Brain-tissue acidosis inferred by cerebrospinal fluid (CSF) lactic acidosis is considered to play an important role in the clinical course of severe head injury. Ventricular CSF lactate concentration was studied in 19 patients during the first 5 days after severe head injury. All patients were intubated, paralyzed, and artificially ventilated so that PaCO$_2$ was kept at 33.2 ± 5.0 mm Hg and PaO$_2$ at 122 ± 18 mm Hg (mean ± standard deviation). The mean Glasgow Coma Scale score on admission was 5.73 ± 2.42. The first CSF sample was drawn within 18 hours after head injury. Over the first 4 days postinjury, patients with a poor outcome had significantly higher ventricular CSF lactate levels than did those with moderate disabilities or a good outcome. Patients showing favorable outcome had a significant decrease in ventricular CSF lactate levels 48 hours after injury. This decrease was not observed in patients with a poor outcome. Increased ventricular CSF lactate concentration was also reliably associated with increased intracranial pressure (ICP). Ventricular CSF lactate levels did not correlate with the magnitude of intraventricular bleeding. Arterial and jugular venous blood lactate levels, although high after head injury, were usually lower than the levels in the ventricular CSF and reached a normal range by the 3rd day following head trauma. At that time, the ventricular CSF lactate concentration was still above normal in patients with a poor outcome but had decreased to normal in patients with moderate disabilities or a good outcome. Ventricular CSF pH did not generally correlate with the ventricular CSF lactate concentration in patients under controlled ventilation; however, in a few patients close to death or with ventricular infection, a correlation was noted. Ventricular CSF lactate levels were not related to cerebral blood flow. In this study, profiles of ventricular CSF lactate concentration are defined in relation to the patients' clinical course and outcome. High ventricular CSF lactate concentration is present within 18 hours after severe head injury. Its decrease to normal in the following 48 hours is a reliable sign of clinical improvement; however, ventricular CSF lactate levels that are persistently high or that increase over time indicate the patient's deterioration. Serial assessment of ventricular CSF for acid-base status and metabolites in head-injured patients with a ventricular catheter already placed for ICP monitoring is useful in the evaluation of prognosis and clinical course.

**KEY WORDS**  head injury  cerebrospinal fluid  lactic acidosis  prognosis
of cerebral ischemia and/or hypoxia. These patients were selected for treatment of brain-tissue acidosis and were selected on the basis of the level of hyperventilation. Only patients whose PaCO₂ was maintained above 28 mm Hg were accepted for this study. Following diagnosis and treatment of any intracranial mass large enough to warrant surgical decompression, consent was obtained and patients were randomly assigned to one of three protocol groups. Group I was the control group treated with mild hyperventilation (PaCO₂ maintained at 33 to 37 mm Hg); Group II received tromethamine (THAM)* plus hyperventilation (PaCO₂ maintained at 22 to 26 mm Hg); Group III was treated with hyperventilation only (PaCO₂ maintained at 22 to 26 mm Hg). All patients were managed in a standard fashion as described elsewhere. This group of 19 patients with mild hyperventilation was selected for this study because high levels of hyperventilation may increase CSF lactate concentration. These patients were kept on controlled ventilation with PaCO₂ maintained at 33.2 ± 5.0 mm Hg and PaO₂ at 122 ± 18 mm Hg. End-expiratory CO₂ was monitored continuously with a capnometer, which allowed us to keep the PaCO₂ within this range.

