Cerebral Apoplexy (Stroke) Treated With or Without Prolonged Artificial Hyperventilation: 2. Cerebrospinal Fluid Acid-Base Balance and Intracranial Pressure

BY M. STIG CHRISTENSEN, M.D., POUL BRODERSEN, M.D., JES OLESEN, M.D., AND OLAF B. PAULSON, M.D.

Abstract:
Cerebral Apoplexy (stroke) in the acute phase. Thirty-three of the patients were treated afterward with artificial hyperventilation for 72 hours (15 hypocapnic [PaCO₂ 25 mm Hg] and 18 normocapnic). The remaining 17 patients were breathing spontaneously throughout. Arterial PaCO₂, CSF lactate, pyruvate and bicarbonate and ICP were followed during the course.

Compared to a control group initial mean values showed significant increases of CSF lactate (2.36 mmol per liter) and pyruvate (0.183 mmol per liter) but with a normal lactate/pyruvate ratio (13.3), a reduced bicarbonate (22.0 mmol per liter), and reduced PaCO₂ (34 mm Hg), indicating spontaneous hyperventilation. No correlation between the degree of initial hyperventilation or CSF lactate and the mortality rate was found. ICP averaged initially 15 mm Hg.

The untreated patients had almost unchanged CSF values and PaCO₂ during the following six days. During induced and sustained hypocapnia and normocapnia, CSF bicarbonate slowly followed changes in PaCO₂, with CSF pH tending to return toward normal. The time course of this CSF pH adaptation had an estimated half-time of about six hours, and was complete within 30 hours. A similar time course of changes induced in ICP by ventilation was observed.

Additional Key Words lactate pyruvate hypocapnia pH adaptation

Previous studies of acid-base variables in cerebral apoplexy have shown an increase in cerebrospinal fluid (CSF) concentrations of lactate and pyruvate, reduced CSF bicarbonate and a normal, or slightly alkaline, lumbar CSF pH; furthermore, arterial PaCO₂ was below normal and the arterial Po₂ also was slightly decreased. The hypocapnia found in cerebral apoplexy, and to an even more pronounced degree in other acute brain lesions,2 indicates that the patients are hyperventilating actively. The pathogenesis behind this hyperventilation is not clear. Recent discussions of the mechanism have been focused on the possible role of arterial hypoxemia, CSF acidosis or neurogenic mechanisms.2,4 It has been claimed that the degree of hypocapnia is correlated to the mortality rate in patients with cerebral apoplexy, so that a more pronounced hypocapnia initially would be followed by a higher mortality rate.1,6

A controlled clinical study of the therapeutic effect of prolonged hypocapnia in severe cases of cerebral apoplexy afforded the occasion to study CSF acid-base variables, PaCO₂ and intracranial pressure (ICP) in the acute phase, in an attempt to clarify these problems. Furthermore, the degree and duration of changes following induced and sustained variations of PaCO₂ could be evaluated. Inducing a hypocapnic state (by either spontaneous or artificial hyperventilation) in a patient very soon will be followed by an increase of the CSF pH and a decrease in ICP. After a certain period the CSF pH and the ICP will become normal again, “adapting”
CSF CHANGES BY HYPERVENTILATION IN STROKE

to the hypocapnic level. The time course of the complete adaptation has not been reported in man, where it will cause a limitation of some of the beneficial effects supposed to follow induced hypocapnia in acute brain lesions.6

**Methods**

The 50 patients studied belonged to a series of 71 patients selected for a controlled clinical trial of therapeutic use of prolonged artificial hyperventilation.6 The series included only patients admitted to the hospital less than 24 hours after the onset of an attack of cerebral apoplexy (stroke). Furthermore, patients with only pronounced focal signs were chosen. Of the 71 patients selected 24 patients were treated with artificial hyperventilation at a moderate hypocapnic level (PacO₂ about 25 mm Hg) and 26 patients were hyperventilated at a normocapnic level by adding about 3% CO₂ to the inspiratory air. The artificial hyperventilation was performed during general anesthesia (barbiturates and curare) and continued for 72 hours. The last 21 of the 71 patients selected had no ventilatory treatment.

