Cerebral acid-base and gas metabolism in brain injury

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Acid-base and gas parameters of CSF, jugular venous and arterial blood were measured in 45 patients with brain injury in the first 12 days after trauma or operation. CSF metabolic acidosis together with respiratory alkalosis and hypoxemia in the cerebral venous and arterial blood were the most characteristic findings. A close correlation between the severity of brain damage and the intensity of the CSF metabolic acidosis and arterial hypocapnia was revealed. It was concluded that brain hypoxia and acidosis play an important role in the development of cerebral edema and permanent brain damage.

**Key Words** - cerebrospinal fluid · cerebral gas exchange · brain hypoxia · brain acidosis · brain injury · cerebral edema

Experimental work has revealed a close similarity between the cerebrospinal fluid (CSF) and brain extracellular fluid (ECF) proper. Hence, investigation of appropriate metabolites under various experimental conditions has been well explored in studies of cerebral blood flow (CBF) and metabolism. Similar studies have shown the primary role of alterations in extracellular fluid [H⁺] in the regulation of cerebral blood flow and of the pulmonary ventilation.

Although the similarity between the CSF and brain ECF composition also offers an excellent opportunity for research on brain metabolism during the course of various brain disorders, information on the CSF acid-base status in patients with acute brain damage is scanty. The main aim of the present work was to study the role of disturbances in brain gas exchange and disorders of the cerebral acid-base balance on the development of brain damage and on the outcome of the diseased state in patients with acute brain injuries. An effort was made to investigate the importance of brain ECF [H⁺] to the regulation of brain oxygen availability and pulmonary ventilation. Therefore, parameters of acid-base and gas metabolism were measured in samples from the CSF, and venous and arterial blood.

**Material and Methods**

The investigations were carried out in 45 patients; severe brain concussion was diagnosed in 14, acute subdural hematoma in 12, chronic subdural hematoma in 11, acute extradural hematoma in 5, and an intracerebral traumatic hematoma in 2. One patient had an acute subdural empyema. On the basis of various indications, 40 patients were operated on. The patients with brain injury showed varying degrees of severity; 12 of them died in hospital; eight, after a long period of treatment, were transferred to a nursing home for continuous care. All patients were given modern intensive care, the principles of which have been described earlier. A control group of 39 persons without
Acid-base and gas metabolism in brain injury

cerebral abnormalities or metabolic disorders was used for comparative study.

The investigations were performed repeatedly within the first 12 days after the injury or operation. None of the patients was critically ill at the time of sampling. The CSF was collected from the lumbar subarachnoid space. To obtain a fully anaerobic sample, 0.5 cm$^3$ of CSF was first withdrawn into a glass syringe; the syringe was then disconnected and the air bubbles and all the CSF except that filling the syringe’s dead space ejected. Finally, a 4 to 6 cm$^3$ sample was withdrawn with a heparinized syringe; arterial blood was sampled from the brachial artery, and venous blood from the right jugular bulb. All samples were taken in immediate succession. Particular attention was paid to the steady state of the patient’s breathing and circulation at the time of sampling.

The CSF and blood pH values were measured by means of a Radiometer PM-27 pH meter. Blood pCO$_2$ values were ascertained by the equilibration method using the Sigggaard-Andersen nomogram.$^{21}$ Actual and standard bicarbonate concentrations in the blood were calculated from the same nomogram. The CSF pCO$_2$ value was ascertained in a similar manner but here a specially designed nomogram employing a pK value of 6.13 was used. The CSF bicarbonate concentration was calculated by means of the Henderson-Hasselbach equation$^{20}$ by using a pK of 6.13 and S of 0.0314. The CSF and blood pO$_2$ values were measured with the Radiometer electrode.

All samples were also analyzed colorimetrically for lactate and pyruvate concentrations.$^{5,5}$ Immediately after the sampling, all samples were precipitated by means of ice-cold perchloric acid. Statistical analyses of the data were performed by use of the electronic computer “Ural-4.”

The patients studied were divided into three groups depending on their state of consciousness at the time of sampling. If the patients were drowsy or sleeping but could still be aroused by more or less strong stimuli, they were considered as “stuporous.” Their speech was usually incoherent but they generally obeyed simple orders. Patients were placed in the “mild coma” group if in general they could not be aroused by painful stimuli; less severe cases in this group commonly reacted to external nociceptive stimuli with more-or-less coordinated movements while more severe cases could not coordinate their defense movements. Patients were categorized as in the “severe coma” group if they had bilateral decerebrate rigidity; their ocular reflexes were often absent but in some cases were still present.

