Cerebral acid–base homeostasis after severe traumatic brain injury

TOBIAS CLAUSEN, M.D., AHMAD KHALDI, M.D., ALOIS ZAUNER, M.D., MICHAEL REINERT, M.D., EGGON DOPPENBERG, M.D., MATTHIAS MENZEL, M.D., PH.D., JENS SOUKUP, M.D., OSCAR LUIS ALVES, M.D., AND M. ROSS BULLOCK, M.D., PH.D.

Department of Anesthesiology and Intensive Care Medicine, Martin-Luther-University Halle-Wittenberg, Halle/Saale, Germany; Division of Neurosurgery, Virginia Commonwealth University Health System, Richmond, Virginia; Department of Neurosurgery, University of Miami Lois Pope Life Center, Miami, Florida; Department of Neurosurgery, Inselspital Bern, Switzerland; and Servico de Neurocirurgia, Centro Hospitalar de Gaia, Faculdade de Medicina da Universidade do Porto, Portugal

Object. Brain tissue acidosis is known to mediate neuronal death. Therefore the authors measured the main parameters of cerebral acid–base homeostasis, as well as their interrelations, shortly after severe traumatic brain injury (TBI) in humans.

Methods. Brain tissue pH, PCO$_2$, PO$_2$, and/or lactate were measured in 151 patients with severe head injuries, using a Neurotrend sensor and/or a microdialysis probe. Monitoring was started as soon as possible after the injury and continued for up to 4 days.

During the 1st day following the trauma, the brain tissue pH was significantly lower, compared with later time points, in patients who died or remained in a persistent vegetative state. Six hours after the injury, brain tissue PCO$_2$ was significantly higher in patients with a poor outcome compared with patients with a good outcome. Furthermore, significant elevations in cerebral concentrations of lactate were found during the 1st day after the injury, compared with later time points. These increases in lactate were typically more pronounced in patients with a poor outcome. Similar biochemical changes were observed during later hypoxic events.

Conclusions. Severe human TBI profoundly disturbs cerebral acid–base homeostasis. The observed pH changes persist for the first 24 hours after the trauma. Brain tissue acidosis is associated with increased tissue PCO$_2$ and lactate concentration; these pathobiochemical changes are more severe in patients who remain in a persistent vegetative state or die. Furthermore, increased brain tissue PCO$_2$ (> 60 mm Hg) appears to be a useful clinical indicator of critical cerebral ischemia, especially when accompanied by increased lactate concentrations.

Key Words • traumatic brain injury • cerebral acid–base homeostasis • carbon dioxide • lactate/ischemia • multimodal monitoring

SEVERE head injury is one of the principal causes of death and disability in Western society, especially among younger people. Annually, approximately 1.5 million US citizens sustain a mild, moderate, or severe TBI; 50,000 people die, 230,000 people are hospitalized and survive, and an estimated 80,000 to 90,000 people experience the onset of long-term disability as a result of these injuries. Despite tremendous progress made in the area of brain trauma research, our knowledge about the exact mechanisms and biochemical cascades that lead from trauma to the development of secondary brain injury is still poor—many pieces of the puzzle remain unsolved.

Relatively well-established factors initiating secondary brain damage include posttraumatic reduced CBF, hypoxia, and excessive release of excitatory amino acids. These mechanisms may result in the development of cerebral acidosis, mainly due to the failure of oxidative energy metabolism. Tissue acidosis in turn has been associated with the formation of intracellular edema, increased [Ca$^{2+}$]$_i$ concentrations, enzyme inactivation, mitochondrial impairment, and free radical formation. Nevertheless, although brain tissue acidosis has been well examined and documented after stroke and global brain ischemia, comparatively little information is available on this condition following human TBI. The goal of the present study, one of the first continuous assessments of these parameters in a large cohort of patients with severe TBI, was therefore to relate the time course of cerebral acid–base homeostasis (brain tissue pH, PCO$_2$, and lactate values) to good and bad outcomes, early after a severe head injury.

Clinical Material and Methods

The investigational protocol of these studies was approved by the Committee for Conduct of Human Research of VCUHS and Virginia Commonwealth University. Writ-
potension was treated aggressively by delivery of positive inotropic drugs and vasopressors; if arterial hypotension was caused by either impaired cardiac contractility or inadequate systemic vascular resistance or if hypotension was caused by a fluid deficit, an infusion of isotonic electrolyte solutions or plasma expanders was administered until normovolemia could be achieved. Furthermore, if hyperthermia was present, external cooling was applied until normothermia was obtained.