In table 1 a detailed description of the stroke cases in whom CSF studies were available initially and later on is given. Of the 50 patients with an initial CSF study 15 patients belonged to the group treated with hypocapnic hyperventilation later on (CSF: nonhemorrhagic in 13 cases, hemorrhagic in two cases), 18 patients belonged to the group treated with normocapnic hyperventilation later on (CSF: nonhemorrhagic in 17 cases, hemorrhagic in one case), and 17 patients belonged to the group in whom no ventilatory treatment was given (CSF: nonhemorrhagic in 16 cases, hemorrhagic in one case). After three weeks, 20 of the 50 patients studied were dead (40%; 95% confidence limits: 26% to 55%) compared to 27 deaths among the 71 patients for the clinical trial (38%; 95% confidence limits: 27% to 50%).

Normal values of the CSF variables studied were obtained in 13 normal adults suspected of herniation of a lumbar disk. At myelography samples of arterial blood and CSF were taken for analysis.

**ANALYSES**

CSF bicarbonate was analyzed using the Conway method.7 Enzymatic spectrophotometric methods were used for determination of lactate and pyruvate in CSF and blood.6,9 Paco₂ was measured in a Teflon covered glass electrode (Radiometer, Denmark) and pH was measured using the Astrup microtechnique (Radiometer, Denmark). For CSF pH measurements the precautions stated by Leusen10 were taken into account.

On admission the arterial oxygen saturation was determined spectrophotometrically in 29 of the stroke cases. The arterial Pao₂ was calculated from the measured oxygen saturation, using simultaneously measured values of arterial pH and PacO₂, hemoglobin and body temperature.11 The pH and Paco₂ were in all cases measured at 38°C, but all values given in this paper are corrected to the actual body temperature.11 The CSF pH was corrected to body temperature using ΔpH/ΔT = -0.0037/°C.12

ICP was measured as the height of the water column in a disposable tube before tapping and given in mm Hg. The measurements always were done with the patient in a side position, completely relaxed (curare) and with the spine in the horizontal plane. The arterial blood pressure was measured by the cuff method. Mean arterial blood pressure (MABP) was calculated as the diastolic pressure plus one-third of the pulse pressure.

**SAVING**

The following time schedule for the routine sampling of arterial blood and CSF in the stroke cases who were treated with hyperventilation was used. The initial PacO₂ was determined in samples taken before anesthesia was induced. The first CSF pressure reading and sampling were done a few minutes after induction of anesthesia when normal ventilation was aimed at. As the CSF changes at this early moment might not have reached a steady state, suboccipital taps were used in these situations.13 About 5 ml CSF were withdrawn for the analyses of lactate, pyruvate and bicarbonate, and arterial blood was analyzed for lactate and pyruvate. The second sampling of arterial blood and CSF (including pressure reading) was done at the end of the third day, i.e., just before discontinuation of hyperventilation. The CSF samples in this situation were in several cases drawn simultaneously via the suboccipital and lumbar routes. The third examination of arterial blood and CSF (only lumbar taps) was done at the end of the sixth day when all the patients were nonanesthetized and breathing spontaneously again.

In patients who had no ventilatory treatment, arterial blood and CSF (only lumbar) were sampled at the same time intervals as mentioned above.

In addition to the routine sampling, more frequent lumbar taps for analysis of bicarbonate concentration were carried out in 12 selected cases during sustained hypocapnia (six cases) or normocapnia (six cases). ICP measurements were done before each of these taps and MABP was simultaneously determined. In four of the 12 selected cases additional measurements of the pH and Paco₂ in CSF were done using an anaerobic sampling technique. Immediately after the CSF sampling, simultaneous arterial and internal jugular venous blood samples were taken for Paco₂ determinations.

