Background and Purpose—Patients with large middle cerebral artery infarction and elevated intracranial pressure (ICP) who are undergoing invasive intensive care therapy require technical monitoring. However, the effectiveness of the current gold standard, measurement of ICP, is limited. Furthermore, the effects of what is considered to be standard antiedema medical treatment are not fully understood. We studied whether multimodal monitoring can help to overcome this problem.

Methods—ICP, cerebral perfusion pressure (CPP), and partial brain tissue oxygen pressure (Pbr O2) were continuously measured within the white matter of the frontal lobe unilaterally or bilaterally. We analyzed the effects of antiedema drugs and looked for pattern changes in the Pbr O2 before transtentorial herniation in patients in whom this could not be prevented. Furthermore, complications were registered.

Results—We performed 27 measurements in 21 patients. A total of 297 antiedema drug administrations were analyzed in 11 patients. Hyper-HAES and mannitol were most often associated with an increase in CPP and Pbr O2, whereas the use of thiopental and tromethamine led to negative or contrary effects, although ICP was decreased in every case. Pattern changes in the Pbr O2 curve could be observed between 6 to 18 hours before transtentorial herniation. No bleeding complication or infections were observed.

Conclusions—Multimodal monitoring can be used to monitor antiedema drug effects. Our data suggest that with multimodal monitoring, pathophysiological changes could be predicted considerably in advance. ICP alone is of questionable use. Furthermore, this method might help to optimize the timing of invasive therapy in space-occupying infarction. (Stroke. 2001;32:2500-2506.)

Key Words: brain edema | intracranial pressure | monitoring, physiologic | oxygen | partial pressure | stroke
in feasibility and safety and in the question of whether this type of monitoring can help to improve the quality of the monitoring and our understanding of the effects of drug therapy.

Subjects and Methods

Patients and Treatment Protocol

Patients with MCA stroke were transferred to our neurological intensive care unit (NICU) for observation if the area of infarction was greater than two thirds of the MCA territory and patients presented with high-grade hemiparesis and forced eye/head deviation. Patients were included in this multimodal monitoring study if 1 of the following 2 scenarios arose: (1) A patient was scheduled for decompressive surgery or for moderate hypothermia treatment at 33°C if further clinical deterioration within the subsequent 24 hours was caused by space-occupying hemispheric edema formation as proved with cerebral CT (CCT) or MRI. In this case, multimodal monitoring was installed at the time of surgery or beginning of hypothermia. (2) If edema formation and clinical deterioration were delayed, within the next 3 to 5 days, or if for other reasons surgery or hypothermia could not be conducted as scheduled, monitoring devices were installed to monitor the effectiveness of conservative antiedema therapy before surgery or hypothermia. One of these forms of treatment was initiated in case of further clinical deterioration after an institutional protocol, which has already been described elsewhere. All monitored patients were anesthetized, intubated, and mechanically ventilated. The standard monitoring protocol included measurement of mean arterial blood pressure (MAP), heart rate, and transcutaneous oxygen saturation. Patients were excluded if informed consent could not be obtained, if there were contraindications to surgery, or if hypothermia was present. The investigation was approved by the Institutional Review Board of the University of Heidelberg Clinic and started as a prospective study in August 1995.

We assessed the influence of antiedema drugs, hemicraniectomy, and moderate hypothermia on ICP, CPP, and PbrO₂. Administration of the following intravenous drugs was directly registered and stored in an online mode: glycerol (10%, 150 to 250 mL), mannitol (15%, 100 mL), thiopental (300 to 500 mg), hyper-HAES (NaCl 7.5% and HES 6%, 150 mL), and the buffer tromethamine (THAM) (1 mmol/kg body wt bolus). These drugs were applied if ICP increased either clinically or was measured as >20 mm Hg. Only glycerol was given in a repetitive mode independently of the development of ICP in a few cases. A postoperative increase in PbrO₂ and decrease in ICP within >180 minutes after the procedure were regarded as a positive therapeutic effect of hemicraniectomy. Because to date no reference PbrO₂ values have been established under hypothermic conditions, we only describe the curves.

During the first measurements, we observed a change in the shape of the PbrO₂ curve, which had occurred in 2 patients a few hours before death as a result of transtentorial herniation. This change in pattern was of sudden onset, within 10 to 20 minutes, and characterized by an increase in the amplitude of the oscillations (Figure 1). We therefore looked for such a change in the curve pattern in association with transtentorial herniation.

Complications and technical disturbances were registered in an open list.