Brain Tissue Monitoring

Microdialysis. A sterile microdialysis probe (CMA 20; CMA Microdialysis, Acton, MA) was introduced into cortical tissue that had no sign of an injury such as a hematoma or contusion on computerized tomography scans. The probe was usually placed in the right frontal lobe by using a special custom-made three-lumen polycarbonate bolt. We deliberately tried to refrain from inserting the probes into pathologically altered tissue, because the purpose of the monitoring setup was to detect secondary brain injury rather than damage directly caused by the primary injury. The skull bolt also served as an entrance for the ventriculostomy catheter and, in most cases, for a Neurotrend multiparameter sensor. Bolt placement and probe insertion as well as the introduction of the ventriculostomy catheter were performed as early as possible, either in the operating room after the initial evacuation of a mass lesion or immediately after arrival of the patient at the neuroscience ICU.

The length of the active membrane of the microdialysis probe was 10 mm, with a molecular cut-off rate of 20 kD. The probe was perfused with sterile 0.9% NaCl solution at a flow rate of 2 µL/minute. After a stabilization period of at least 1 hour, sampling was started to allow for an adequate equilibration between cerebral ECF and perfusate. Microdialysate samples were collected every 30 minutes into sealed glass tubes by using an automated refrigerated (4°C) collector system (Honeycomb; Bioanalytical Systems, West Lafayette, IN). Cerebral ECF concentrations of lactate were analyzed by performing enzymic fluorometric assays on a CMA 600 Microdialysis Analyzer (CMA/Microdialysis, Solna, Sweden). The results were transferred to a relational database (Microsoft Access; Microsoft, Redmond, WA) for further analysis. Throughout this article, cerebral lactate concentrations are presented as concentrations measured in the microdialysate without corrections for probe recovery rates.

Neurotrend Sensor. The Neurotrend sensor, a minimally invasive multiparameter sensor for continuous measurement of brain tissue PO₂, PCO₂, pH, and temperature, was introduced via the polycarbonate skull bolt into unlesioned brain tissue. Before its insertion into the patient, the sensor was calibrated with special calibration gas mixtures in a tonometer under sterile conditions, according to the manufacturer’s specifications. The technical specifications of the Neurotrend sensor are shown in Table 2. All data that were obtained were digitally transferred from the Neurotrend patient data monitor to a Macintosh computer at intervals of 5 minutes, and from there into a relational database (Microsoft Access) for further analysis.

No complications that could be ascribed to either the microdialysis catheter or the Neurotrend sensor were detected in these patients.

**TABLE 1**

**Characteristics in 151 patients with severe TBI**

<table>
<thead>
<tr>
<th>GOS Score</th>
<th>No. of Patients</th>
<th>Age (yrs)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total Male</td>
<td>Female</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>5 (good recovery)</td>
<td>27</td>
<td>19</td>
<td>8</td>
</tr>
<tr>
<td>4 (moderate disability)</td>
<td>24</td>
<td>18</td>
<td>6</td>
</tr>
<tr>
<td>3 (severe disability)</td>
<td>37</td>
<td>26</td>
<td>11</td>
</tr>
<tr>
<td>2 (persistent vegetative state)</td>
<td>20</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>1 (death)</td>
<td>43</td>
<td>32</td>
<td>11</td>
</tr>
<tr>
<td>total</td>
<td>151</td>
<td>113</td>
<td>38</td>
</tr>
</tbody>
</table>

* SD = standard deviation.

**Patient Population**

A total of 151 patients with severe closed head injury (Glasgow Coma Scale Scores 3–8 at admission or within 12 hours after admission), who were admitted to the neuroscience ICU at VCUHS, were included in the study (Table 1). Medical exclusion criteria consisted of rapid neurological improvement after admission, the presence of brain death or near brain death, or any form of coagulopathy. The average age of the study participants was 35.5 years (mean ± standard deviation); 113 patients were male (75%) and 38 were female (25%). Patient outcome was graded according to the GOS at 3 months postinjury. At this time 27 patients (18%) demonstrated good recovery, 24 (16%) were moderately disabled, 37 (25%) suffered from severe disability, 20 (13%) remained in a persistent vegetative state, and 43 (28%) had died (Table 1).

In 80 patients concurrent multimodal monitoring could be performed using microdialysis and the Neurotrend sensor system (Neurotrend; Codman, Johnson & Johnson Professional, Inc., Raynham, MA). Microdialysis measurements without Neurotrend monitoring were performed in an additional 59 patients and 12 patients were only monitored with the aid of the Neurotrend system because of delayed microdialysis probe failure. Thus, microdialysis monitoring was performed in 139 patients, whereas the Neurotrend sensor system was used in 92 patients.

