Cerebral Effects of Extended Hyperventilation in Unanesthetized Goats

Ronald F. Albrecht, David J. Miletich, and Mark Ruttle

Thirty-six adult, male unanesthetized goats were hyperventilated to a PacO₂ level of 16–18 mm Hg for 6 hours. Arterial and sagittal sinus blood and cerebrospinal fluid were analyzed for pH, blood gases, bicarbonate, lactate, and pyruvate before hyperventilation, during hyperventilation, and after the termination of hyperventilation. Total cerebral blood flow, regional brain blood flows, and cerebral metabolic rate for oxygen were calculated from the distribution of radioactive microspheres. Intracranial pressure was measured in either the right or left cerebral ventricle. With the initiation of hyperventilation, cerebral blood flow and cerebral metabolic rate for oxygen fell significantly (64 ± 5 ml/100 g/min to 41 ± 3; 4.6 ± 0.3 ml O₂/100 g/min to 3.6 ± 0.2), but both returned to prehyperventilation values within 6 hours of hyperventilation. With termination of hyperventilation, cerebral blood flow and cerebral metabolic rate for oxygen increased significantly above control levels (64 ± 5 vs. 105 ± 9; 4.6 ± 0.3 vs. 5.4 ± 0.4). Intracranial pressure was unaffected by hyperventilation or its termination. Arterial and sagittal sinus blood and cerebrospinal fluid pH increased with hyperventilation but returned to control values by 6 hours. However, pH was still significantly elevated at 6 hours.

Lactate and pyruvate followed a similar pattern except in the cerebrospinal fluid, where both increased throughout the course of hyperventilation. There were no significant differences in the lactate:pyruvate ratio. On termination of hyperventilation, pH of the arterial and sagittal sinus blood and cerebrospinal fluid fell below control levels. Bicarbonate values decreased in all fluid compartments and were still below control values 2 hours after the cessation of hyperventilation. Blood flows to the cerebral cortex, thalamus, hypothalamus, medulla, and cerebellum fell significantly with hyperventilation and, with the exception of the thalamus, all recovered during hyperventilation. On termination of hyperventilation, blood flows to the cortex, thalamus, medulla, and cerebellum increased significantly above control values. Only the brainstem (except the medulla) appeared unresponsive to hyperventilation. Hyperventilation had little effect on mean arterial blood pressure and heart rate. However, hyperventilation did cause a 20% reduction in cardiac output, which gradually recovered throughout the course of hyperventilation. On termination of hyperventilation, cardiac output rebounded above control values by approximately 20% and remained elevated 2 hours after hyperventilation. The results of this study indicate that in unanesthetized goats cerebral blood flow adapts to the imposition of hyperventilation and returns to normal despite continued hyperventilation. Although cerebrospinal fluid lactate levels increased, there was no evidence of cerebral hypoxia since pyruvate showed a proportionate increase. (Stroke 1987;18:649–655)

Despite many years of clinical experience, the value of hyperventilation in the treatment of head injury remains uncertain.1 2 While ethical and experimental limitations have obscured the effectiveness of hyperventilation in many instances, a dearth of information regarding the overall cerebral effects of protracted hyperventilation must be viewed as a major factor contributing to the present uncertainty. It is surprising how few laboratory studies that have evaluated the effects of hyperventilation over clinically relevant periods of time have been reported. Those studies that have appeared are in serious disagreement. For example, evidence exists that cerebral blood flow (CBF) may adapt to extended periods of hyperventilation and eventually return to prehyperventilation levels,3 4 but not all studies have shown a recovery of CBF during hyperventilation.5 6 Because a sustained reduction in CBF is central to the theory of hyperventilation therapy, one would think that the behavior of CBF during extended hyperventilation would be understood and well documented. The absence of consensus on this crucial point clearly suggests a need for studies concerned with the physiologic effects of prolonged hyperventilation. The purpose of this study, therefore, was to conduct a comprehensive analysis of the effects of protracted hyperventilation on CBF, cerebral metabolic rate for oxygen (CMRO₂), and other cerebral parameters in normal, unanesthetized goats. Hopefully, information gained from experiments with unanesthetized animals will provide a view of hyperventilation which will contribute to a better understanding of its treatment potential.