Monitoring Protocol

For assessment of safety, practicability, and feasibility, we decided on a stepwise extension of the measurements with the ultimate goal of bilateral, multimodal monitoring of ICP/CPP, PbrO₂, and temperature (Figure 1). In the first step, we performed unilateral monitoring of PbrO₂ and ICP/CPP within the white matter of the noninfarcted hemisphere, to which we will henceforth refer to as the “contralateral” hemisphere. We decided to start measurements in the contralateral hemisphere for 2 reasons: (1) measurement on the side of the infarction might lead to difficulties in the interpretation of PbrO₂ values, because it is difficult to differentiate between ischemic, normal, and penumbral PbrO₂ values, and (2) this uncertainty might have influenced a whole series of measurements and made it useless. In the second phase of measurements, we extended and included the hemisphere of the infarct, to which we will refer as the “ipsilateral” hemisphere.

ICP was measured using either piezoelectronic (Codman MicroSensor ICP transducer) or pneumatic (Spiegelberg III) signal-transmitting probes. PbrO₂ was registered using a polarographic Clarke-type microprobe (Clark-type flexible catheter; GMS). Technical data and reliability of this probe were confirmed in several studies on patients with subarachnoid hemorrhage (SAH) or traumatic brain injury (TBI). Temperature was measured continuously with microprobes (temperature probe; GMS) and processed in a computer to compensate for the temperature dependency of PbrO₂. Probes were inserted through 1 screw (1-, 2-, and 3-lumen screw; GMS). Only pneumatic ICP probes required a separate burr hole. If a hemicraniectomy was performed, we inserted this probe through the trepanation. All probes were located within the white matter of the frontal lobe. Positioning of the probes was documented by CCT, sometimes during the postoperative course. The distance between the probes on each side was between 3 and 8 mm. ICP, PbrO₂, MAP, and temperature signals were continuously registered and stored every 10 seconds using a multimodal interface (LICOX-MM System for multimodal monitoring; GMS) and a portable personal computer (notebook).

Statistical Methods

For the analysis of drug influences on the monitored parameters (ICP, CPP, PbrO₂), the ICP was regarded between an interval lasting...
from 25 minutes before the administration of a drug either until the administration of the next one or at least up to 100 minutes thereafter. ICP values were then smoothed using a moving average. The minimum of the smoothed curve was used to estimate the duration of the drug effect. Within the same length of interval of the drug effect, we fit a univariate autoregressive (AR) process for PbrO
sub2
 and CPP. With these AR processes, we predicted the values for the PbrO
sub2
 and CPP and calculated pointwise 95% CIs for the prediction for the duration of the drug effect. Then, we compared the prediction with the actual measurement. We distinguished between values that were smaller than the lower boundary, larger than the upper boundary, between the boundaries of the CI, and others (mostly when some of the data were smaller than the lower boundary and some were larger than the upper boundary). Because all drugs led to a more or less decrease in ICP, the effect of a particular drug on PbrO
sub2
 and CPP was observed over the period of ICP decrease. We defined 5 effects, which are listed in Table 1.

**Results**

Multimodal monitoring was performed in 21 patients (17 men and 4 women, mean age 54 years, age range 32 to 72 years) with space-occupying MCA infarction. The mean±SD Glasgow Coma Scale (GCS) score on admission was 11±2, and the mean±SD National Institute of Stroke Scale Score (NIHSS) was 19±5. Eight of 10 patients who underwent hemicraniectomy, 4 of 7 patients treated with hypothermia, and 1 patient in whom hypothermia was added after hemicraniectomy survived. None of the 3 conservatively treated patients survived. Mean time between the occurrence of first symptoms and admission to our NICU was 9 hours (range 2 to 53 hours), where treatment was given for 1 to 44 days (mean±SD 14±11 days).

Multimodal monitoring was started within 6.5 and 104 hours (mean±SD 33±29 hours) and continued for between 19 hours and 11.7 days (mean±SD 5.4±3.1 days). In total, we performed 27 continuous multimodal measurements, with 6 bilaterally.

We analyzed 297 drug applications (Table 2). The most positive effects (increase in CPP and PbrO
sub2
) were observed after the administration of hyper-HAES and mannitol. These drugs were associated with the lowest rate of negative or contrary effects. Most negative or contrary effects occurred after thiopental and tromethamine (Figure 3).

A decrease in ICP and an increase in PbrO
sub2
 immediately after hemicraniectomy occurred in 6 of 10 patients (Figure 4). In 1 patient, we only observed a decrease in ICP and an increase in PbrO
sub2
 5 hours after hemicraniectomy, when a postoperative epidural hematoma was drained. The postoperative PbrO
sub2
 values were measured between 28 and 35 mm Hg. In 2 of 10 cases, we only observed a statistical trend of ICP decrease and PbrO
sub2
 elevation. However, the values did not exceed the predefined levels of significance.

