Bedside microdialysis for early detection of cerebral hypoxia in traumatic brain injury

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Object. The authors evaluated the use of bedside cerebral online microdialysis for the detection of impending and present cerebral hypoxia in patients who had sustained traumatic brain injury.

Methods. Thirty-five severely head injured patients (with Glasgow Coma Scale scores \( \leq 8 \)) were studied. Patients underwent continuous brain tissue PO\(_2\) (PtiO\(_2\)) monitoring. The PtiO\(_2\) catheter was placed into the unaffected frontal white matter within 32.2 hours postinjury (range 7–48 hours). The microdialysis catheter was placed close to the PtiO\(_2\) probe via a 2- or 3-way skull screw that was connected to a pump and perfused with Ringer’s solution at 0.3 µl/minute. The microdialysis samples were collected hourly and analyzed at the bedside for glucose, lactate, lactate–pyruvate ratio, and glutamate. Data were analyzed for identification of episodes of impending (PtiO\(_2\) 10–15 mm Hg > 5-minute duration) and present cerebral hypoxia (PtiO\(_2\) 10 mm Hg > 5-minute duration). In 62% of the patients hypoxic episodes occurred and were most frequently associated with hyperventilation (p < 0.001). During impending hypoxia, extracellular glutamate concentrations were increased (p = 0.006) whereas energy metabolites remained stable. During cerebral hypoxia, the extracellular glutamate (p < 0.001) and lactate (p = 0.001) concentrations were significantly higher than during normal oxygenation, whereas the lactate–pyruvate ratio was only slightly increased (p = 0.088, not significant).

Conclusions. The authors conclude that a PtiO\(_2\) below 10 mm Hg is critical to induce metabolic changes seen during hypoxia/ischemia. Early markers of cerebral hypoxia are increased levels of glutamate and lactate. Regional hypoxia is not always associated with anaerobic cerebral metabolism. In the future, this technology of bedside monitoring may allow optimization of the treatment of severely head injured patients.

Key Words • cerebral metabolism • microdialysis • cerebral oxygenation • multimodal monitoring • severe head injury • brain tissue PO\(_2\)

Patients who have sustained a traumatic brain injury have been shown to be more vulnerable to secondary insults caused, for example, by hypoxemia or compromised CPP as compared with patients with no cerebral lesions.\(^2\) Cerebral ischemia may occur as a result of cerebral vasospasm, local compression of vessels due to hemorrhage, contusions, and brain edema, or because of vasoconstriction resulting from uncontrolled hyperventilation therapy. During the hospital course, transient episodes of global ischemia occur in 39% of patients due primarily to intracranial hypertension, systemic hypotension, and hypcapnia. The consequence of cerebral ischemia and hypoxia, as manifested by jugular venous oxygen desaturation or reduced PtiO\(_2\), is development of secondary brain damage leading to deterioration of the neurological status. Jugular venous oxygen saturation is a measure of global oxygenation whereas PtiO\(_2\) is a measure of oxygenation in a very localized area of the brain. In the brain that has sustained a contusion, PtiO\(_2\) is extremely low, whereas in pericontusional tissue regional oxygenation may vary depending on the presence of reactive hyperemia. When measured in unaffected cerebral white matter, there is a high correlation between global SjvO\(_2\) and regional PtiO\(_2\) in severely head injured patients.\(^5\) A decrease of PtiO\(_2\) below 10 mm Hg in the unaffected white matter is thought to be a critical marker in severely head injured patients and correlates with jugular venous desaturation (SjvO\(_2\) < 50%). The longer cerebral hypoxia (PtiO\(_2\) < 10 mm Hg) is present, the higher the likelihood of an adverse outcome.\(^4,15\) It is not known whether impending hypoxia (PtiO\(_2\) < 10–15 mm Hg) itself induces the development of secondary brain damage. Many of these episodes of secondary ischemia are treatable if recognized. The metabolic alterations detected during ischemia with intracerebral microdialysis