**Results**

ACID-BASE VARIABLES IN THE INITIAL PHASE

Table 2 shows CSF and arterial blood values found initially in 46 patients with nonhemorrhagic CSF. Comparison is made to normal values found in the 13 control cases. In apoplexy a highly significant increase of CSF lactate (0.8 mmol per liter) and pyruvate (0.06 mmol per liter) was found, whereas the L/P ratio remained unchanged. The mean CSF bicarbonate decreased 1.6 mmol per liter, a decrease which was statistically significant. The arterial
TABLE 1
CSF Studies Available Among 71 Patients With Cerebral Apoplexy (Stroke) Classified According to Carotid Angiography and Clinical Findings, and Treated With or Without Prolonged Artificial Hyperventilation (Three Days)

<table>
<thead>
<tr>
<th>Carotid angiography</th>
<th>State of consciousness</th>
<th>Clinical findings</th>
<th>Degree of focal signs</th>
<th>Group</th>
<th>Clinical study</th>
<th>Number of patients for CSF study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial occlusion</td>
<td>stuporous or comatose</td>
<td>subtotal or total hemiparesis</td>
<td>A</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>awake or lethargic</td>
<td>slight or moderate hemiparesis</td>
<td>B</td>
<td>16</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>subtotal or total hemiparesis</td>
<td>CI</td>
<td>18</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(occlusion of internal carotid artery)</td>
<td>CM</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>subtotal or total hemiparesis</td>
<td>D</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(occlusion of middle cerebral artery)</td>
<td>E</td>
<td>19</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>subtotal or total hemiparesis</td>
<td>F</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>slight or moderate hemiparesis</td>
<td>G</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>slight or moderate hemiparesis</td>
<td>H</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>subtotal or total hemiparesis</td>
<td>I</td>
<td>5</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>slight or moderate hemiparesis</td>
<td>K</td>
<td>50</td>
<td>33</td>
<td>23</td>
</tr>
<tr>
<td>Neither arterial occlusion nor intracerebral hematoma</td>
<td>stuporous or comatose</td>
<td>subtotal or total hemiparesis</td>
<td>L</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>awake or lethargic</td>
<td>slight or moderate hemiparesis</td>
<td>M</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total: 71

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*CSF = cerebrospinal fluid, Stroke = Cerebral Apoplexy*
CSF CHANGES BY HYPERVENTILATION IN STROKE

TABLE 2
Comparison of Some Variables in CSF and Arterial Blood From Normal Man and From 50 Patients With Cerebral Apoplexy (Stroke), Studied Before 24 Hours Had Elapsed After Onset of the Attack

<table>
<thead>
<tr>
<th></th>
<th>Normal man</th>
<th>Cerebral apoplexy, nonhemorrhagic</th>
<th>Cerebral apoplexy, hemorrhagic</th>
<th>Significance of difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 13</td>
<td>N = 46</td>
<td>N = 4</td>
<td></td>
</tr>
<tr>
<td><strong>CSF:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactate (mmol/1)</td>
<td>mean</td>
<td>1.54</td>
<td>2.36</td>
<td>4.60</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.31</td>
<td>0.63</td>
<td>0.38</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.010</td>
<td>0.050</td>
<td>0.030</td>
</tr>
<tr>
<td>Pyruvate (mmol/1)</td>
<td>mean</td>
<td>0.124</td>
<td>0.183</td>
<td>0.278</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>1.24</td>
<td>3.3</td>
<td>2.5</td>
</tr>
<tr>
<td>L/P ratio</td>
<td>mean</td>
<td>12.3</td>
<td>13.3</td>
<td>16.7</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>1.9</td>
<td>3.3</td>
<td>2.5</td>
</tr>
<tr>
<td>Bicarbonate (mmol/1)</td>
<td>mean</td>
<td>23.6</td>
<td>22.0</td>
<td>18.4</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.9</td>
<td>2.3</td>
<td>2.3</td>
</tr>
<tr>
<td><strong>Arterial:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactate (mmol/1)</td>
<td>mean</td>
<td>0.70</td>
<td>0.87</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.35</td>
<td>0.40</td>
<td></td>
</tr>
<tr>
<td>P CO₂ (mm Hg)</td>
<td>mean</td>
<td>40.3</td>
<td>34</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>1.1</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>A - B</th>
<th>B - C</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactate (mmol/1)</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Pyruvate (mmol/1)</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>L/P ratio</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Bicarbonate (mmol/1)</td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.01</td>
<td></td>
</tr>
</tbody>
</table>