**Results**

**General Observations**

The data given in Table 1 summarize the mean values for the complete period of investigation for the whole series of 45 patients with brain injury. A considerable decrease of the CSF pCO$_2$, pH, and bicarbonate concentration was characteristic of brain injured patients. At the same time there was a remarkable increase in lactate and pyruvate concentrations in the CSF. Due to the simultaneous increase of the lactate and pyruvate concentrations, their ratio did not change noticeably. The results indicated that the development of CSF metabolic acidosis was the most common disorder in patients with brain injury. Repeated investigations showed that the acidosis was most pronounced in the very first days following the injury or operation. In the succeeding days there was a tendency for the CSF acid-base status to return to normal; this was especially noticeable in cases with good recovery.

The correlation analysis revealed that the decrease of the CSF bicarbonate concentration was in close relation with the increase of the CSF lactate concentration ($r = -0.698$). At the same time, there was no connection between the increase of the CSF lactate concentration and the red cell count in the CSF. The decrease of the CSF pO$_2$ was relatively small but statistically significant.

The most common finding in the cerebral venous blood was the considerably decreased pCO$_2$ and venous pO$_2$. When compared with the pCO$_2$ value, the bicarbonate concentration of the cerebral venous blood was relatively less decreased. Hence, the pH value was remarkably increased, and the cerebral venous blood acid-base equilibrium was shifted toward the respiratory alkalosis. Both the lactate and pyruvate concentrations in the jugular venous blood appeared elevated.

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but the lactate/pyruvate ratio remained unchanged.

Respiratory alkalosis with hypocapnia and elevated pH was the most striking finding in the arterial blood. In comparison with the control group, there were no significant changes in the arterial values, either in the standard bicarbonate or in the lactate and pyruvate concentrations. Hence, there were no nonrespiratory alterations in the arterial blood acid-base status, and the arterial hypocapnia was primarily caused by respiratory factors, namely, hyperventilation. At the same time, a slight arterial hypoxemia was also present.

Analysis revealed a rather close relation between the increase of CSF lactate concentration and the decrease of arterial pCO₂ (r = -0.669), but no correlation between the CSF pH values and the arterial pCO₂ (r = 0.263). A medium negative correlation was found between the CSF lactate and cerebral venous pO₂ values (r = -0.429). The arterial pO₂ values were not related either to cerebral venous pO₂ or to the CSF pO₂ values (the correlation coefficients were 0.361 and 0.207 respectively). However, there was a medium positive correlation between the venous and CSF pO₂ values (r = 0.506).

**Dependence of the Parameters on the State of Consciousness**

The data given in Table 2 indicate that the scope of the alterations was in many respects correlated with severity of the disorders of consciousness. The results of the biochemical measurements of the CSF in patients with clear consciousness did not differ substantially from the corresponding data obtained in the controls. The patients with disturbed consciousness showed, on the contrary, a remarkable CSF metabolic acidosis which was most pronounced in a deep coma state. The last group also had the lowest pO₂ of the CSF.

Both venous and arterial pCO₂ had a tendency to decrease in proportion to the severity of the state of consciousness. However, since the decrease in pCO₂ was accompanied by a diminished bicarbonate concentration, only a modest increase in pH was noted.