Abbreviations used in this paper: CPP = cerebral perfusion pressure; ECF = extracellular fluid; etCO\(_2\) = end tidal CO\(_2\); ICP = intracranial pressure; MABP = mean arterial blood pressure; PtiO\(_2\) = brain tissue partial pressure of oxygen; SjVO\(_2\) = jugular venous oxygen saturation.
have been extensively studied in experimental animals. Recently in vivo sampling and bedside analysis of the neuronal microenvironment of the brain has been performed in patients with traumatic injury, epilepsy, and subarachnoid hemorrhage for the detection of cerebral vasospasm.\textsuperscript{5,13} Ischemia is associated with metabolic alterations of brain energy metabolism characterized by increased anaerobic glycolysis with decreased glucose, elevated lactate, and elevated lactate–pyruvate ratio concentrations in the ECF. A second condition of disturbed energy metabolism described in patients who have sustained traumatic brain injury is hyperglycolysis characterized by increased glucose metabolism without concurrent oxygen deficiency as demonstrated with positron emission tomography. Furthermore, such excitotoxic amino acids as glutamate and aspartate are released into the ECF in conjunction with ischemia and trauma; this event may have toxic effects that lead to cell damage, membrane degradation, and consequent glycerol.\textsuperscript{1,16} Bedside microdialysis, a new method to evaluate online cerebral metabolism in a clinical setting, is used to measure the extracellular concentrations of glucose, pyruvate, lactate, glutamate, and glycerol in the brain tissue. The advantage of the bedside system is that, in contrast to previous studies in which using the high-liquid gas chromatography was used, the analysis can be performed immediately in the patient’s room, and results for four parameters are available within 15 minutes.

The purpose of this study was to combine PtiO\textsubscript{2} monitoring, microdialysis, and physiological measurements to evaluate critical thresholds of cerebral oxygenation on metabolism, as well as to identify possible causes for cerebral hypoxia. Our overall goal was to improve future prognoses of severely head injured patients.

Our major hypotheses were that 1) during cerebral hypoxia (PtiO\textsubscript{2} < 10 mm Hg) there are metabolic changes indicative for anaerobic metabolism and 2) that the degree of metabolic changes are correlated to the severity of cerebral maloxygenation in patients with severe head injury. To test these hypotheses, we studied 35 severely head injured patients by using continuous intracerebral microdialysis analyzed at the bedside, and we have related the neurochemical data to clinical parameters, ICP, CPP, and cerebral oxygenation.

CLINICAL MATERIAL AND METHODS

All studies were approved by the ethics committee for conduct of human research at the Charité Campus Virchow Medical Center, Humboldt University of Berlin.

Patient Characteristics and Management

We studied 35 severely head injured patients (Glasgow Coma Scale score < 8) who were admitted to the Neurointensive Care Unit at the Charité Campus Virchow Medical Center of Berlin. They ranged in age from 25 to 76 years. On admission, trauma-induced lesions were confirmed by computerized tomography scanning and graded accordingly.\textsuperscript{1} Patients who were hemodynamically unstable and close to brain death at admission or for whom informed consent could not be obtained were excluded from this study. Mass lesions were immediately evacuat- ed. All patients underwent an ICP/CPP-directed management according to a standardized protocol at our institution. Intracranial hypertension (ICP > 20 mm Hg) was managed according to the American Association of Neurological Surgeons’ guidelines for the management of severe head injury; cerebrospinal fluid drainage, boluses of mannitol (0.5–1 g/kg body weight over a period of 20 minutes) and moderate hyperventilation (PaCO\textsubscript{2} 30–35 mm Hg). Barbiturate coma was induced in patients with otherwise uncontrollable intracranial hypertension and guided by a burst-suppression electroencephalographic pattern. Cerebral perfusion pressure was maintained above 60 mm Hg using colloidal and noncolloidal agents, blood products and catecholamines if necessary. Decompressive surgery was performed when this treatment was not sufficient to obtain an adequate ICP and CPP.

Physiological Monitoring

Data collected for each patient included the following: hemodynamic data (heart rate, systemic systolic, diastolic, and MAP) and respiratory data (fraction of inspired O\textsubscript{2}, ratio of fraction of inspired O\textsubscript{2}/PaO\textsubscript{2}, etCO\textsubscript{2}, and ventilatory settings). After admission to the neurosurgical intensive care unit, an arterial/venous catheter line was inserted to measure arterial and venous blood pressure, and values were recorded as MABP and mean central venous pressure. In all patients ICP was monitored continuously by means of a ventricular drainage and/or intraparenchymal device. Cerebral perfusion pressure was calculated (CPP = MABP – ICP). Patients underwent continuous PtiO\textsubscript{2} monitoring. A catheter was placed into the nonlesioned frontal white matter within 32.2 hours postinjury (range 7–48 hours). Correct positioning of the PtiO\textsubscript{2} catheter tip was verified by computerized tomography. The mean monitoring duration including PtiO\textsubscript{2} and microdialysis was 8.95 days (range 1–11 days). After monitoring, the PtiO\textsubscript{2} catheters were checked for sensitivity drifts.