Clinical Material and Methods

Patient Population

The 19 patients in the study were selected from a group of 36 severely head-injured patients who remained unresponsive at least 6 hours after admission to the hospital (mean Glasgow Coma Scale (GCS)) score of 5.97 ± 2.12 (standard deviation)). The study group patients were aged 18 to 81 years (average 36 years) and had a mean GCS score of 5.73 ± 2.42. These patients comprised the control group of a clinical trial for treatment of brain-tissue acidosis and were selected on the basis of the level of hyperventilation. Only patients whose PaCO₂ was maintained above 28 mm Hg were accepted for this study. Following diagnosis and treatment of any intracranial mass large enough to warrant surgical decompression, consent was obtained and patients were randomly assigned to one of three protocol groups. Group I was the control group treated with mild hyperventilation (PaCO₂ maintained at 33 to 37 mm Hg); Group II received tromethamine (THAM)* plus hyperventilation (PaCO₂ maintained at 22 to 26 mm Hg); Group III was treated with hyperventilation only (PaCO₂ maintained at 22 to 26 mm Hg). All patients were managed in a standard fashion as described elsewhere. This group of 19 patients with mild hyperventilation was selected for this study because high levels of hyperventilation may increase CSF lactate concentration. These patients were kept on controlled ventilation with PaCO₂ maintained at 33.2 ± 5.0 mm Hg and PaO₂ at 122 ± 18 mm Hg. End-expiratory CO₂ was monitored continuously with a capnometer, which allowed us to keep the PaCO₂ within this range.

Sample Collection and Analysis

All 19 patients in this study had undergone placement of a polyethylene catheter in the lateral ventricle for monitoring ICP, from which ventricular CSF was collected within 18 hours after injury and then at regular intervals of 12 hours. Arterial blood was obtained from a catheter inserted into the radial artery for continuous monitoring of arterial blood pressure, and jugular venous blood was drawn from a catheter inserted in the jugular vein with the tip placed into the jugular bulb. Blood samples were gathered at the same time as the collection of ventricular CSF samples.

Lactate concentrations in the ventricular CSF and blood were determined by an Automated Clinical AutoAnalyzer modification of the method by Marbach and Weil in which lactate is oxidized to pyruvate. Ventricular CSF and blood pyruvate concentrations were determined by the method of Marbach and Weil. Ventricular CSF hemoglobin concentration was determined according to the spectrophotometric technique of Shinowara.

Ventricular CSF and arterial blood acid-base parameters were measured in a blood gas analyzer. The pH values were corrected for the patient's temperature. Bicarbonate concentration was calculated from the pH and pCO₂ values, using the Henderson-Hasselbach equation with a coefficient of dissociation (pK) of 6.10 for blood 22 and 6.13 for CSF. The solubility coefficient of CO₂ was 0.031 for blood and 0.032 for CSF. Before the CSF samples were collected through the intraventricular catheter, the syringe was flushed with the patient's ventricular CSF and no air bubbles were allowed to enter. Arterial blood was collected in a heparinized syringe with the same care. No more than a 2-minute interval was allowed between collection of ventricular CSF and arterial blood. The normal range of lactate levels has two standard deviations of confidence.

For analysis of the biochemical data, the patients were separated into two groups based on their Glasgow Outcome Scale score. The favorable category included those patients who had good outcome or were moderately disabled. Patients with poor outcome were severely disabled, vegetative, or dead. The follow-up period was from 6 months to 2 years. In addition, patients were separated into three groups according to the course profile of their ventricular CSF lactate values. In Profile 1, the values rapidly reached normal range within 48 hours after injury; in Profile 2, the values were abnormally elevated until Day 4 after injury, then declined slowly; in Profile 3, values presented a sustained increase above the level measured on Day 1.

In classifying the ICP, care was taken to exclude

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* Hydroxymethyl aminomethane (tromethamine) is an intra- and extracellular buffer used in addition to hyperventilation to reverse brain acidosis.
† Capnometer, Model HP 47210A, manufactured by Hewlett-Packard, Waltham, Massachusetts.
CSF lactic acidosis in severe head injury

spuriously high ICP recordings attributable to suctioning, coughing, gross head movements, or improper transducer calibration. Patients were considered to have a high ICP when their ICP reached high levels in spite of aggressive therapy previously described, and were classified according to the highest sustained ICP level. "Sustained" was defined as a period of at least 2 minutes during the 5 days of study. Four groups were established: Group I included those whose ICP remained under 20 mm Hg; Group II comprised those who had ICP levels between 20 and 40 mm Hg; Group III was composed of those with ICP reaching levels between 40 and 60 mm Hg; and Group IV included those whose ICP reached levels above 60 mm Hg.