NS: not significant (P > 0.05).

lactate, pyruvate and L/P ratio showed no significant changes, whereas a spontaneous hyperventilation, as indicated by the significant fall in arterial P CO₂ to a mean of 34 mm Hg, was disclosed. It will be noticed that the percent fall in P CO₂ is greater than the percent reduction of CSF bicarbonate in this early phase of the disease, a finding suggesting CSF alkalosis. Comparison of four patients with hemorrhagic CSF to the 46 patients with nonhemorrhagic CSF also is shown in table 2. Hemorrhagic CSF was associated with significantly higher lactate and pyruvate concentrations, with an unchanged L/P ratio, and with a significant reduction of CSF bicarbonate. The distinction between hemorrhagic and nonhemorrhagic CSF was made by macroscopic examination.

In table 3 the material has been analyzed for eventual prognostic value of the initially measured P CO₂ and CSF lactate. No significant differences between survivors and patients, who died before three weeks, were found in any of the three different treatment groups. On the contrary, among the untreated patients there was a tendency, although not statistically significant, suggesting that a high initial P CO₂ was followed by a higher mortality rate.

TABLE 3
Clinical Course Compared to P CO₂ and Lactate Content in Nonhemorrhagic CSF Analyzed Before 24 Hours Had Elapsed After Onset of a Cerebral Apoplectic Attack, Treated Afterward With or Without Prolonged Artificial Hyperventilation (Three Days)

<table>
<thead>
<tr>
<th>Treatment afterward</th>
<th>P CO₂ mm Hg</th>
<th>Difference</th>
<th>CSF lactate mmol/l</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S</td>
<td>D</td>
<td>NS</td>
<td>S</td>
</tr>
<tr>
<td>Hypocapnic hyperventilation</td>
<td>Mean 34</td>
<td>33</td>
<td>NS</td>
<td>Mean 2.00</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>4.0</td>
<td>2.0</td>
<td>SD</td>
</tr>
<tr>
<td>Normocapnic hyperventilation</td>
<td>Mean 34</td>
<td>38</td>
<td>NS</td>
<td>Mean 2.29</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>3.3</td>
<td>5.0</td>
<td>SD</td>
</tr>
<tr>
<td>Spontaneous respiration</td>
<td>Mean 33</td>
<td>38</td>
<td>NS</td>
<td>Mean 2.34</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>3.5</td>
<td>5.0</td>
<td>SD</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>12</td>
<td>7</td>
<td>N</td>
</tr>
</tbody>
</table>

S: patients surviving 21 days.
D: patients dead before day 21.
NS: not significant (P > 0.05).

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CHANGES IN CSF BICARBONATE, CSF LACTATE AND ARTERIAL PCO₂ IN 23 CASES OF SEVERE CEREBRAL APOPLEXY.

![Graphs showing changes in CSF lactate, CSF bicarbonate, and arterial PCO₂ over initial, third day, and sixth day for normal adults, normocapnic ventilated, hypocapnic ventilated, and spontaneous respirating groups.]

- **CSF Lactate mmol/l**
  - Initial: 2.00
  - 3rd day: 2.00
  - 6th day: 2.00

- **CSF Bicarbonate mmol/l**
  - Initial: 1.00
  - 3rd day: 1.00
  - 6th day: 1.00

- **Arterial PCO₂ mm Hg**
  - Initial: 30
  - 3rd day: 30
  - 6th day: 30

Legend:
- 13 Normal Adults
- 7 Normocapnic Ventilated
- 6 Hypocapnic Ventilated
- 10 Spontaneous Respirating
CSF CHANGES BY HYPERVENTILATION IN STROKE

The arterial $P_{\text{a}}$, was available in 29 of the patients studied initially, showing an uneven distribution around a median value of 114 mm Hg (95% confidence limits: 79 to 150 mm Hg). At the same time a hypocapnia ($P_{\text{aco}}$, 33 mm Hg [SD 4.5]) and normothermia were present.