Microdialysis Procedure

Sterile custom-built microdialysis probes (outer diameter 0.9 mm, dialysis membrane 10 mm, and a molecular weight cutoff 20,000) were used to determine cortical levels of glucose, lactate, lactate–pyruvate ratio, glutamate, and glycerol. The probe was placed in a standard fashion close to the PtiO\textsubscript{2} probe via a 2- or 3-lumen bolt that was tapped and screwed into the nonlesioned frontal skull. The microdialysis catheters were connected to a pump and perfused with sterile Ringer’s solution (0.3 µl/minute). The dialysates were collected hourly, analyzed immediately at the bedside for glucose, lactate, lactate–pyruvate ratio and glutamate, and saved after removal for in vitro calibration and later analysis of glycerol. The reagents were daily controlled with a standard calibration.

Secondary Insults Analysis

Analog signals of MABP, ICP, etCO\textsubscript{2}, and PtiO\textsubscript{2} were continuously digitized, displayed, and stored on a Windows-based platform running a software program for multimodal data acquisition. Data were analyzed in a stepwise fashion according to the following criteria: 1) identification of episodes of impending (PtiO\textsubscript{2} 10–15 mm Hg >
Bedside microdialysis

**TABLE 1**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tr>
<td>age in years (range)</td>
<td>32.5 ± 3.3 (25–76)</td>
</tr>
<tr>
<td>male/female ratio</td>
<td>31:4</td>
</tr>
<tr>
<td>Glasgow Coma Scale score at admission</td>
<td>6 ± 3</td>
</tr>
<tr>
<td>initiation of monitoring posttrauma (hrs)</td>
<td>32.2 ± 3.4</td>
</tr>
<tr>
<td>duration monitoring (hrs)</td>
<td>214.8 ± 20.2</td>
</tr>
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5-minute duration) and present hypoxia (PtiO\(_2\) < 10 mm Hg, > 5-minute duration). (The end of an episode was defined as following 5 minutes of normal brain tissue PO\(_2\) values); 2) occurrence of hypoxic episodes in relation to the day after trauma; and 3) presence of intracranial hypertension (ICP > 20 mm Hg), arterial hypotension (MABP < 70 mm Hg), low CPP (CPP < 60 mm Hg), presence of hyperventilation (etCO\(_2\) < 30 mm Hg) during impending/present hypoxia.

**Statistical Analysis**

All summary data are expressed as means ± standard error of the means values if normally distributed or as median values (interquartile range) if the distribution was not normal. Hourly microdialysis values sampled during impending/present hypoxia for each patient were analyzed. The first 12-hour period after insertion of the microdialysis and PtiO\(_2\) probe was excluded from analysis. A one-way analysis of variance was used for normally distributed data. For data that were distributed normally, non-parametric tests were used. A chi-square analysis was performed to compare categorical data. A p < 0.05 was statistically significant.

**Sources of Supplies and Equipment**

Intracranial pressure was monitored using an intraventricular drainage device obtained from Camino (San Diego, CA) and an intraparenchymal device acquired from Codman, Johnson & Johnson Medical (Arlington, TX). The LICOX microcatheter, manufactured by GMS mbH (Kiel-Mielkendorf, Germany) was used to monitor PtiO\(_2\). The microdialysis probes (CMA 100 and 600) were acquired from (CMA Microdialysis, Solna, Sweden). Analog signals of the various parameters were generated on a computer system (model M1020A; Hewlet Packard, Waltham, MA) that ran computer software (LabVIEW) obtained from National Instruments (Austin, TX).

**RESULTS**

**Patient Characteristics**

The study population consisted of 35 patients (age range 25–76 years) with severe head injury. Demographic data are listed in Table 1. There were no hemorrhagic or infectious complications related to the PtiO\(_2\) and microdialysis catheter insertion. In seven patients the monitor-}

ing had to be discontinued prematurely (microdialysis or PtiO\(_2\) catheter defects, surgical revision requiring removal [two patients]). In seven patients the monitoring had to be discontinued prematurely (microdialysis or PtiO\(_2\) catheter defects [five patients], surgical revision requiring removal [two patients]).

**Occurrence of Impending/Present Hypoxia**

In 62% of our patients hypoxic episodes were present. Two hundred fifty-two episodes of impending hypoxia (PtiO\(_2\) < 15 mm Hg, 11,810 minutes) and 38 episodes of present hypoxia (PtiO\(_2\) < 10 mm Hg, 1996 minutes) were identified. The mean duration of impending hypoxia was 65 ± 33 minutes and that of present hypoxia was 85 ± 21 minutes. Intracranial hypertension was the parameter most frequently associated with impending hypoxia (77% of cases; p = 0.02), whereas in cases of cerebral hypoxia (PtiO\(_2\) < 10 mm Hg) hyperventilation was most frequently found (97% of cases; p < 0.001) (Fig. 1).