Eleven patients underwent CBF measurements within 2 hours of the time of ventricular CSF collection for lactate determination. Cerebral blood flow was measured by the xenon-133 inhalation technique as described by Obrist, et al. Details of the procedures were reported elsewhere.

Statistical Analysis

Student’s unpaired or paired t-tests were employed for parametric analysis. Variability is expressed as the standard deviation.

Results

The eight patients with favorable outcome had significantly elevated lactate concentrations in the ventricular CSF and in the arterial and jugular venous blood on the day of head injury (p < 0.001) which returned to normal on the 2nd day. The 11 patients with poor outcome had elevated ventricular CSF lactate concentrations during the entire period of study (p < 0.001).

The course of the arterial and jugular venous blood lactate concentrations was dissociated from that of the ventricular CSF in this poor-outcome group. Lactate levels reached the normal range in blood on the 3rd day after injury, but were still elevated in the ventricular CSF on the 4th day (p < 0.001). Comparing the two outcome groups, our results indicated that ventricular CSF lactate concentration remained higher in the group with poor outcome during the entire period of study (p < 0.01). In blood, this was the case only on the day of head injury (p < 0.05).

Bleeding in the ventricular compartment was not the main cause of lactate increase in ventricular CSF; this was concluded because the highest lactate concentration was not associated with the highest hemoglobin concentration and because there was no significant difference in hemoglobin concentration in the ventricular CSF.

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between the two outcome groups (Fig. 3). No association was observed between the high lactate concentration and low pH in the ventricular CSF of head-injured patients under controlled ventilation (Fig. 4); however, in four patients with extremely high ventricular CSF lactate concentration due to infection or in those approaching death, pH fell to values lower than the normal range. Ventricular CSF values of buffer base (bicarbonate) were significantly low in all patients in this study (p < 0.005). No significant difference in ventricular CSF pH, buffer base, or pCO2 was found between the two outcome groups (Table 2).

Ventriculitis occurred in two patients in this series. This complication caused a striking increase in ventricular CSF lactate concentration as well as a decrease in ventricular CSF pH (Fig. 5).

High levels of ventricular CSF lactate were present by Day 2 in patients who tended to develop high ICP

### TABLE 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Outcome</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>lactate (mmol/liter)</td>
<td>favorable</td>
<td>mean</td>
<td>4.0</td>
<td>2.1</td>
<td>1.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SD</td>
<td>0.9</td>
<td>0.4</td>
<td>0.2</td>
</tr>
<tr>
<td>poor</td>
<td>mean</td>
<td>5.5</td>
<td>4.8</td>
<td>4.4</td>
<td>3.2</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>1.8</td>
<td>1.9</td>
<td>2.2</td>
<td>0.9</td>
</tr>
<tr>
<td>p value</td>
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<td>&lt;0.005</td>
<td>&lt;0.05</td>
<td>&lt;0.005</td>
<td></td>
</tr>
<tr>
<td>L/P ratio</td>
<td>favorable</td>
<td>mean</td>
<td>14.5</td>
<td>15.5</td>
<td>14.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SD</td>
<td>4.1</td>
<td>1.6</td>
<td>6.7</td>
</tr>
<tr>
<td>poor</td>
<td>mean</td>
<td>22.5</td>
<td>21.6</td>
<td>23.6</td>
<td>18.5</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>6.6</td>
<td>7.5</td>
<td>11.8</td>
<td>9.2</td>
</tr>
<tr>
<td>p value</td>
<td>0.05</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

* CSF = cerebrospinal fluid; SD = standard deviation; NS = not significant. Day 1 = day of injury.
† Normal range for lactate: 0.8—2.2 mmol/liter; normal range for L/P ratio: 4.3—20.3.

