potentially life-saving procedures, it is of crucial importance to determine critical thresholds for intervention. The clinical usefulness of such procedures is strongly dependent on the dynamics of brain edema and the time course of biochemical markers. Microdialysis has been shown to be a promising tool to monitor brain edema development and efficacy of antiedema therapy. Although it is a useful tool to study brain edema in controlled settings, it needs to be considered that microdialysis reflects brain tissue metabolism and may not always provide immediate information about the onset of brain herniation.

Table 1: Basic Characteristics and Clinical Course of 9 Patients With Large MCA Infarction

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex/age, y</th>
<th>NIHSS, Baseline</th>
<th>NIHSS, 24–48 h</th>
<th>Malignant Edema</th>
<th>Decompressive Surgery</th>
<th>Outcome (mRS at 3 mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F/51</td>
<td>19</td>
<td>17</td>
<td>–</td>
<td>–</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>M/59</td>
<td>15</td>
<td>37</td>
<td>+</td>
<td>+</td>
<td>†</td>
</tr>
<tr>
<td>3</td>
<td>F/76</td>
<td>29</td>
<td>24</td>
<td>+</td>
<td>–</td>
<td>†</td>
</tr>
<tr>
<td>4</td>
<td>M/70</td>
<td>15</td>
<td>20</td>
<td>–</td>
<td>–</td>
<td>†</td>
</tr>
<tr>
<td>5</td>
<td>M/70</td>
<td>17</td>
<td>19</td>
<td>–</td>
<td>–</td>
<td>†</td>
</tr>
<tr>
<td>6</td>
<td>M/52</td>
<td>23</td>
<td>39</td>
<td>+</td>
<td>–</td>
<td>†</td>
</tr>
<tr>
<td>7</td>
<td>M/20</td>
<td>18</td>
<td>18</td>
<td>–</td>
<td>+</td>
<td>4</td>
</tr>
<tr>
<td>8</td>
<td>M/54</td>
<td>18</td>
<td>21</td>
<td>–</td>
<td>–</td>
<td>4</td>
</tr>
<tr>
<td>9</td>
<td>M/55</td>
<td>21</td>
<td>21</td>
<td>+</td>
<td>–</td>
<td>†</td>
</tr>
<tr>
<td>10</td>
<td>M/53</td>
<td>16</td>
<td>16</td>
<td>+</td>
<td>–</td>
<td>†</td>
</tr>
</tbody>
</table>

mRS indicates modified Rankin Scale.
†Patient died.

August 2001
1864 Stroke
found to be helpful in the early detection of secondary ischemia in patients with subarachnoid hemorrhage. In these patients, glutamate and lactate as well as the L/P ratio were sensitive and early indicators of ischemia.\textsuperscript{6–9} Little is known about microdialysis in ischemic stroke. Recently, Berger et al.\textsuperscript{10} reported the results of microdialysis in a single patient with fatal MCA infarction caused by malignant edema. In that case report, the authors described specific neurochemical alterations preceding clinical signs of herniation for several hours. There was a dramatic increase of glutamate as well as an increase of the L/P ratio in the primarily nonaffected contralateral frontal lobe. From these results, the authors speculated that microdialysis might be able to predict secondary deterioration in large hemispheric stroke.

The main objective of the present study was to investigate the reliability of this method in a larger series of patients. Our results suggest that patients without malignant edema generally demonstrate a pattern with low extracellular substances and low and stable ICP values. From patients with malignant space-occupying infarction, completely different monitoring patterns were obtained: There, substantially increased concentrations of glutamate, lactate, and the L/P ratio were detected. Correspondingly, ICP increased over time up to peak levels of 124 mm Hg. The temporal profile of these alterations and the absolute values of measured substances, however, widely varied: Whereas in patient 6 the concentration of glutamate and the L/P ratio showed a moderate initial increase with a sudden dramatic increase during the progression of the infarction, in patient 9 microdialysis revealed high concentrations of the measured substances from the beginning without further increase over time. In patient 6 and patient 2, the increase of ICP preceded the increase of the extracellular substances, whereas in patient 9, who initially had normal ICP values, increased levels of glutamate and an increase of the L/P ratio preceded the increase of ICP. Although we used a standardized procedure for probe implantation, such a variability of monitoring patterns might theoretically derive from methodological problems as the distance between site of infarction and probe position obviously differ to some extent in individual patients. However, the different patterns may also reflect different pathophysiological changes leading to the development of space-occupying edema. Thus far, there is little known about mechanisms that prompt the development of malignant edema in MCA stroke. Recently, it was suggested that the involvement of adjacent arterial territories into the ischemic process might be a key factor.\textsuperscript{11} This hypothesis is supported by our data: We placed the probes into the ipsilateral frontal lobe, which was—according to the CT findings—not involved in the ischemic process at that point of time. Increase of glutamate and the L/P ratio in areas outside the primary ischemic territory indicate secondary changes that might be related to the formation of malignant brain edema. For the development of malignant edema—which usually occurs after the acute stage—factors contribute in addition to the primary ischemic cell damage, which include diffusion of potentially damaging biochemical substances from the ischemic territory,\textsuperscript{12} reperfusion into tissue with damaged blood-brain barrier, shift of tissue compartments, and even delayed procedures in patients with malignant MCA infarction.\textsuperscript{4,5} there is a need for early indicators of secondary deterioration in large hemispheric stroke. Invasive monitoring with measurement of tissue oxygen and microdialysis was recently

ICP values and levels of glutamate, lactate, and L/P ratio in patients with a benign course of infarction (A) and with development of space-occupying edema in later CT (B through D). Figure demonstrates heterogeneous time course of alterations observed in patients with malignant MCA infarction. Dilation of pupils is marked by arrow.
and remote effects of ischemia such as inflammation and apoptosis. All these various pathophysiologically alterations affect the pattern of the monitored variables.