All patients were treated according to the VCUHS standard protocol for management of severe head injury, which emphasizes prevention of secondary brain damage and control of ICP. The mean arterial blood pressure, ICP, and CPP were monitored continuously. Intermittent arterial blood gas analysis was performed every 4 to 6 hours or when needed. Intubation and mechanical ventilation were used in all patients to maintain PaCO₂ at approximately 35 mm Hg (4.7 kPa) and PaO₂ at higher than 100 mm Hg (13.3 kPa). The goal of therapy was to achieve an ICP of less than 20 mm Hg by using a “staircase” algorithm that included sedation, analgesia, and neuromuscular paralysis; moderate head-up posture (10–20°); ventricular drainage; mannitol infusion; mild or moderate hypothermia; surgical decompression; and barbiturate-induced coma. Significant mass lesions were evacuated as soon as possible after their detection. Blood pressure management was directed to maintain the CPP higher than 70 mm Hg whenever possible. Arterial hy-
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Statistical Analysis

All clinical parameters were downloaded from the bedside monitor and logged into a VAX mainframe computer (Neurocore; VCUHS Databases) throughout the monitoring period. These data were then time-locked with the data on lactate concentrations, which were obtained from microdialysis as well as the Neurotrend database, and stored in a relational database (Microsoft Access) for further analysis.

For statistical analysis the patients were grouped according to their GOS scores at 3 months after injury, into patients with good outcomes (GOS Scores 5 and 4), patients with severe disabilities (GOS Score 3), and patients with poor outcomes (GOS Scores 2 and 1).

To elucidate the pathophysiological role of brain tissue pH, PCO₂, and lactate, we compared the mean values of these parameters at different levels of CPP, as well as at different levels of brain tissue PO₂. Because the ischemic threshold for O₂ is still under dispute, we chose the following levels for brain tissue PO₂: 10 mm Hg as a potentially insufficient O₂ supply; values between 10 and 20 mm Hg as insufficient O₂ supply; and values higher than 20 mm Hg as a sufficient O₂ supply. As for levels of CPP, we differentiated between values less than 70 mm Hg (the clinical standard in most neurosurgical ICUs), and values greater than 90 mm Hg.

The analysis, including descriptive statistics, was performed using statistical software (StatView; Abacus Concepts, Berkeley, CA). A statistical analysis was performed to compare mean values within a group at several different time points. Means between different outcome groups at corresponding time points were compared using the unpaired t-test. Differences were considered statistically significant if the probability value was less than 0.05. To determine the degrees of relationship among brain tissue pH, PCO₂, and lactate, both simple and multiple regression analyses were performed. Values are expressed as means ± SEMs unless otherwise indicated.

Results

Lactate Concentrations

The mean dialysate lactate concentration of all patients during the entire monitoring period was 976 ± 71 μmol/L. During that time the mean lactate concentration was 785 ± 119 μmol/L in patients with good outcomes (GOS Scores 4 and 5) and 1051 ± 118 μmol/L in patients with poor outcomes (GOS Scores 1 and 2). A continuous decline in the mean microdialysate lactate concentration of all patients from 1136 ± 76 μmol/L on Day 1 to 777 ± 85 μmol/L on Day 4 after injury was observed. The differences in mean lactate concentration between the 1st day after injury and each following day was statistically significant (p < 0.05).

The mean dialysate lactate concentration decreased from 951 ± 138 μmol/L on Day 1 to 672 ± 109 μmol/L on Day 2 after injury and then remained relatively stable for the rest of the monitoring period in patients with good outcomes. The differences in mean dialysate lactate concentration were statistically significant between the 1st day after injury and the following days was not statistically significant in these patients.

On the other hand, the lactate concentration decreased continuously from 1197 ± 111 μmol/L on Day 1 to 718 ± 151 μmol/L on Day 4 after injury in patients with poor outcomes. The differences in mean dialysate lactate concentration were statistically significant between the 1st day after injury and Days 3 and 4 (p < 0.05).

The mean lactate concentration was higher in patients who died or remained in a persistent vegetative state (GOS Scores 1 and 2, respectively) compared with patients with good recoveries and moderate disabilities (GOS Scores 5 and 4, respectively) throughout the first 4 days after the injury, even though the difference between these two groups was not statistically significant (Fig. 1).