### Table 1

<table>
<thead>
<tr>
<th>Parameter*</th>
<th>CSF</th>
<th>Jugular Venous Blood</th>
<th>Arterial Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Brain Injury</td>
<td>Control</td>
</tr>
<tr>
<td>pH</td>
<td>7.338 ± 0.005</td>
<td>7.308†</td>
<td>7.360 ± 0.005</td>
</tr>
<tr>
<td>pCO₂ (mm Hg)</td>
<td>46.3 ± 0.6</td>
<td>41.5†</td>
<td>48.4 ± 0.7</td>
</tr>
<tr>
<td>HCO₃⁻ (mEq/L)</td>
<td>23.5 ± 0.3</td>
<td>19.7†</td>
<td>26.2 ± 0.5</td>
</tr>
<tr>
<td>St-HCO₃⁻ (mEq/L)</td>
<td>—</td>
<td>—</td>
<td>24.3 ± 0.4</td>
</tr>
<tr>
<td>pO₂ (mm Hg)</td>
<td>41.2 ± 1.4</td>
<td>37.1†</td>
<td>43.0 ± 1.0</td>
</tr>
<tr>
<td>La (mEq/L)</td>
<td>2.03 ± 0.14</td>
<td>4.98†</td>
<td>1.52 ± 0.09</td>
</tr>
<tr>
<td>Py (mEq/L)</td>
<td>0.079 ± 0.006</td>
<td>0.176†</td>
<td>0.086 ± 0.007</td>
</tr>
<tr>
<td>La/Py</td>
<td>26.0 ± 3.9</td>
<td>29.9</td>
<td>18.1 ± 1.8</td>
</tr>
</tbody>
</table>

* Abbreviations: St-HCO₃⁻ = standard bicarbonate; La = lactate; Py = pyruvate; La/Py = the lactate/pyruvate rate.
† p < 0.01.
‡ p < 0.05.
Acid-base and gas metabolism in brain injury

**TABLE 2**

CSF, venous, and arterial blood acid-base and gas values correlated with state of consciousness in patients with traumatic brain injury

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CSF</th>
<th>State of Consciousness</th>
<th>Arterial Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clear</td>
<td>Drowsiness, Stupor</td>
<td>Mild Coma</td>
</tr>
<tr>
<td>pH</td>
<td>7.328 ± 0.008</td>
<td>7.313 ± 0.013</td>
<td>7.313 ± 0.012</td>
</tr>
<tr>
<td>pCO₂</td>
<td>46.4 ± 1.1</td>
<td>39.7 ± 1.7</td>
<td>42.4 ± 1.7</td>
</tr>
<tr>
<td>pO₂</td>
<td>22.9 ± 0.5</td>
<td>19.9 ± 0.8</td>
<td>20.2 ± 0.9</td>
</tr>
<tr>
<td>HCO₃⁻</td>
<td>33.8 ± 1.7</td>
<td>37.7 ± 2.7</td>
<td>39.9 ± 3.4</td>
</tr>
<tr>
<td>pH</td>
<td>7.407 ± 0.007</td>
<td>7.409 ± 0.007</td>
<td>7.407 ± 0.010</td>
</tr>
<tr>
<td>pCO₂</td>
<td>42.1 ± 1.4</td>
<td>39.8 ± 1.1</td>
<td>37.7 ± 1.4</td>
</tr>
<tr>
<td>pO₂</td>
<td>25.5 ± 0.6</td>
<td>24.3 ± 0.5</td>
<td>22.8 ± 0.7</td>
</tr>
<tr>
<td>HCO₃⁻</td>
<td>37.9 ± 1.6</td>
<td>39.0 ± 1.4</td>
<td>40.8 ± 1.7</td>
</tr>
<tr>
<td>pH</td>
<td>7.455 ± 0.006</td>
<td>7.462 ± 0.007</td>
<td>7.466 ± 0.007</td>
</tr>
<tr>
<td>pCO₂</td>
<td>35.8 ± 0.6</td>
<td>32.9 ± 1.0</td>
<td>31.9 ± 1.1</td>
</tr>
<tr>
<td>pO₂</td>
<td>24.7 ± 0.4</td>
<td>22.9 ± 0.5</td>
<td>22.4 ± 0.6</td>
</tr>
<tr>
<td>HCO₃⁻</td>
<td>25.6 ± 0.3</td>
<td>24.8 ± 0.3</td>
<td>24.2 ± 0.4</td>
</tr>
<tr>
<td>St·HCO₃⁻</td>
<td>89.8 ± 2.4</td>
<td>91.7 ± 2.8</td>
<td>87.9 ± 2.9</td>
</tr>
</tbody>
</table>

It seems worth mentioning that the alterations of jugular venous pO₂ were not related to the state of consciousness, but that the most decreased arterial pO₂ was recorded in deep coma. Judged from the arterial standard bicarbonate concentration, all patients with clear consciousness had a slight inclination toward metabolic alkalosis, while the arterial standard bicarbonate values of the unconscious patients did not differ from those of the controls.