In 4 of 7 patients treated with hypothermia, we registered a decrease in ICP after induction of cooling (1 patient had ICP values <15 mm Hg at the beginning of cooling/monitoring; in 2 patients, we could not register the ICP, because the probes were implanted after the target temperature had been reached). In 2 of these patients, we observed an increase in ICP values during rewarming to >20 mm Hg. During moderate hypothermia (32° to 33°C), PbrO
sub2
 values on the contralateral side of 5 patients were measured between 14 and 25 mm Hg and rose up to 18 and 36 mm Hg during rewarming.

**TABLE 1. Definition of Drug Effects on CPP and PbrO
sub2
 During the Period of ICP Decrease**

<table>
<thead>
<tr>
<th>Effect</th>
<th>CPP/PbrO\textsubscript{2}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>↑↑/↑↑, O/↑↑, ↑/0</td>
</tr>
<tr>
<td>Negative</td>
<td>↓/↓, O/↓↓, ↓/0</td>
</tr>
<tr>
<td>Contrary</td>
<td>↑/↓</td>
</tr>
<tr>
<td>None</td>
<td>00</td>
</tr>
<tr>
<td>Other</td>
<td>CPP or PbrO\textsubscript{2} not measured during observation period, multiple crossings of the confidence interval</td>
</tr>
</tbody>
</table>

↑ Indicates increase; ↓, decrease; 0, no change.
In 9 patients, we could not prevent transtentorial herniation. In 6 of these patients, we saw changes in the pattern of the PbO2 curve before transtentorial herniation. Two of these patients were treated conservatively, 4 with hypothermia, and 2 patients had received hemicraniectomy. These patients died between 6 and 18 hours after the first appearance of the pattern change. In 1 of these patients, we had performed bilateral monitoring (Figure 1).

The following technical problems were registered. In 2 patients, we could not analyze the postoperative data because of an instance of intraoperative infringement of a PbO2 probe and 1 of postoperative breakage of the connecting cable. There were no bleedings or infections caused by the probes or the installation of the devices. The duration of implantation of the probes was highly dependent on the experience of the neurosurgeon and the support team on duty. With an experienced neurosurgeon and a good team, implantation of the 6-channel monitoring system (consisting of bilateral ICP, temperature, and PbO2 via 3-lumen screw) in an operating room, including transportation time, calibration, and set-up of the system, takes around 70 to 90 minutes. On the other hand, we have seen implantation times of up to 120 minutes. Implantation times could be shortened considerably (to 45 minutes) if performed in the intensive care unit by an experienced team. Probes were implanted in the NICU in 8 patients and did not cause an increase in the rate of complications.

**Discussion**

Continuous multimodal monitoring has increasingly been applied during the past 7 years, especially in neurosurgical patients and mostly those with TBI and SAH. However, the pathophysiological mechanisms after diffuse brain damage and SAH cannot be compared with the space-occupying edema after large focal ischemia, which might affect the value of the monitoring in these patients. So far, no other studies of multimodal monitoring have been conducted in patients with large hemispheric infarction. In space-occupying MCA infarction, sooner or later primarily healthy brain tissue of the contralateral hemisphere becomes involved in the process of expanding edema. Therefore, protection of the contralateral hemisphere is the major therapeutic and, hence, monitoring target in these patients.

This was considered in our protocol. We installed the monitoring probes at an early stage of the disease primarily to ensure that the healthy tissue of the contralateral side was measured.

Edema formation starts within the infarcted area of the MCA territory. Therefore, we positioned the probes within the white matter of the frontal lobe, assuming that the anterior cerebral artery territory is normally perfused at least at the
beginning of edema formation. In a few patients we did indeed observe changes from high to very low PbrO₂ levels during the period of high ICP values. At least in 2 of these patients, we could prove by CCT that an anterior cerebral artery infarction had occurred in the area where the probe was located.

Normal PbrO₂ values were measured with 25 to 30 mm Hg (with PaO₂ 25 mm Hg) and 33 to 36 mm Hg (PaO₂ 146 to 170 mm Hg) in patients with brain tumors or SAH. In our normothermic patients, PbrO₂ values of between 25 and 35 mm Hg were measured after hemicraniectomy and of 18 to 36 mm Hg after rewarming in the contralateral hemisphere and under normoxic conditions.

We observed a decrease in ICP after all administrations of antiedema drugs. Regarding osmotic agents (hyper-HAES, mannitol), 50% to 60% of these episodes were associated with a positive effect on PbrO₂ and CPP. This effect was registered less often after glycerol. One reason for this observation might be that in some patients, glycerol was routinely applied during the initial course of disease, independently of whether these patients had elevated ICP. Thus, in some episodes, there was only little effect on CPP and/or PbrO₂ because the decrease in ICP was too little. This suggestion is supported by Unterberg and coworkers, who observed significant increases in PbrO₂ when the CPP was in the range between 50 and 70 mm Hg. However, further increases in CPP did not lead to further significant increases in PbrO₂.