### TABLE 2

<table>
<thead>
<tr>
<th>Parameter†</th>
<th>Outcome</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
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<td>mean</td>
<td>7.32</td>
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<td>7.36</td>
</tr>
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<td>0.03</td>
<td>0.02</td>
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<tr>
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<td>mean</td>
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<td>7.31</td>
<td>7.37</td>
<td>7.30</td>
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<tr>
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<td>0.01</td>
<td>0.06</td>
</tr>
<tr>
<td>p value</td>
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<td>NS</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>bicarbonate</td>
<td>favorable</td>
<td>mean</td>
<td>18.9</td>
<td>19.0</td>
<td>19.5</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>1.8</td>
<td>2.4</td>
<td>2.4</td>
<td>1.5</td>
</tr>
<tr>
<td>poor</td>
<td>mean</td>
<td>17.9</td>
<td>17.1</td>
<td>19.9</td>
<td>17.9</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>3.0</td>
<td>2.2</td>
<td>1.8</td>
<td>5.7</td>
</tr>
<tr>
<td>p value</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>pCO2</td>
<td>favorable</td>
<td>mean</td>
<td>38</td>
<td>35</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>5</td>
<td>1</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>poor</td>
<td>mean</td>
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<td>NS</td>
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<td>NS</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

* CSF = cerebrospinal fluid; SD = standard deviation; NS = not significant. Day 1 = day of injury.
† Normal range for pH: 7.32—7.36; normal range for bicarbonate: 19.9—23.7 mmol/liter; normal range for pCO2: 38—46 mm Hg.
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FIG. 5. Time course of lactate values in the ventricular cerebrospinal fluid (CSF) in a severely head-injured patient with ventriculitis. Notice the abnormally sustained high lactate concentrations over the 4 days following injury and the sudden striking increase coupled with the onset of ventriculitis. *Hatched area* = normal range of ventricular CSF lactate concentrations.

(p < 0.005). This correlation started to appear by the day of injury (Day 1, p < 0.01); however, it became more evident on Day 2 (Fig. 6). All patients classified in ICP Group IV presented uncontrollable ICP. Patients in Group III required intensive treatment for lowering ICP (ventricular drainage and mannitol). One patient had only one episode in which ICP rose above 40 mm Hg; his ICP responded promptly to treatment and did not increase again. His initial ventricular CSF lactate concentration was 5.5 mmol/liter and remained above the normal range during the entire period of study. Patients in Group II required less intensive ICP treatment. One patient in this group presented only one peak of ICP above 20 mm Hg; his initial ventricular CSF lactate level was 3.9 mmol/liter and reached a normal level the next day. All other patients in Group II presented sustained periods of ICP above 20 mm Hg.

Four of the five patients whose ICP rose to over 60 mm Hg may have had episodes of cerebral hypoperfusion as assessed by low cerebral perfusion pressure (CPP). The patient who did not present critically low CPP during the period of study had serial CBF measurements of 48, 32, and 41 ml/100 gm/min on Days 1, 2, and 3, respectively. No hypoperfusion was detected. In this patient, the ventricular CSF lactate level increased from 3.9 mmol/liter on Day 1 to 7.6 mmol/liter on Day 3 with apparently sufficient CBF. No correlation was observed between the ventricular CSF lactate level and CBF measured within 18 hours after injury. The highest ventricular CSF lactate concentrations were not associated with critically low CBF's. No large hemispheric or regional blood flow differences were detected in these patients. Therefore, we have combined the regional and hemispheric measurements into one mean value (Table 3).

The profiles of the ventricular CSF lactate course in the 19 patients in this series were as follows: eight patients exhibited Profile 1, with a rapid decrease of lactate to the normal range within 24 to 48 hours after injury, associated with favorable outcome; seven patients showed a Profile 2 course, with slow decrease of lactate over the 5-day period after injury, associated with a clinical course of difficult management and poor outcome; and four patients had a Profile 3 course with

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Lactate (mmol/liter)</th>
<th>CBF (ml/100 gm/min)</th>
<th>PaCO₂ (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.4</td>
<td>55</td>
<td>44</td>
</tr>
<tr>
<td>2</td>
<td>2.0</td>
<td>35</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>4.7</td>
<td>36</td>
<td>34</td>
</tr>
<tr>
<td>4</td>
<td>4.9</td>
<td>20</td>
<td>35</td>
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<td>5</td>
<td>3.9</td>
<td>13</td>
<td>30</td>
</tr>
<tr>
<td>6</td>
<td>7.0</td>
<td>21</td>
<td>32</td>
</tr>
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<td>7</td>
<td>3.9</td>
<td>48</td>
<td>38</td>
</tr>
<tr>
<td>8</td>
<td>8.0</td>
<td>26</td>
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<td>9</td>
<td>7.6</td>
<td>24</td>
<td>35</td>
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<td>4.1</td>
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<td>29</td>
</tr>
<tr>
<td>11</td>
<td>2.8</td>
<td>15</td>
<td>28</td>
</tr>
</tbody>
</table>