**Microdialysis-Detected Changes During Impending/Present Hypoxia**

Microdialysis data collected during the occurrence of impending/present hypoxia (within 60 minutes of sampling) were divided into three groups: no hypoxia present (PtiO\(_2\) > 15 mm Hg [2083 hours]), impending hypoxia present (PtiO\(_2\) 10–15 mm Hg [310 hours]), and hypoxia present (PtiO\(_2\) < 10 mm Hg [120 hours]).

In Fig. 2, the microdialysis parameters (means ± standard error of the means) are shown. Baseline glucose levels were extremely low (< 0.5 mmol/L) and further decreased during impending (p = 0.069) and present hypoxia (p = 0.015). The extracellular concentrations of glutamate were elevated during impending hypoxia (p = 0.03) and further increased during cerebral hypoxia (p = 0.008). The extracellular lactate levels were stable during impending hypoxia but significantly increased during present hypoxia (p = 0.045). The lactate–pyruvate ratio remained unchanged during impending hypoxia, and there was only a slight increase during present hypoxia (p = 0.088 [not significant]), suggesting no anaerobic metabolism.

**DISCUSSION**

In this study with prospectively collected data, 35 patients with severe head injury underwent bedside cerebral microdialysis and PtiO\(_2\) monitoring and were treated according to the latest neurological and critical care practice. We evaluated bedside microdialysis as a monitoring technique in severely head injured patients and compared the observed regional cerebral hypoxia with metabolic changes and clinical parameters. Our major findings were that bedside cerebral microdialysis is a safe technique to indicate cerebral hypoxia in severely head injured patients when inserted into nonlesioned brain tissue. A PtiO\(_2\) below 10 mm Hg is critical to induce metabolic changes seen during hypoxia/ischemia. We identified glutamate as the most sensitive and early marker of impending cerebral hypoxia. Cerebral hypoxia was characterized by elevated extracellular glutamate and lactate concentrations. Regional hypoxia is not always associated with anaerobic cerebral metabolism. Cerebral hypoxia was most frequently...
associated with hyperventilation therapy. In the future, this technology may allow for the optimization of the treatment for patients with severe head injuries.

Cerebral hypoxia/ischemia is a major contributor of poor outcome in severe head injury. New monitoring devices have been developed for early detection of cerebral ischemia/hypoxia to minimize secondary brain damage. Measurement of PtiO\textsubscript{2} has been shown to monitor reliably regional cerebral oxygenation and to be closely correlated with cerebral perfusion. When inserted into nonlesioned white matter, a good correlation between global ischemia monitored by SjvO\textsubscript{2} and regional brain tissue PtiO\textsubscript{2} is found. When cerebral desaturation (SjvO\textsubscript{2} < 50%), indicative of global ischemia, occurs, brain tissue PtiO\textsubscript{2} has been found to be approximately 8.5 mm Hg. The major limitation of SjvO\textsubscript{2} monitoring is the absence of a global measure to detect regional ischemia. Monitoring of PtiO\textsubscript{2} has the potential to overcome this limitation by providing a local measure of brain oxygenation, which, if the catheter is placed in an appropriate area of the brain, could detect regional ischemia. Valadka, et al., found that the likelihood of death after severe head injury increased with an increasing time of PtiO\textsubscript{2} of less than 15 mm Hg and with any occurrence of a PtiO\textsubscript{2} of less than 6 mm Hg. In our study, the major contributor to impending hypoxia was the presence of intracranial hypertension and the major contributor to cerebral hypoxia was hyperventilation therapy. Both conditions are known to correlate with metabolic changes. In severely head injured patients, secondary increases of extracellular glutamate have been found to correlate with intracranial hypertension and severe ischemia. Analysis of our data suggests that when intracranial hypertension is treated with hyperventilation during impending hypoxia, cerebral hypoxia developed. Hyperventilation has traditionally been used in the treatment of intracranial hypertension. However prophylactic prolonged hyperventilation may be deleterious to the outcome of severely head injured patients because this treatment induces cerebral vasoconstriction. It is known that hyperventilation-induced ischemia is reflected by a decrease in PtiO\textsubscript{2}. In this study, patients were treated with moderate hyperventilation (PaCO\textsubscript{2} ≥ 30 mm Hg) under continuous control of endtidal etCO\textsubscript{2} and frequent arterial blood gas analysis. It may be argued that in some patients treatments of intracranial hypertension with hyperventilation were deleterious. In our study, the major contributor to impending hypoxia was the presence of intracranial hypertension and the major contributor to cerebral hypoxia was hyperventilation therapy. Both conditions are known to correlate with metabolic changes. In severely head injured patients, secondary increases of extracellular glutamate have been found to correlate with intracranial hypertension and severe ischemia. Analysis of our data suggests that when intracranial hypertension is treated with hyperventilation during impending hypoxia, cerebral hypoxia developed. Hyperventilation has traditionally been used in the treatment of intracranial hypertension. However prophylactic prolonged hyperventilation may be deleterious to the outcome of severely head injured patients because this treatment induces cerebral vasoconstriction. It is known that hyperventilation-induced ischemia is reflected by a decrease in PtiO\textsubscript{2}. In this study, patients were treated with moderate hyperventilation (PaCO\textsubscript{2} ≥ 30 mm Hg) under continuous control of endtidal etCO\textsubscript{2} and frequent arterial blood gas analysis. It may be argued that in some
cases PaCO₂ dropped below 30 mm Hg. However, the high percentage of hypoxic episodes related to a low etCO₂ (etCO₂ < 30 mm Hg) indicates that moderate hyperventilation may also be deleterious in individual patients. Therefore, treatment of intracranial hypertension with hyperventilation should only be used with alertness to potentially adverse effects, and treatment should continuously be adapted to cerebral oxygenation and possibly be avoided during impending hypoxia.