Increased lactate concentrations were observed during episodes of low CPP and/or poor brain tissue oxygenation. The highest lactate concentration was found at the lowest CPP level. When CPP was less than 70 mm Hg, the mean dialysate lactate concentration was 1027 ± 58 μmol/L. When CPP ranged from 70 to 90 mm Hg, the lactate concentration was 874 ± 27 μmol/L mm Hg, and when the CPP was higher than 90 mm Hg, the mean lactate concentration was 910 ± 42 μmol/L. The difference in mean lactate concentration between the lowest CPP level and the medium CPP level was statistically significant (p < 0.05). A similar pattern was observed when the mean lactate concentrations were compared at different levels of brain tissue PO₂. The highest mean lactate concentration (910 ± 114 μmol/L) was found when the brain tissue PO₂ was lower than 10 mm Hg. When the PO₂ ranged from 10 to 20 mm Hg, the mean lactate concentration was 774 ± 49 μmol/L. The lowest mean lactate concentration (712 ± 24 μmol/L) was seen when the PO₂ was higher than 20 mm Hg. The difference in dialysate lactate concentrations between the lowest (< 10 mm Hg) and highest (> 20 mm Hg) levels of brain tissue PO₂ was statistically significant (p < 0.05).

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In addition, moderate elevations in dialysate lactate concentrations, which were not related to brain tissue PO$_2$, CPP, or any other obvious hypoxic or clinical event, have been observed in some patients. These increases in lactate lasted for several hours and in a few cases for days, and were mostly accompanied by a moderate decrease in the concentration of brain tissue glucose. The in vitro recovery rate for lactate, using this microdialysis system, was 42%.

**Brain Tissue PCO$_2$**

The mean brain tissue PCO$_2$ of all patients throughout the entire monitoring period was 48 ± 1 mm Hg. Although pa-
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![Graph showing the time course of brain tissue PCO₂ during the first 4 days after TBI.](Image)

Fig. 3. Graph showing the time course of brain tissue PCO₂ during the first 4 days after TBI. The initially high mean brain tissue PCO₂ of all patients was almost entirely due to patients with poor outcomes, whereas the mean PCO₂ in patients with good outcomes was within the normal range throughout the monitoring period, despite slightly higher values during the first 24 hours after injury. Brain tissue PCO₂ was significantly higher in patients with poor outcomes compared with patients with good outcomes at 6 hours after injury (71 ± 10 and 47 ± 3 mm Hg, respectively; p < 0.05).

Patients with good outcomes (GOS Scores 4 and 5) had a mean brain tissue PCO₂ of 46 ± 1 mm Hg, a mean brain tissue PCO₂ of 52 ± 3 mm Hg was seen in patients with poor outcomes (GOS Scores 1 and 2). The mean brain tissue PCO₂ of all patients was significantly higher during the first 24 hours after the injury compared with all the remaining monitoring days. It decreased from 51 ± 1 mm Hg on Day 1 postinjury to 46 ± 1 mm Hg on Day 2, and remained at approximately that value for the rest of the monitoring period.

The mean brain tissue PCO₂ in patients with good outcomes was 50 ± 1 mm Hg on Day 1 postinjury, decreased to 45 ± 1 mm Hg on Day 2 (p < 0.05), and stabilized at approximately this level over the following days. The brain tissue PCO₂ in patients with poor outcomes was 53 ± 3 mm Hg on Day 1 postinjury and continuously decreased to 45 ± 1 mm Hg on Day 4 (Fig. 2).

When we looked at the time course of brain tissue PCO₂ in more detail, we found that the mean PCO₂ of all patients reached its maximum value 6 hours after injury (the earliest time of monitoring), continuously declined for approximately 24 hours, and stabilized for the rest of the monitoring period. When we categorized patients by outcome, we found that this initial increase in PCO₂ was almost entirely due to values obtained in patients who had died or remained in a persistent vegetative state (poor outcome; GOS Scores 1 and 2, respectively), whereas the mean PCO₂ in patients with good recoveries or moderate disabilities (good outcome; GOS Scores 5 and 4, respectively) was within the normal range, as reported previously.³⁰¹⁰ Brain tissue PCO₂ was higher in patients with poor outcomes than in patients with good outcomes almost throughout the entire monitoring period. At 6 hours postinjury, the difference between these two outcome groups was significant (71 ± 10 mm Hg compared with 47 ± 3 mm Hg, p < 0.05; Fig. 3).

Moreover, brain tissue PCO₂ was different at different levels of CPP. The mean brain tissue PCO₂ was 50 ± 1 mm Hg at CPP values lower than 70 mm Hg, 46 ± 1 mm Hg at CPP values between 70 and 90 mm Hg, and 45 ± 1 mm Hg at CPP values higher than 90 mm Hg. The difference between the lowest CPP level and the two higher levels was statistically highly significant (p < 0.0001). Furthermore, considerable increases in brain tissue PCO₂ were observed during periods of drastically decreased CPP. When the CPP decreased to lower than 40 mm Hg, we observed a mean brain tissue PCO₂ of 56 ± 8 mm Hg.