ICP IN THE INITIAL PHASE

Forty-one of the patients who were treated with artificial hyperventilation had a pressure reading just after induction of anesthesia when normal ventilation still was aimed at. ICP averaged 13.9 mm Hg (SD 6.8 mm Hg). In 20 patients who had the nonventilatory treatment the measurements were done in an awake condition disclosing an average value of 15.3 mm Hg (SD 9.1 mm Hg). An initial ICP value exceeding 20 mm Hg was found in only nine of the 61 patients. Before three weeks had elapsed, four of these patients were dead (three following ventilation treatment), giving a mortality rate not differing from the whole material studied. The highest measured ICP was 37 mm Hg found in a patient who died within the first day from an intracerebral hematoma. Another patient with intracerebral hematoma disclosed an ICP of 34 mm Hg but improved clinically.

ACID-BASE VARIABLES DURING THE FIRST SIX DAYS

Simultaneous suboccipital and lumbar nonhemorrhagic taps were obtained in 11 patients on the third day after the attack (table 4). No significant differences in the concentrations of lactate or bicarbonate in cisternal and lumbar CSF were found. As a consequence of these findings, comparison of the CSF changes listed below is justified.

The changes in CSF lactate and bicarbonate and arterial $P_{\text{aco}}$, before, during, and after three days of artificial hyperventilation (either hypocapnic or normocapnic) as well as in patients not given ventilatory treatment are illustrated in figure 1. The initial CSF lactate values were significantly increased in all three groups of stroke patients compared to the normal values. During hypocapnia hyperventilation a significant further increase of CSF lactate was found. In the nonventilated group a gradual although insignificant fall of CSF lactate was noticed during the first six days after the attack.

After three days of induced and sustained hypocapnia a significant and further decrease of CSF bicarbonate from 22.0 to 18.4 mmol per liter was found. Following three days of normocapnic hyperventilation a restoration to normal value (23.6) of CSF bicarbonate was achieved. The nonventilated patients had a rather constant CSF bicarbonate varying only between 21.4 and 22.0 mmol per liter during the six-day observation period.

Three days after cessation of hyperventilation, all three groups ended up with practically the same values of CSF lactate and bicarbonate. Likewise, the initial spontaneous hyperventilation was restored again ($P_{\text{aco}}$, about 33 mm Hg).

CSF pyruvate and L/P ratio, and arterial lactate, pyruvate and L/P ratio did not show any significant changes from initial values during the course.

RATE OF ADAPTATION

The above-mentioned CSF bicarbonate changes on the third day indicated adaptation in the sense of a tendency to normalization of the CSF pH in face of a sustained change of $P_{\text{aco}}$. To analyze the rate of this adaptation, repeated examinations of the $P_{\text{aco}}$ and CSF bicarbonate concentration were done in 12 selected patients.

The findings in six of these patients studied during prolonged hypocapnia are illustrated in figure 2. The drop in $P_{\text{aco}}$ was followed by both a rapid and a delayed decrease in CSF bicarbonate until reaching a constant level first at 30 hours. The time course during prolonged normocapnia—constituting a state of relative “hypercapnia” in these spontaneously overbreathing patients—is illustrated in figure 3, where grossly the inverse relation was

<table>
<thead>
<tr>
<th>TABLE 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Comparison of CSF Lactate and Bicarbonate Taken Simultaneously Via the Suboccipital and the Lumbar Route From Patients With Cerebral Apoplexy Three Days After Onset of the Attack. All Samples Were Nonhemorrhagic</strong></td>
</tr>
<tr>
<td>Lactate (mmol/l)</td>
</tr>
<tr>
<td>Subocc.</td>
</tr>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>SD</td>
</tr>
<tr>
<td>N</td>
</tr>
<tr>
<td>Difference</td>
</tr>
</tbody>
</table>

Statistical analysis: Student's $t$-test for paired observations. NS = not significant.
Changes in CSF bicarbonate following changes in arterial PCO₂ before, during and after artificial hyperventilation in severe cerebral apoplexy.