Only recently has bedside microdialysis, a well-established neurochemistry technique, been available for online detection of regional cerebral biochemical changes in patients.13 Earlier microdialysis studies used the high-performance liquid chromatography technique for analyzing microdialysis samples with the related disadvantages of offline analysis.1,4,16,17 In previous studies the authors confirmed the usefulness of the microdialysis technique in a clinical setting.5 To date, no adverse effect has been observed in patients, and because of its small size, the dialysis catheter is expected to cause only minimal damage. In this study there was no bleeding or infection caused by the PtiO₂ or microdialysis catheter.

In one study, during transient episodes of regional (PtiO₂ < 10 mm Hg) or global ischemia (SjvO₂ < 50%), the relevant metabolic changes of increased lactate and decreased glucose concentrations were found in severely head injured patients.11 The authors concluded that microdialysis provides additional indication of how severely the reduction in oxygenation is affecting the brain’s metabolism. In contrast to our study, measurements were obtained in frontal white matter in normal-appearing brain and also in brain regions underlying an evacuated hematoma or near contusion. Nevertheless, the results are similar to our findings, thus demonstrating that during regional cerebral hypoxia significant metabolic changes occur. Additionally we observed that during impending cerebral hypoxia (PtiO₂ 10–15 mm Hg) a significant increase in extracellular glutamate concentrations has already occurred. However, increased ECF levels of glutamate could be caused by several mechanisms such as transmitter release and unspecific leakage from injured cells. Because we found that energy metabolism was stable during impending hypoxia, we do not know if these elevations in extracellular glutamate indicate a relevant metabolic deterioration. Nevertheless, changes in extracellular glutamate have been proposed as useful indicators to predict the outcome in severe head injury.1

A major limitation of the microdialysis method is the relatively poor temporal resolution, because measurements are performed on samples collected over 30-minute epochs.4 It remains unclear whether the microdialysis concentrations collected with bedside units represent the integrated values during 60 minutes or during the last 15 minutes before analysis is performed, as postulated by the manufacturer. Brief hypoxic episodes occurring within the 60 minutes of sampling may not induce metabolic changes and may explain the lack of a significant increase in the lactate–pyruvate ratio in this study.

CONCLUSIONS

In summary, our data demonstrate that bedside cerebral microdialysis is a safe technique to indicate cerebral hypoxia in severely head injured patients when inserted into apparently nonaffected brain tissue. A PtiO₂ below 10 mm Hg was found to be critical to induce metabolic changes seen during hypoxia/ischemia and was most frequently associated with hyperventilation therapy. Early markers of
cerebral hypoxia are increased glutamate and lactate concentrations. Regional hypoxia is not always associated with anaerobic cerebral metabolism and possibly depends on the duration of the hypoxic episode. Future research should concentrate on identifying how treatment management may be optimally guided in these patients.

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References


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