Episodes of increased PCO₂, frequently coincided with episodes of poor brain tissue oxygenation. When brain tissue PO₂ decreased to less than 10 mm Hg, the mean PCO₂ was 49 ± 1 mm Hg. In contrast, when the PO₂ was between 10 and 20 mm Hg or higher than 20 mm Hg, the mean PCO₂ was 45 ± 0.5 mm Hg or 45 ± 0.2 mm Hg, respectively. The difference in mean brain tissue PCO₂ between the lowest brain tissue PO₂ level (10 mm Hg) and each of the two higher PO₂ levels (10–20 mm Hg and > 20 mm Hg) was statistically highly significant (p < 0.0005).

Arterial PCO₂ remained stable throughout the monitoring period. No relevant differences in mean PaCO₂ between the various outcome groups were observed during the first 4 days after injury.

**Brain Tissue pH**

The mean brain tissue pH of all monitored patients was 7.13 ± 0 for the entire monitoring period. In patients with good outcomes (GOS Scores 4 and 5) the mean pH was 7.13 ± 0.01, whereas in patients with poor outcomes (GOS Scores 1 and 2) it was 7.12 ± 0.01. The mean brain tissue pH of all patients was significantly lower on the 1st day after injury, compared with the following 3 days. It increased...
from 7.06 ± 0.01 on Day 1 postinjury to 7.14 ± 0.01 on Day 2 and further to 7.16 ± 0.01 on both Days 3 and 4 (p < 0.01).

In patients with good outcomes the mean brain tissue pH increased from 7.08 ± 0.02 on Day 1 postinjury to 7.13 ± 0.01 on Day 2 and 7.16 ± 0.01 on Day 3; it remained approximately at this level on Day 4 as well. Differences in the mean pH of patients with good outcomes between the 1st day after injury and the following days were statistically significant (p < 0.01). In patients with poor outcomes the mean brain tissue pH was also significantly worse on the 1st day after injury compared with the following days. In these patients the pH increased from 7.02 ± 0.02 on Day 1 postinjury to 7.15 ± 0.01 on Day 2; it remained at that level for the rest of the monitoring period (p < 0.01). Although brain tissue pH was considerably lower in patients with poor outcomes compared with patients with good outcomes on Day 1 postinjury, the difference between both groups was not statistically significant. When we looked at the time course of brain tissue pH in more detail, we found that the lowest mean pH occurred immediately after injury in patients with poor outcomes. Approximately 21 hours after injury the pH was similar in both outcome groups (Fig. 4).

In all patients the brain tissue pH was significantly inversely correlated with the brain tissue PCO₂ (r = −0.53, p < 0.0001) and, to a lesser degree, with the dialysate lactate concentration (r = −0.34, p < 0.0001). The strength of the relationships between brain tissue pH and brain tissue CO₂ and lactate, respectively, differed greatly between the different outcome groups. In patients with good recoveries and moderate disabilities (good outcome, GOS Scores 5 and 4, respectively) the correlation between brain tissue pH and PCO₂ was relatively weak (r = −0.30, p < 0.0001) and the correlation between brain tissue pH and lactate was even weaker (r = −0.13, p < 0.01). In patients who died or remained in a persistent vegetative state (poor outcome, GOS Scores 1 and 2, respectively), however, brain tissue pH and PCO₂ were correlated to a considerably stronger degree (r = −0.70, p < 0.0001), whereas the correlation between brain tissue pH and lactate (r = −0.34, p < 0.0001) was also higher than that found in patients with good outcomes.

When the combined influence of brain tissue PCO₂ and lactate concentration on brain tissue pH was examined, the same phenomenon was observed. Overall, in brain tissue the pH was inversely correlated with the PCO₂ and lactate (r = −0.59, p < 0.0001). This correlation was considerably stronger in patients with poor outcomes (r = −0.80, p < 0.0001) compared with patients with good outcomes (r = −0.38, p < 0.001).

Brain tissue pH varied substantially at the different levels of CPP, with significantly decreased pH values during episodes of low CPP. The lowest brain tissue pH (7.06 ± 0.02) was found at CPP values lower than 70 mm Hg; at CPP values between 70 and 90 mm Hg, a mean pH of 7.13 ± 0.01 was observed, whereas at values higher than 90 mm Hg, the mean pH was 7.17 ± 0.01. The differences among all three levels were statistically highly significant (p < 0.0001).