6 HYPOCAPNIC CASES

<table>
<thead>
<tr>
<th>CSF pH</th>
<th>(calc.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>7.42</td>
</tr>
<tr>
<td>8</td>
<td>7.38</td>
</tr>
<tr>
<td>12</td>
<td>7.34</td>
</tr>
</tbody>
</table>

Changes in CSF bicarbonate following changes in arterial PCO₂ before, during and after artificial hyperventilation (72 hours) at a hypocapnic level in six patients with cerebral apoplexy (stroke). CSF pH had been calculated assuming (CSF—arterial) PCO₂ differences of 4, 8 and 12 mm Hg, respectively. Bars = ± SEM. All CSF samples were nonhemorrhagic.

found. These CSF bicarbonate changes suggest that partial CSF pH adaptation had taken place at four hours and that further adaptation took place until 30 hours after institution of artificial ventilation.

To clarify this point further the CSF pH was calculated using the Henderson-Hasselbalch equation: pKₐ values according to Mitchell and coworkers,¹² CSF bicarbonate as measured, and CSF PCO₂ calculated as PaCO₂ + ΔPCO₂ (gradient between CSF and arterial blood). Three different estimates of ΔPCO₂ were used: 4, 8 and 12 mm Hg, respectively. The three different CSF pH values calculated for each corresponding mean value of PaCO₂ and CSF bicarbonate are listed in figures 2 and 3. For each of the three ΔPCO₂ assumptions, the CSF pH was alkaline during hypocapnia and acidic during normocapnia. At 30 hours both groups had a stable and almost identical calculated CSF pH value for each assumed ΔPCO₂. This we consider strong evidence that complete adaptation had taken place after 30 hours. However, we cannot say from these calculations whether the CSF pH after adaptation remained normal (7.32), slightly alkaline, or slightly acidotic.

In four patients, of the 12 in whom the adaptation rate was studied, the pH was measured in anaerobically obtained CSF after adaptation was completed (table 5). The CSF pHs found on the third and sixth days after onset of the apoplectic attack were all slightly alkaline or normal. The corresponding ΔPCO₂ was measured and found to average 5.7 mm Hg.

Changes in the MABP and the ICP following sustained hypocapnia or normocapnia are given in figures 4 and 5, respectively. The changes in MABP were similar in both groups. All the patients had a
CSF CHANGES BY HYPERVENTILATION IN STROKE

CHANGES IN CSF BICARBONATE FOLLOWING CHANGES IN ARTERIAL PCO₂ BEFORE, DURING AND AFTER ARTIFICIAL HYPERVENTILATION IN SEVERE CEREBRAL APoplexy

6 NORMOCAPNIC CASES

<table>
<thead>
<tr>
<th>CSF pH (calc.)</th>
<th>4</th>
<th>8</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.38</td>
<td>7.28</td>
<td>7.28</td>
<td>7.35</td>
</tr>
<tr>
<td>7.36</td>
<td>7.39</td>
<td>7.36</td>
<td>7.38</td>
</tr>
<tr>
<td>7.34</td>
<td>7.25</td>
<td>7.24</td>
<td>7.31</td>
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<tr>
<td>7.32</td>
<td>7.35</td>
<td>7.31</td>
<td>7.34</td>
</tr>
<tr>
<td>7.29</td>
<td>7.22</td>
<td>7.20</td>
<td>7.27</td>
</tr>
<tr>
<td>7.28</td>
<td>7.31</td>
<td>7.28</td>
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Changes in CSF bicarbonate following changes in arterial PCO₂ before, during and after artificial hyperventilation (72 hours) at a normocapnic level in six patients with cerebral apoplexy (stroke). CSF pH had been calculated assuming (CSF—arterial) PCO₂ differences of 4, 8 and 12 mm Hg, respectively. Bars = ± SEM. All CSF samples were nonhemorrhagic.

Discussion

ACID-BASE VARIABLES IN THE INITIAL PHASE

Our findings in the CSF samples taken before treatment (table 2) were similar to previous studies in cerebral apoplexy.1,2

We also found that stroke patients with hemorrhagic CSF had CSF lactate concentrations of 4 to 5 mmol per liter, i.e., much higher CSF lactate values than stroke patients with nonhemorrhagic CSF. Simultaneously a significant lower bicarbonate was found in the hemorrhagic CSF, indicating an acidic CSF pH in these cases compared to the nonhemorrhagic cases where a normal or slightly alkaline CSF pH is normally found.2 In spite of this CSF lactacidosis no difference in PaCO₂ between patients with or without hemorrhagic CSF was found in our series.