**Dependence of CSF pH, Jugular Venous and Arterial pCO₂, and pO₂ Values on Outcome**

The results of this study are indicated in Table 3. The CSF pH in patients who completely recovered did not differ from that in the controls. Those who made a recovery with more or less permanent neurological or psychological sequelae had a markedly decreased pH in the acute stage; in fatal cases the CSF pH was even further decreased.

It is interesting that the cerebral venous hypoxemia was greatest among the survivors. In fatal cases, the jugular venous pO₂ was nearly equal to the control value. In some of these patients the venous pO₂ exceeded the normal data substantially, reaching values as high as 57 mm Hg. Nevertheless, the cases with an unfavorable course of the disease showed the lowest venous pCO₂ values. All this indicates that both the O₂ and CO₂ production was relatively more depressed in the group consisting of persons who did not survive.

The values for arterial blood gases were also closely related to the outcome of the disease, so that arterial hypocapnia and hypoxemia were both most severe in the group that died and less obvious in patients who improved without sequelae.

**Discussion**

The results of this work show that patients with acute severe brain injury have a CSF metabolic acidosis that is mainly caused by accumulation of lactate in the CSF spaces. Earlier experimental studies have revealed that the alterations of the CSF lactate concentrations reflect identical shifts of brain tissue values. Consequently, the results of the present work establish the presence of hypoxia and anaerobic glycolysis on the brain tissue level. If the degree of consciousness is taken for the criterion of the severity of brain tissue damage, the results of this study allow the conclusion that the intensity of brain acidosis is closely correlated with the extent of the damage to brain tissue.

The results obtained in other experimental work have indicated that cerebral hypoxia leads to a remarkable accumulation of lactate in the CSF which by far exceeds the cor-
The increased output of lactate in brain tissue was also confirmed by the elevated lactate concentration in cerebral venous blood. The last was, however, noticeably less obvious than in the CSF, a difference probably caused by the relatively low diffusibility of lactate through the brain-blood barrier.1,27

The presence of brain hypoxia was also certified by the cerebral venous pO2 measurements. However, the extent of cerebral venous hypoxemia appeared not to be correlated with the extent of brain damage and was probably caused by relatively high cerebral pO2 values recorded in several patients with very severe brain lesions. Higher than normal cerebral venous pO2 values were mostly observed in patients who ultimately died, and indicate the presence of diffuse reactive hyperemia, the “luxury perfusion.”17,23 The same group of patients also had the most remarkable CSF acidosis. This supports the point of view that brain reactive hyperemia is caused by cerebral tissue acidosis.29 If one bears in mind the extensive brain tissue damage in many patients included in this series, it seems likely that the hyperemia was only relative in the great majority of cases. Nevertheless, some patients with small impairment of brain function may have had focal reactive hyperemia not revealed by changes of jugular venous blood pO2.

A fairly close relation was found between the extent of the CSF lactacidosis and the intensity of pulmonary hyperventilation. This suggests that the hyperventilation represents a compensatory reaction to the brain tissue acidosis which is destined to bring the tissue pH to normal because of the decreased pCO2 in the brain. The normalized acidity of the brain becomes, in turn, a premise in the restoration of a normal vasomotor state. However, it is worth mentioning that we never observed that hyperventilation caused the CSF pH to return to normal in severe cases.

At the same time, no correlation was found between the alterations of arterial pCO2 and CSF pH values. The explanation for this may be as follows. Simultaneous measurements of lumbar and cisternal CSF samples indicated that the lactate concentrations were always equal in both samples, but the cisternal pH values were usually noticeably higher than the lumbar values. This depended on the relatively lower pCO2 in the cisternal CSF under the equal bicarbonate concentrations.37 This finding suggests that the lactate concentration in the lumbar CSF is the best indicator of acidity near the medullary chemoreceptors. A close relationship between CSF acidosis and hyperventilation in patients with brain damage has also been noted by other investigators.9,28

One other question arouses great interest, namely, to what extent does the CSF pO2 reflect brain tissue oxygenation in patients with acute brain damage? Several investigators have concluded on the basis of exper-

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TABLE 3

CSF pH, arterial and jugular venous blood pCO2 and pO2 values correlated with the outcome of the brain injury