A very similar pattern was seen when pH was analyzed for different levels of brain tissue oxygenation. The lowest pH was observed at the worst PO₂ level and the highest pH was seen at the highest level of brain tissue oxygenation; when the PO₂ was lower than 10 mm Hg, an average brain tissue pH of 7.02 ± 0.02 was seen; when the PO₂ ranged from 10 to 20 mm Hg the pH was 7.09 ± 0.01; and when the PO₂ was higher than 20 mm Hg the mean pH was 7.16 ± 0.0 (Fig. 5). Differences in the mean brain tissue pH between the lowest PO₂ level (< 10 mm Hg) and each of the two higher levels (p < 0.0001) as well as the difference between the medium PO₂ level (10–20 mm Hg) and the highest level (> 20 mm Hg) (p < 0.0001) were highly statistically significant.

The mean arterial pH of all patients was 7.43 ± 0, and this value remained stable throughout the monitoring period. In patients with good outcomes the arterial pH was 7.43 ± 0, with no significant changes over time. The mean arterial pH in patients with poor outcomes was 7.42 ± 0, and this demonstrated a slightly decreasing trend during
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Fig. 5. Bar graph depicting mean brain tissue pH at different levels of brain tissue oxygenation after TBI. Brain tissue pH varies substantially between different levels of brain tissue oxygenation. The lowest pH is observed at the worst brain tissue PO$_2$ (pO$_2$) level and the highest pH is seen at the best brain tissue oxygenation; when the PO$_2$ is below 10 mm Hg the mean brain tissue pH is 7.02 ± 0.02; when the PO$_2$ ranges from 10 to 20 mm Hg the pH is 7.09 ± 0.01; and when the PO$_2$ is higher than 20 mm Hg the mean pH is 7.16 ± 0. The differences in mean brain tissue pH between the lowest PO$_2$ level (< 10 mm Hg) and each of the two higher levels (p < 0.0001) as well as the difference between the medium (10–20 mm Hg) and highest (> 20 mm Hg) level of brain tissue PO$_2$ (p < 0.001) is highly significant.

Discussion

Brain tissue acidosis has been reported to mediate brain damage after traumatic and ischemic injuries. Increased [Ca$^++$] concentrations cause a decline in brain tissue pH when the physiological buffer systems are exhausted. An elevated generation of lactate in turn can impair mitochondrial metabolism. Furthermore, the formation of free radicals, one of the principal pathomechanisms leading to delayed cell death after TBI, has been shown to be enhanced at lower pH values. Several factors contribute to the regulation of brain tissue pH: 1) brain tissue PO$_2$ (via the carbonic anhydrase reaction); 2) physiological buffer systems (in the case of cerebral interstitial fluid, primarily the bicarbonate system); and 3) the metabolic production of acidic substances (chiefly lactate and unbuffered H$^+$). The interrelationship between brain tissue PO$_2$ and pH will be discussed in greater detail later in this section. Although the roles of PO$_2$ and the bicarbonate buffer system in the regulation of cerebral pH are closely related (H$^+$ + HCO$_3^-$ $\rightarrow$ CO$_2$ + H$_2$O), our knowledge about the significance of other buffer systems in cerebral interstitial fluid is rather limited. By far the most important acid generated by cerebral metabolism is lactic acid. Increased lactate production causes a decline in brain tissue pH when the physiological buffer systems are exhausted. An elevated generation of lactate in turn has been reported after TBI as a product of anaerobic glycolysis during cerebral ischemia or hypoxia; as a result of a failure in mitochondrial metabolism, even during preserved CBF and oxygenation; and during compensatory glycolysis following a massive posttraumatic release of glutamate and the attempt to restore disturbed ionic homeostasis. All these pathomechanisms may contribute, alone or together, to lactate-mediated brain tissue acidosis after TBI.

In the present study, the lactate increases observed in the cerebral ECF of patients with severe head injuries may be attributed to several mechanisms. The lactate peak observed during the first 24 hours postinjury is most likely due to a
combination of different mechanisms. 1) There is increased compensatory astrocytic glycolysis to restore posttraumatically disturbed ionic homeostasis.22,46 2) Excitatory amino acids, chiefly glutamate, are removed from the extracellular space by astrocytes via an Na+/H+ cotransport; the ensuing rise in the intracellular Na+ concentration activates Na+/K+–ATPase, thus stimulating glycolysis and lactate production in astrocytes. (Glutamate is then converted to glutamine and shuttled back to the neurons.) Severe hypoxic events, such as cerebral ischemia or hypoxia, may result in a substantial accumulation of brain tissue lactate after TBI. Mitochondrial impairment after TBI may instigate an increase in glycolytic activity, even in the absence of concurrent ischemia or hypoxia. Acidosis itself may, in turn, promote the formation of mitochondrial permeability transition pores with a subsequent failure in mitochondrial metabolism, thus initiating a vicious cycle. Gln = glutamine; Glt = glutamate; Lac = lactate; MPT = mitochondrial permeability transition.