* CSF = cerebrospinal fluid; CBF = cerebral blood flow, reported as the average of the two hemispheres. PaCO₂ was determined at the time of CBF measurement.
Fig. 7. Profiles of the ventricular cerebrospinal fluid (CSF) lactate concentration course in three head-injured patients with different outcomes. Hatched area = normal range of ventricular CSF lactate concentration. A: Profile of a 20-year-old man with an admission Glasgow Coma Scale (GCS) score of 6. His intracranial pressure (ICP) reached levels near 30 mm Hg. He is moderately disabled 8 months after trauma. B: Profile of a 44-year-old man with an admission GCS score of 5. His ICP started to rise on the day after injury and reached levels over 40 mm Hg during the period of the study. He survived in a vegetative condition. C: Profile of an 18-year-old man with an admission GCS score of 4. The ICP rose to over 30 mm Hg on the 3rd day after trauma and he died on the 5th day when his ICP became uncontrollable.

Discussion

These studies demonstrate that high ventricular CSF lactate concentrations that are sustained or increase further are associated with poor outcome. Moreover, the increase in lactate concentration after a period of decrease appears to be an important indicator of onset of secondary insult. The cause of increase in CSF lactate concentration following head injury is still unresolved. It is possible that the initial high lactate levels are a consequence of the mechanical injury itself. It may cause an impairment of mitochondrial function, impeding the pyruvate molecule from being metabolized through the Krebs cycle, resulting in accumulation of lactic acid in the intracellular as well as in the extracellular space, and subsequently appearing in the ventricular compartment. A further ventricular CSF lactate increase, found mainly in patients with a Profile 3 course, and the sustained high lactate levels found in patients with a Profile 2 course, suggest that the mitochondrial dysfunction caused by the mechanical injury may persist.

Recent studies in our laboratory support this hypothesis. They have demonstrated development of brain-tissue lactic acidosis in white and gray matter far from areas of contusion in experimental traumatic brain injury. Data extracted from other experimental series with similar mechanical injury showed no reduction in CBF or development of hypoxia. Low brain cortical extracellular pH measured in patients during surgery correlated well with low ventricular CSF pH and high ventricular CSF lactate concentrations as well (unpublished data). However, undetected hypoxia at the scene of injury may also be considered as an initial causal factor of increased ventricular CSF lactate concentration in our patients. Also, although the CBF measured in these patients did not indicate association of high ventricular CSF lactate levels with critically low CBF, these data do not completely exclude the possibility of episodes of global or regional cerebral hypoperfusion as one of the causes of ventricular CSF lactate increase. In a recent study, Yoshino, et al., have presented data suggesting cerebral hypoperfusion in patients within 2 to 3 hours after severe head injury. It is possible that our CBF measurements were performed during the phase of reperfusion. Similar CBF findings following severe head injury were observed by Obrist, et al., and Mendelow, et al. The CBF measurements in these two studies were made at least 6 hours after the time of injury, as were ours.

Jenkins, et al., have shown that traumatized cells are more vulnerable to ischemia. This finding supports the idea of subcellular dysfunction following traumatic brain injury; for example, traumatized cells are less

TABLE 4

Correlation of ventricular CSF lactate course profiles with outcome in 19 head-injured patients

<table>
<thead>
<tr>
<th>Lactate Course</th>
<th>No. of Cases</th>
<th>Glasgow Outcome Scale Score at 6 Mos*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Profile 1</td>
<td>8</td>
<td>5 good</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 moderately disabled</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 vegetative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 death†</td>
</tr>
<tr>
<td>Profile 2</td>
<td>7</td>
<td>3 severely disabled</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 dead‡</td>
</tr>
<tr>
<td>Profile 3</td>
<td>4</td>
<td>4 dead</td>
</tr>
</tbody>
</table>