We were unable to find any correlation between the lowering of the initial PaCO₂ and the prognosis even in the untreated group (table 3). Thus we could not confirm the findings by Zupping and coworkers1 or Lane and coworkers.2 On the contrary, we found the highest PaCO₂ among patients with moderate decrease in MABP, which was most pronounced about 12 hours after induction of ventilation. The initial ICP values were within normal limits in all the 12 patients. During ventilation the changes in ICP were discrete but oppositely directed in the two groups. Within the first 30 hours of sustained hypocapnia the average ICP was slightly below the initial level, and within the first 30 hours of sustained normocapnia the average ICP was slightly above the initial level.

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with a high mortality rate although those findings were not statistically significant. Differences in the selection of material might be a possible explanation.

An old stroke patient with a severe brain lesion might sometimes disclose a normal PaCO₂, because his general condition is so bad that he is unable to perform an active hyperventilation “corresponding” to the brain lesion.

As a lactate formation probably takes place locally in the damaged brain area, it could be expected that the highest lactate formation was correlated to the highest mortality rate. In the

![Figure 4](http://stroke.ahajournals.org/)

Changes in MABP and ICP following changes in arterial PaCO₂ before, during and after artificial hyperventilation (72 hours) at a hypocapnic level in six patients with cerebral apoplexy (stroke). Bars = ± SEM.
present study no such correlation between the initial CSF lactate concentration and the prognosis could be demonstrated (table 3). This may be because a high lactate production is not necessarily reflected in the CSF lactate concentration.

MECHANISM OF SPONTANEOUS HYPERVENTILATION

A typical finding in this study was the spontaneous moderate hypocapnia indicating an active hyperventilation in acute stroke cases as also reported by others.\(^1,2\)

The mechanism of this spontaneous hyperventilation in apoplexy has not been clarified. Lane and coworkers\(^2\) found average \(P_{\text{a}}O_2\) values of about 70 mm Hg and considered these \(P_{\text{a}}O_2\) values too high for stimulation of respiration, as it is well documented that alveolar ventilation does not increase until alveolar \(P_{\text{a}}O_2\) drops to values below 60 mm Hg in acute experiments.\(^14\) Plum\(^1\) recently drew attention anew to the importance of hypoxia in patients spontaneously hyperventilating as, e.g., apoplectics. In the present material only eight out of 29 patients had initial \(P_{\text{a}}O_2\) values below 70 mm Hg. The initial \(P_{\text{a}}CO_2\) in these eight patients averaged 31 mm Hg compared to the mean \(P_{\text{a}}CO_2\) of the 29 patients of 33 mm Hg. So even in these eight patients only a slight hypoxic drive to hyperventilation could be suspected.

A constant finding in the stroke cases was the increased content of lactic acid in the CSF. This might be due, as suggested by Lane and coworkers,\(^2\) to the hypocapnia because several animal experiments have shown an increase in CSF lactate during hyperventilation to \(P_{\text{a}}CO_2\) values about 30 mm Hg\(^15-17\) and 20 mm Hg.\(^18\) The increase in CSF lactate during hyperventilation is considered a CSF pH regulatory mechanism.\(^10\) Our data disclosed a further significant increase in CSF lactate when a further \(P_{\text{a}}CO_2\) reduction was sustained (fig. 1: \(P_{\text{a}}CO_2\) 34 → 27 mm Hg). Despite the accumulation of lactate, a normal or slightly alkaline CSF pH is usually found in apoplexy except when hemorrhagic CSF is present.\(^1,2\) In patients with
brain injuries, however, higher levels of CSF lactate and acidic CSF pH is found. In these patients the CSF lactacidosis probably causes—or contributes to—the active hyperventilation. But even in stroke cases the hyperventilation might still be explained by a slightly acidic shift of the CSF pH, when one considers the high pH gain of the respiratory center and the difficulties in measuring such small pH differences in the unbuffered CSF.