Compared with the continuously increasing number of reports about the importance of brain tissue PO2, relatively little is known about the pathophysiological role of brain tissue PCO2 after TBI. Charbel and colleagues8 described elevated brain tissue CO2 levels, with a concomitant drop in brain tissue pH, in patients suffering from severe vasospasm.

**Fig. 6.** Possible mechanisms responsible for increases in brain tissue lactate after TBI. The posttraumatic increases in lactate seen in the cerebral ECF in severely head injured patients in the present study may be attributed to a variety of mechanisms. Glycolytic activity increases due to the need to restore the posttraumatically disturbed ionic homeostasis by means of the ATP-dependent Na+/K+ exchanger. Excitatory amino acids such as glutamate, which are massively released after TBI, are removed from the extracellular space by astrocytes via an Na+/H+ cotransport; the ensuing rise in the intracellular Na+ concentration activates Na+/K+–ATPase, thus stimulating glycolysis and lactate production in astrocytes. (Glutamate is then converted to glutamine and shuttled back to the neurons.) Severe hypoxic events, such as cerebral ischemia or hypoxia, may result in a substantial accumulation of brain tissue lactate after TBI. Mitochondrial impairment after TBI may instigate an increase in glycolytic activity, even in the absence of concurrent ischemia or hypoxia. Acidosis itself may, in turn, promote the formation of mitochondrial permeability transition pores with a subsequent failure in mitochondrial metabolism, thus initiating a vicious cycle. Gln = glutamine; Glt = glutamate; Lac = lactate; MPT = mitochondrial permeability transition.
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after aneurysmal subarachnoid hemorrhage. Increases in brain tissue CO2 accompanied by a concomitant decrease in brain tissue pH and PO2 have also been reported after experimental middle cerebral artery occlusion in a feline model and after temporary clipping of major cerebral arteries during aneurysm surgery in patients.6,31,38 The same constellation, a significant rise in brain tissue PCO2, with a parallel decline in brain tissue pH and PO2, was observed immediately after brain trauma in a feline fluid-percussion-injury model by our group recently.48 Furthermore, brain tissue CO2 levels up to 150 mm Hg have been described during cerebral circulatory arrest and brain death after human TBI.49 In the present study a significant increase in PCO2, with a concomitant drop in brain tissue pH, was found in patients with poor outcomes within 6 hours postinjury. Moreover, increases in brain tissue PCO2 were seen during severe hypoxic episodes, especially when these were due to insufficient CPP.

In general, four main reasons for an increase in brain tissue PCO2 are theoretically possible: 1) an increase in arterial CO2 with consecutive diffusion into the brain; 2) an increase in cerebral CO2 production; 3) a disturbance in the CO2 clearance from the tissue; and 4) profound tissue acidosis with an increase in CO2 generation via the carbonic anhydrase reaction (H+ + HCO3- \( \Delta \) CO2 + H2O).

The first reason is not significant in this study. It is important to note that arterial PCO2 was considerably lower than brain tissue PCO2 in all patients, and remained constant throughout the monitoring period because of the use of vigorously controlled end-tidal CO2–directed ventilation.

An increase in cerebral CO2 production is theoretically possible if the turnover rate of oxidative glucose degradation rises considerably, as in the Krebs cycle. Nevertheless, the results of several studies in animals and humans have demonstrated a major decline in cerebral O2 consumption after TBI.1,3,13,19 Moreover, in the present study the increases observed in brain tissue PCO2 were regularly accompanied by a drop in brain tissue PO2. Given that decarboxylation reactions (for example, decarboxylation of pyruvate, isocitrate, and \( \alpha \)-ketoglutarate before and during the tricarboxylic acid cycle) as part of oxidative glucose metabolism and ATP generation are the main metabolic source of cerebral CO2 production, and because these reactions are inhibited in the absence of sufficient O2 by increased concentrations of the reduced form of nicotinamide adenine dinucleotide, a decrease in CO2 production, instead of a rise, would be expected. Therefore, a rise in "normal physiological" CO2 production is not likely to be the source of the increased brain tissue PCO2 observed in our patients.