*Three of the patients followed for more than 6 months changed their outcome category. One moderately disabled patient recovered completely. Of the two vegetative patients, one died and the other was severely disabled at 1 year.
† Death after the acute phase of trauma due to clinical complications.
‡ Death in the acute phase after trauma.
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capable of overcoming the adverse environment present after injury. Whether this adverse milieu for cell healing is caused by the dysfunctional traumatized cells themselves which may pour acid metabolites into the extracellular space, or is due to development of secondary insults to these already ill cells, is still a matter for further study. After trauma, focal edema may develop in the damaged cortex and white matter. Edematous tissue may become hypoxic if an increase in intercapillary distance impedes the oxygen exchange between the blood vessels and viable parenchyma. Thus, a continuous process of subcellular dysfunction aggravated by local hypoxia in the edematous areas may explain the high ventricular CSF lactate concentration in patients presenting Profile 2 and 3 lactate courses.

Caution must be exercised in evaluating brain metabolic state based on CSF lactate concentration following head injury. Blood is often present in the ventricular CSF in such cases, and blood in the CSF is known to increase lactate concentration. In our study, there was no association between the highest lactate concentration and the highest hemoglobin concentration in the ventricular CSF, neither was there a significant difference in hemoglobin concentration between the two outcome groups. However, the lactate concentration was higher in patients with poor outcome during the entire period of study. These findings suggest that the high ventricular CSF lactate concentration in the poor-outcome group indeed reflects a more severe subcellular disturbance than that present in the good-outcome group. Lactate/pyruvate ratio, believed to better reflect the tissue redox state than does the lactate concentration itself, was also elevated in the poor-outcome group; however, the degree of elevation was not statistically significant, probably due to the small number of patients in this study and the variability of the pyruvate assay technique. The CSF lactate concentration can also be influenced by the serum lactate concentration. While it is possible that serum lactate influenced the ventricular CSF lactate concentration in this study, it is unlikely that it represents the major factor. The lactate concentration was consistently higher in the ventricular CSF than in blood and had a course dissociated from that of blood in both outcome groups. This dissociation was clear in the poor-outcome group (Fig. 1). A high serum lactate concentration is a usual response to systemic injury and does not have the same prognostic significance that CSF lactate concentration has in head injury.

Lactate can be produced by the choroid plexus in vivo or in vitro. However, this source is too small to be responsible for an increase of more than fourfold in the ventricular CSF lactate concentration observed in this study. Valenca, et al., indicated that clearance of lactate from the CSF is accomplished mainly by diffusion into the brain tissue, and that lactate is further metabolized to pyruvate by the cells of the central nervous system (CNS). Prockop demonstrated that processes other than simple bulk flow through the arachnoid villi may be operative in lactate clearance from the CSF; lactate should, in physiological circumstances, be cleared from the CSF compartment only by bulk flow. We have demonstrated that the creatine kinase-BB-isoenzyme (CKBB), a protein that may be removed from CSF mainly by bulk flow, was cleared from the ventricular CSF much faster than was the lactate molecule following severe head injury. Following traumatic brain injury, the bulk CSF flow appears not to be impaired severely enough to disturb the CSF dynamics. Thus, these observations when taken together favor the hypothesis that mechanical brain injury causes a mitochondrial dysfunction that is responsible not only for an overproduction of lactate from brain metabolism, but also for an abnormal ability of these dysfunctioning cells to clear the excess lactate in the tissue, as well as that produced in the choroidal plexus.