In some patients, increased ICP—which was previously not found to be of use for monitoring patients with large hemispheric infarcts—predicted secondary deterioration and preceded the increase of glutamate and the L/P ratio as well as the clinical signs, indicating its important role for secondary brain damage in malignant infarction.

In conclusion, microdialysis might be a valuable tool for neuromonitoring in patients with large hemispheric stroke. As long as there is so little experience in the interpretation of single variables, microdialysis should be integrated in a regimen that includes other monitoring such as measurement of ICP or tissue oxygen as well as functional imaging. A study protocol with a standardized application of the probes as well as repeated recordings of imaging data might be helpful in yielding more information on the underlying pathophysiology of malignant edema formation.

Acknowledgments
This work was supported by a grant of the Bundesministerium für Bildung und Forschung (Kompetenzzentrum Schlaganfall) to M. Grond, R. Graf, and W.-D. Heiss.

References

Abstract.

Editorial Comment

Investigating Acute Stroke: Does Invasive Monitoring Add to Identifying Patients at Risk for Progression?

Progression of neurological symptoms is seen in many patients with a large “malignant” middle cerebral artery (MCA) infarction. This is often secondary to cerebral edema, with subsequent compression of the tissue adjacent to the region of the infarction. Early identification of patients at risk for progression is important, as intervention may offer hope for a better outcome. In recent years, a number of interesting invasive and noninvasive techniques have emerged that may help in predicting patients at risk for an unfavorable outcome. For example, MRI diffusion/perfusion techniques may enable very early determination of patients with large MCA strokes at risk for infarct growth. However, such imaging studies offer very little information on the underlying pathophysiological processes. In vivo microdialysis is an invasive technique in which a bilumen probe with a semipermeable dialysis membrane at its distal end is inserted into the region of interest of the brain and the constituents of the extracellular space measured over a considerable period of time (4 days or longer). This methodology allows for measurements of “minute-to-minute” change as the disease process evolves over time. During the past 20 years, an extensive body of literature has been published on the usefulness of in vivo microdialysis in conditions as diverse as cerebral ischemia, seizures, and cerebral trauma. In vivo microdialysis has been a very important tool to the understanding of the mechanisms underlying cerebral ischemia. Animal research utilizing the technique in models of focal and global ischemia has revealed the fundamental importance of an increase in glutamate in the pathophysiology of cerebral ischemia. The response of the ischemic insult to various neuroprotective strategies has been studied, and it has been shown by several laboratories that an attenuated glutamate release in the extracellular space during ischemia is a key factor associated with protection of cerebral tissue. During the past decade, several reports have been published on the usefulness of in vivo microdialysis in humans with a
variety of cerebral insults, including head injury, subarachnoid hemorrhage, epilepsy, and cerebral ischemia, and in monitoring the tissue concentrations of medications. However, the technique is invasive and may potentially produce infection or cerebral hemorrhage.

In the preceding article, Schneweis et al have very carefully evaluated the relationship between intracranial pressure (ICP), microdialysis measurements of glutamate and lactate-pyruvate, and the clinical outcome in 10 patients with large MCA ischemic stroke. In this study, the microdialysis probe, together with an ICP device, was inserted in the ipsilateral frontal lobe between 18 and 36 hours after onset of symptoms. Repeated measurements over several days revealed that the ICP and biochemical markers of injury (for example, extracellular levels of glutamate) remained stable in the 4 patients who did not show progression. In most of the remaining patients, there was an increase in ICP and extracellular glutamate concentrations at the time when cerebral edema developed. The increase in the extracellular glutamate was not observed in all patients with a poor outcome. In their series, patient 6 had a poor outcome and showed an increase in the ICP 2 to 3 days after the onset of symptoms. Despite the poor outcome and increase in the ICP, the glutamate levels were not increased significantly and remained flat during the time when the ICP was rising.

While the combination of ICP monitoring and microdialysis are promising tools for investigating the risk of progression in patients with large MCA strokes, there are a number of cautionary issues that may require attention. The techniques are invasive and carry a small risk of infection and hemorrhage, and it is not easy to very rapidly commence the procedures. A specific concern with the study of Schneweis et al is that their measurements were started between 18 and 36 hours after onset of symptoms, at a time when the stroke process may be well advanced. The use of these techniques is also not possible in patients treated with tissue plasminogen activator or other thrombolytic agents because of the serious risk of hemorrhage. Another important issue relates to the placement of the microdialysis probe. In most studies the probe has been inserted in the frontal lobes (as was done in the present study). This does not allow for assessment of the tissue at risk of damage but instead for a random evaluation of tissue that may or may not be affected by ischemia. Despite these limitations, the information provided in the study is useful and provides us with important information on the pathophysiology of progression of neuronal damage hours to days after onset of symptoms in patients with large MCA strokes.

Alfred Shuaib, MD, Guest Editor
Division of Neurology
University of Alberta (Canada)

References
Predictive Value of Neurochemical Monitoring in Large Middle Cerebral Artery Infarction

Susanne Schneweis, Martin Grond, Frank Staub, Gerit Brinker, Michael Neveling, Christian Dohmen, Rudolf Graf and Wolf-Dieter Heiss

Stroke. 2001;32:1863-1867
doi: 10.1161/01.STR.32.8.1863

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/32/8/1863

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/