The principle way to eliminate CO2 from brain tissue is diffusion into cerebral capillaries and removal by CBF, as long as there is a PCO2 gradient between brain tissue and blood. If blood flow decreases, the gradient, and thus the driving force for CO2 elimination from the tissue, will also decrease as less CO2 is quantitatively removed by cerebral perfusion per time unit. If relative or complete ischemia occurs, CO2 accumulates in the brain tissue, thereby creating a new diffusion equilibrium between brain tissue and blood in the affected area. Because significant ischemia accompanies a critical reduction in the O2 supply, pathological CO2 production will decrease at some point. A complete cessation of oxidative CO2 production, however, should occur only during absolute anoxia. Concomitantly, the anaerobic lactate generation will increase as long as glucose is available as a substrate. The ensuing lactate acidosis may further contribute to an increase in brain tissue PCO2 levels because, under these conditions, more bicarbonate is converted into CO2 and H2O in an attempt to restore the physiological pH milieu (H+ + HCO3- \( \Delta \) CO2 + H2O). Given that cerebral perfusion has been demonstrated to be critically impaired in a large number of severely head injured patients with poor outcomes immediately posttrauma,6 cerebral ischemia may be a key factor responsible for the large early increase seen in brain tissue PCO2 in patients in this study who died or remained in a persistent vegetative state. Moreover, the fact that brain tissue PCO2 usually normalized within 12 hours postinjury indicates restoration of CBF, and concurs with the observations of Bouma and colleagues,6 who found global and regional cerebral ischemia during the first 4 to 12 hours in approximately 34% of patients with severe TBI by using the stable xenon–enhanced computerized tomography method. This, as well as the fact that the highest levels of brain tissue CO2 were seen during episodes of critically decreased CPP in the present study, lends further support to the thesis that the initial increase in PCO2 in these patients was caused mainly by insufficient CO2 clearance due to impaired CBF.

Given that severe tissue acidosis was present at the same time in patients with poor outcomes, one might argue that the increase in brain tissue PCO2 may be a result of acidosis rather than ischemia. Nevertheless, the two main measurable factors influencing brain tissue pH in these patients were brain tissue PCO2 and extracellular lactate concentration. Of these two, PCO2 was by far the more important factor in patients with poor outcomes. Furthermore, lactate concentrations only started to rise at this time, whereas PCO2 reached its highest values at 6 hours after the trauma. Therefore, we speculate that the initially low brain tissue pH seen in patients with poor outcomes was the result of increased brain tissue PCO2, rather than its cause.

In the present study, brain tissue CO2 recovered considerably faster from the initial derangement than brain tissue pH did. During normalization of PCO2, however, the cerebral concentration of lactate continued to rise, peaking approximately 15 to 18 hours after the injury. Therefore we assume that the initial drop in brain tissue pH was chiefly due to the early increase in PCO2, whereas the prolonged recovery of pH resulted, in large part, from the delayed increase in lactate concentrations.

Apart from the initial increase in brain tissue PCO2 in patients with poor outcomes, elevated values of brain tissue PCO2 were also observed during severe hypoxic events, in which they were typically associated with decreased brain tissue PO2 and pH and increased extracellular lactate concentrations. Whether the increases in brain tissue PCO2 seen during such a hypoxic event were directly due to ischemia or a consequence of tissue lactate acidosis, is difficult to differentiate. The fact that these PCO2 increases were more often observed when the hypoxic event was due to insufficient CPP, at least indicates a direct influence of ischemia as a pathogenetic factor. It is probable that both tissue acidosis and ischemia may contribute to varying degrees to an increase in brain tissue PCO2, under such circumstances.

Conclusions

The results of the present study demonstrate that brain
tissue acidosis occurs during the first hours after severe head injury in humans and that disturbances in acid–base homeostasis are far more pronounced in patients who die or remain in a persistent vegetative state. The main causes for this acidosis were increases in brain tissue PCO₂, most likely as a result of an insufficient CO₂ clearance due to impaired cerebral micro- or macrocirculation, and elevated lactate concentrations, probably caused by increased glycolytic activity. Interestingly, the changes in cerebral pH depend to a considerably greater degree on changes in brain tissue CO₂ and lactate in patients with poor outcomes compared with patients with good outcomes.

Our findings also indicate that a significant rise in brain tissue PCO₂ may be indicative of critical cerebral ischemia. Because high diffusibility is an important property of the CO₂ molecule, however, it can disperse into neighboring capillaries with relative ease. Therefore, a disturbance in CBF needs to affect a larger area of brain tissue before an increase in brain tissue PO₂, We postulate that an increase in brain tissue PCO₂ (>60 mm Hg), especially when it is associated with a decrease in brain tissue PO₂ and/or an increase in cerebral lactate concentration, is an indicator of severe ongoing cerebral ischemia. Furthermore, monitoring of brain tissue PCO₂, pH, and lactate, along with brain tissue PO₂, constitutes a useful tool to assist in the individual optimization of CPP and O₂ delivery to ensure a sufficient CBF and optimized metabolic recovery in patients with severe head injury.

References


Cerebral acid–base homeostasis after severe TBI


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