No correlation was found between ventricular CSF lactate concentration and ventricular CSF pH. The latter is not identical to focal-tissue pH, but is closely related to blood pH, since CSF pH close to the choroid plexus varies almost instantaneously with changes in arterial pH. We have demonstrated that ventricular CSF pH is higher than the extracellular cortical pH in areas of contusion (in preparation). Thus, only in cases with very extensive brain lesions, and/or in cases in which the brain lesions are located near the ventricular system, may the ventricular CSF pH be expected to reflect a degree of acidosis similar to that in the injured tissue. On the other hand, for a decrease in CSF HCO₃⁻ concentration to take place, a flux of H⁺ in or flux of HCO₃⁻ out of the ventricular compartment to the surrounding brain tissue or blood must occur. The level of buffer base was significantly low in all patients in this study, reflecting its expenditure to buffer the lactic acid produced. The H₂CO₃ formed from the interaction between lactic acid and HCO₃⁻ is promptly removed from the CSF compartment in the form of CO₂. Therefore, the level of controlled ventilation applied in these patients appeared to be sufficient to compensate for the ventricular CSF metabolic acidosis. However, it was not sufficient to compensate for patients with extremely high lactate levels in the CSF, and significantly low ventricular CSF pH was found associated with very low ventricular CSF buffer base in a few patients who were close to brain death, or in cases with infection in the ventricular compartment.

Obviously, as discussed above, secondary insults such as hypoxia and/or ischemia can change the profile of the ventricular CSF lactate curve following head injury. Of particular interest is the change caused by CNS infection. The increase in lactate levels when bacterial infection is present in the CSF is well known. Increased lactate concentrations due to infection in the ventricular system were found in two of our patients, causing a striking rise in lactate concentration. Therefore, increase in the CSF lactate concentration in a patient with a clinically favorable course after severe...
head injury must be further investigated to rule out the possibility of a bacterial infection in the CSF compartment.

The increased ventricular CSF lactate concentration on the 2nd day after injury was significantly associated with development of pathologic ICP levels during the period of study (patients with lactate Profiles 2 and 3). Cerebral hyperemia has been associated with tissue lactic acidosis in several pathological states, and increased ventricular CSF lactate concentration (reflecting tissue lactic acidosis) was shown to correlate with cerebral hyperemia in severely head-injured patients. Since hyperemia after head injury is known to be a cause of increased ICP, lactate concentration in ventricular CSF may be related to increased ICP.

Brain edema formation is also an important etiological factor associated with development of increased ICP. It is known that the lactate level is increased in brain tissue shortly after experimental head injury, particularly in the white matter within the territory of vasogenic edema of contused areas. Increased tissue osmolality and brain-tissue water content following experimental cerebral ischemia have been attributed in part to tissue lactic acidosis. Busse and Hoffmann reported good correlation between CSF lactate concentration and the extension of brain edema as evaluated by computerized tomography in patients with cerebral ischemia. Moreover, they found that the increase in CSF lactate precedes the formation of brain edema. Also, lactic acidosis is associated with the development of cytotoxic edema. Accumulation of lactic acid in tissue represents failure of the cell energy production to a certain extent. The lack of energy for maintenance of cell ionic homeostasis allows a net accumulation of electrolytes and water into the cytoplasm with consequent cell swelling.

Since lactate concentration in tissue, as well as in CSF, may be related to development of hyperemia and edema after brain injury, it was not unexpected that there is an association between increased ICP and increased ventricular CSF lactate concentration in patients with severe head injury. This association with the high ventricular CSF lactate concentration was clearer on Day 2 than on Day 1 (the day of injury), confirming the importance of sustained tissue lactic acidosis in the clinical course of head-injured patients.

In conclusion, the sustained high concentration of ventricular lactate found in patients with a poor outcome in this study indicates that a persistent dysfunction in brain energy metabolism is present following severe head injury. This dysfunction is associated with a clinical course difficult to manage and development of high ICP. Also, the accumulation of lactic acid requires functioning cells. These cells may be in a borderline state of recovery or death. Therapy that supports these viable cells may improve their quality and rate of healing, improving the clinical course and outcome after severe head injury. Finally, ventricular CSF lactate determination after severe head injury is a convenient procedure to perform in patients who already have a ventricular catheter inserted for ICP monitoring, adding valuable information about the prognosis and clinical course, and also serving as a diagnostic tool in onset of secondary insults over the critical period after severe head injury.

References

CSF lactic acidosis in severe head injury


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Address reprint requests to: Antonio A. F. DeSalles, M.D., Massachusetts General Hospital, 15 Parkman Street - ACC 324, Boston, Massachusetts 02114.