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Survivors</th>
<th>Nonsurvivors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Without Deficit</td>
<td>With Deficit</td>
</tr>
<tr>
<td>CSF pH</td>
<td>7.326 ± 0.007</td>
<td>7.305 ± 0.016</td>
</tr>
<tr>
<td>VJ pCO2</td>
<td>41.4 ± 1.1</td>
<td>37.9 ± 1.0</td>
</tr>
<tr>
<td>VJ pO2</td>
<td>35.5 ± 1.0</td>
<td>38.2 ± 1.6</td>
</tr>
<tr>
<td>A pCO2</td>
<td>34.6 ± 0.7</td>
<td>31.9 ± 0.9</td>
</tr>
<tr>
<td>A pO2</td>
<td>90.0 ± 2.2</td>
<td>85.2 ± 1.9</td>
</tr>
</tbody>
</table>
Acid-base and gas metabolism in brain injury

imental work that the pO₂ of the cisternal CSF reflects the mean cerebral tissue pO₂. Gänschitz⁹ has found that the cisternal CSF pO₂ corresponds to the brain capillary pO₂ in neurological patients. According to the experimental studies of Kazemi, et al.,¹⁹ the CSF pO₂ depends upon various factors such as cerebral tissue pO₂, arterial pO₂, CBF, and CSF sampling point. Yarnell, et al.,³⁶ reached a similar conclusion and did not find any correlation between the cisternal CSF and brain tissue pO₂ values.

In our study, the CSF pO₂ was decreased in most cases. However, the individual values were spread over a large scale of variations, and, therefore, the mean value was noticeably decreased only in deeply comatose patients. At the same time, the correlation of CSF pO₂ with the cerebral venous pO₂, which is known to reflect the brain tissue pO₂ values well,²⁰ was only moderate and leads to the conclusion that the pO₂ of the lumbar CSF in patients with acute brain damage only partially reflects the oxygenation of the brain tissue. It is hardly believable that the brain tissue oxygenation state is better expressed in the cisternal CSF pO₂; this conclusion is supported by results gained from another series of studies that demonstrated the equality of lumbar and cisternal pO₂ values.⁸⁷

It has been demonstrated that, by increasing brain-blood volume, cerebral vasodilation plays a primary role in the development of traumatic brain edema.²² It has also been confirmed that this vasodilation is caused by cerebral acidosis.²³ It is reasonable to suppose that those cases with the most obvious signs of brain damage also have the most severe brain edema. If that supposition holds truth, the results of this study indicate a close relationship between brain tissue acidosis and cerebral edema. Cerebral vasodilation occurs in the first minute after the concussion,²² presumably under the influence of neurogenic factors originating in the brain stem damage.²⁵ The acidosis, which most likely develops a little later, contributes to the maintenance or increase of cerebral vasodilation.

Investigations performed in vitro have revealed that the acidotic brain cells gain sodium and lose potassium.⁴ It is well known that these alterations lead to intracellular edema. Hence, brain acidosis may also give rise to brain edema by direct influence on transport of cations through the cell membrane.

Summary

Forty-five patients with brain injury (severe brain concussion, acute or chronic traumatic intracranial hematomas) were studied within the first 12 days after the injury or operation. The pH, pCO₂, pO₂, bicarbonate, lactate, and pyruvate concentrations in the lumbar CSF, jugular venous and arterial blood were measured. A considerable decrease of CSF bicarbonate, pCO₂, and pH with a concomitant increase of both CSF lactate and pyruvate concentrations were revealed. There was good correlation between the CSF bicarbonate and lactate changes. However, the CSF pO₂ was significantly decreased only in deeply comatose patients. Characteristic changes in jugular venous and arterial blood were respiratory alkalosis and hypoxemia. Lactate and pyruvate concentrations in jugular venous blood were elevated. Decrease of arterial pCO₂ was in close correlation with the increase of CSF lactate concentration. CSF metabolic acidosis and venous and arterial hypocapnia were most marked in the comatose state and in the lethal group. In patients with a good recovery, venous pO₂ was relatively more decreased. In patients who died, the jugular pO₂ often exceeded the control value substantially, thus indicating the presence of brain "luxury perfusion." The fatal cases had also the most marked CSF metabolic acidosis. These results suggest that "luxury perfusion" is caused by brain tissue acidosis. It was also concluded that the brain acidosis plays an important role in the development of compensatory pulmonary hyperventilation and cerebral edema.

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