Primary or central neurogenic hyperventilation has been described in brain stem lesions. Other neurogenic mechanisms more relevant to cerebral apoplexy might be an altered suprapontine influence on respiration or increased sympathetic activity leading to increased blood pressure and pulmonary congestion which, along with hypoxemia, stimulates ventilation. It is concluded that hypoxemia was an unlikely cause of hyperventilation in the present material. We can exclude neither a metabolic (CSF acidosis) nor a neurogenic drive on the respiratory center, although the first-mentioned concept is strongly supported by the findings of Pappenheimer and coworkers.

RATE OF ADAPTATION
The \( \Delta P_{\text{CO}_2} \) gradient from CSF to arterial blood (\( \Delta P_{\text{CO}_2} \)) is normally 8 mm Hg. In cerebral apoplexy gradients of 4.5 mm Hg have been reported. But in acute brain lesions and in experimental studies with pronounced hypocapnia values up to 15 and 12 mm Hg, respectively, have been reported. Based on these observations we have used three different estimates of \( \Delta P_{\text{CO}_2} \) for the CSF pH calculation in figures 2 and 3.

According to these calculations hypocapnia acutely induced an alkaline CSF pH and normocapnia (a relative "hypercapnia" for these patients) and acidic pH. CSF bicarbonate will now change slowly tending to normalize CSF pH again. As shown in figures 2 and 3, marked changes of CSF bicarbonate occurred within four hours, although a stable level was not reached before 30 hours had passed. This time course, suggesting a half-time of CSF pH adaptation of approximately six hours, is in agreement with previous studies of CSF adaptation in animal experiments during prolonged hypercapnia and hypocapnia. It is in agreement also with CSF adaptation in clinical studies of metabolic acidosis. It should be noted that only a few of the mentioned studies had been extended to cover the entire time course of the adaptation process.

It is important to realize that when the CSF bicarbonate has changed enough to normalize the CSF pH again, the induced and sustained \( P_{\text{CO}_2} \) changes are without influence on the acid-base balance of the brain any more.

With a few exceptions the average ICP findings in the acute phase were within normal limits and no correlation to the clinical course was disclosed.

The changes in ICP following induced and sustained \( P_{\text{CO}_2} \) changes were only slight but in predicted directions. The duration of the changes induced by ventilation was similar to the duration of the induced CSF pH changes. This observation suggests an interrelationship between CSF pH, cerebral blood flow, and ICP. Epidural pressure gradients between cerebral infarctions and the opposite hemisphere have been demonstrated experimentally. Therefore, even slight changes of the CSF pressure (measured via suboccipital or lumbar taps) might be important for local perfusion in the diseased area.

Clinical Comments
Patients with brain damage of different etiology such as trauma, infections, or cerebrovascular accidents as in the present study have been found to hyperventilate spontaneously for several days. This hyperventilation may be exhaustive in a diseased patient, especially if decreased pulmonary function and/or pulmonary complications are present. For this reason and because induced hypocapnia will both counteract the cerebral lactacidosis typically found in these patients and decrease ICP, artificial hyperventilation has been used therapeutically in such cases.

With the use of prolonged artificial hyperventilation in brain-damaged patients, beneficial effects can be expected only during the first one or two days because of the CSF pH adaptation. But defeating an intracranial hypertension initially may well be decisive for the clinical course.

During discontinuation of prolonged hyperventilation therapy in a brain-damaged patient, the \( P_{\text{CO}_2} \) has to be followed closely during the first one or two days. Any abrupt increase of \( P_{\text{CO}_2} \) invariably means a CSF acidosis (sudden increase of CSF bicarbonate) and ICP increase which is dangerous in these patients. In this context it must be noted that a \( P_{\text{CO}_2} \) of 40 mm Hg may not be "normal" in a brain-damaged patient but often means a "relative hypercapnia."

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CHRISTENSEN, BRODERSEN, OLESEN, PAULSON

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Cerebral Apoplexy (Stroke) Treated With or Without Prolonged Artificial Hyperventilation:  
2. Cerebrospinal Fluid Acid-Base Balance and Intracranial Pressure  
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