Interestingly, pharmacologically induced decreases in ICP did not always lead to an improvement in PbrO₂ (and/or CPP). In contrast, we observed bilateral decreases in PbrO₂ in a significant number of cases. This effect was mainly registered after the administration of drugs such as thiopental and tromethamine, which led to a decrease in the ICP through a reduction in cerebral blood flow (Table 2). Thiopental reduces cerebral metabolism, cerebral blood flow (CBF), and, to a certain extent, systemic pressure.

The effect of tromethamine is probably mediated by pH-coupled vasoconstriction and reduction in CBF. We used both drugs in cases of ICP crises, when other antiedema drugs failed or could not be used anymore (had exceeded therapeutic levels, contraindications) or to bridge the gap in time until invasive strategies such as hemicraniectomy or hypothermia could be undertaken. This is the reason for the comparatively low number of applications of these drugs. However, the relative number of negative or contrary effects is high. Our results led us to suspect that the use of certain antiedema drugs might have facilitated ischemic events: From the treatment of TBI, it is well known that ischemic events occur despite “successful” ICP treatment. Adding PbrO₂ to ICP/CPP monitoring might help to detect drug-associated ischemic events. On the other hand, it is known that the PbrO₂ is the product of oxygen supply and demand. Thus, we should also take into consideration that a decrease in PbrO₂ might be the result of an autoregulatory response to a drug-associated depression of cerebral metabolism. To answer this question conclusively, more measurements must be performed and the monitoring perhaps be extended, for example, to microdialysis or CBF measurements, to better assess the “branches” of supply and demand of cerebral oxygen metabolism.

We found a pattern change in the PbrO₂ curve to occur between 6 to 18 hours before transtentorial herniation. Obviously, it is too soon and the number of such observations is too small at this moment to draw any conclusions. It would be necessary to know whether this phenomenon can be reproduced by other groups, because this would have a major impact on prognosis and therapy planning.

In 1 patient, we observed a spread of ipsilateral and contralateral ICP 2 and 2.5 days before herniation, whereby the ipsilateral pressure became higher than the contralateral ICP (Figure 1). This spread might have been the expression of an interhemispheric pressure difference, illustrating the driving force for midline shifting. Obviously, changes like those that have just been described can only be observed with bilateral multimodal monitoring. These observations are examples of how monitoring might be used to predict pathophysiological changes at an early stage of the course of the disease.

Technically, the use of multimodal monitoring is highly dependent on the experience of the operator and the users of the system. We registered a large variation between teams who were experienced and those who were not. There were no complications that harmed the patient. White matter tissue destruction as regularly seen in patients with extraventricular drainage do not occur, because the probes that were used in our protocol are much smaller in diameter.

The advantage of this type of multimodal monitoring over other methods such as near infrared spectroscopy, Doppler ultrasound to observe midline shift, or microdialysis lies in the continuity of data acquisition and in its availability. Dynamic changes in ICP, CPP, and cerebral oxygenation as they occur in patients with large strokes, who develop progressing hemispheric edema, call for continuous monitoring. Only in this way can conclusions be drawn from trends, which is hardly possible with serial observations. Furthermore, using this protocol of multimodal monitoring, the gain of information seems to be associated with fewer complications than with conventional methods of ICP monitoring. This is because probes and burr holes are smaller, and fewer burr holes are needed, because up to 3 probes can be inserted through 1 screw. The smaller diameter of the probes and how the probes can be fixated within the insertion screw reduces bleedings, infections, and disconnections.

It should be borne in mind that we deal with a subgroup of seriously ill and mostly relatively young stroke patients. We have repeatedly seen and reported that these patients can profit from invasive treatment if the timing of treatment is optimized. It would be very dangerous to transport these patients during the period of critically elevated ICP, and thus it is not possible to perform CCT or MRI. On the other hand, several studies have shown that the type of monitoring that was used in our investigation is not linked with an increased risk of complications if used by experienced personnel. Furthermore, it has yet not been shown that other noninvasive methods can provide similar information. Thus, we be-
lieve that multimodal monitoring is ethically acceptable in this subgroup of patients. Although the number of patients is relatively small, the number of measured episodes is comparatively large. Our results, however, indicate that multimodal monitoring might have a major impact on therapy guided by monitoring. Multimodal monitoring might help not only to control therapy but also to optimize the timing of invasive therapies in 2 ways: by avoiding a potentially dangerous therapy and by identifying those patients who will profit most from this therapy at an early stage in the course of the disease. Furthermore, multimodal monitoring might help to increase our understanding of the pathophysiological mechanisms underlying posts ischemic edema formation. The number of patients does not allow any conclusions to be drawn about risk and cost-effectiveness at this stage; these questions can only be answered in larger, carefully performed studies.

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Multimodal Online Monitoring in Middle Cerebral Artery Territory Stroke
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