Materials and Methods

Thirty-six goats, 30–40 kg, were surgically prepared for study under halothane anesthesia. Catheters were implanted in the sagittal sinus, cisterna magna,
left or right cerebral ventricle, femoral artery and vein, and left atrium of the heart. The catheters were placed in their respective cranial spaces after the drilling of a small 0.5-cm diameter hole in the skull. An electromagnetic blood flow probe was then placed around the pulmonary artery for the measurement of cardiac output (CO) and calculation of CBF by the radioactive microsphere technique. All skull catheters were then anchored in place, and the entry hole through the skull was closed with dental cement. The remaining catheters and flow probe lead were tunneled percutaneously and exited on the back of the goat. After surgery and for the next 48 hours, the goats were treated with morphine sulfate for control of postoperative pain and were then permitted to recover for at least 10 days before study. One day prior to study, each goat was anesthetized with thiopental, and a tracheostomy was quickly performed. The stoma was allowed to remain open until the next day, at which time a standard 7-mm tube was inserted after a local anesthetic was sprayed on the stoma to facilitate a painless intubation. After intubation, the goats were placed in a restraining stall and allowed approximately 1 hour to adjust to the stall before the beginning of the experiment. During this hour, an i.v. saline drip was started. Throughout the study, saline was administered as needed to replace fluid lost as a result of hyperventilation. No sedation or anesthetic was used at any time during the study. The goats appeared to tolerate hyperventilation well and showed no ill effects or restlessness. The methods used in the study were determined by the Laboratory Animal Care Committee of Michael Reese Hospital to be ethical and not painful to the animals employed.

At the beginning of each study, i.e., before hyperventilation was initiated, control intracranial pressure (ICP) and hemodynamic measurements were made. Blood samples were drawn from the sagittal sinus and femoral arterial catheters for the measurement of blood gases, pH, bicarbonate, and lactate-pyruvate values. A 0.1-ml cerebrospinal fluid (CSF) sample was rapidly drawn from the cisterna magna for the measurement of blood gases, pH, bicarbonate, and lactate-pyruvates. A 0.1-ml volume of mock CSF replaced the removed CSF. Precautions were taken to prevent exposing the CSF sample to atmospheric air.

On removal of CSF, control CBF was determined using the radioactive microsphere technique. CMRO₂ was determined by multiplying the difference in oxygen between arterial and sagittal sinus blood by the total CBF. Approximately 5 × 10⁶ microspheres 15 ± 2 μm in diameter, labelled with ⁵⁷Co, ⁶⁵Sc, ⁸⁵Sr, or ¹¹³Sn at a specific activity of 10 mCi/g (Amersham Corp.), were suspended in 10 ml of saline, sonicated for mixing purposes, and injected into the left atrial catheter. This dose resulted in 400–500 microspheres/g brain tissue. At the completion of the study, the goats were killed, the brain was removed, weighed, and bisected along the longitudinal axis, and 1-g portions of the frontal cortex, thalamus, hypothalamus, medulla, cerebellum, and brainstem were placed in counting tubes for radioactivity determinations. The remaining portions of the brain were used for determining total CBF with provisions made for the 1-g portions. Blood flow in ml/100 g/min was calculated as CBF = CO × %iD, where CO = cardiac output in liters per minute measured by the electromagnetic flow probe, and %iD = percent of the injected dose of microspheres found in the brain.

After the control measurements on the 36 goats were completed, mechanical hyperventilation was initiated with a Harvard model 613 piston-driven dual-phase controlled ventilator. The respiration rate was adjusted to 36 breaths/min at a tidal volume of 10 ml/kg body wt. Twenty minutes of hyperventilation generally reduced Paco₂ to approximately 16-18 mm Hg (32–35 mm Hg is considered normocarbic in goats). While most goats responded in a similar fashion to hyperventilation, it was sometimes necessary to adjust either tidal volume or respiration rate to achieve an endpoint of 16–18 mm Hg Paco₂. Regardless of the rate or volume used, care was taken to keep the end-expiratory pressure as close to 0 as possible and the mean positive inspiratory pressure at about 15 mm Hg.

Once 16–18 mm Hg Paco₂ was reached, blood samples were again drawn for blood chemistries as previously described, and a second dose of radioactive microspheres was injected for CBF and CMRO₂ calculations. These processes were repeated twice more, after 6 hours of hyperventilation and 2 hours later, after termination of hyperventilation. Hyperventilation was terminated by simply returning the respiration rate to normal, i.e., approximately 14 breaths/min. With return to normal respiration, Paco₂ slowly rose and took approximately 2 hours to reach beginning levels (33–35 mm Hg). Blood CO₂ was monitored frequently throughout this period. In all, a total of 4 microsphere injections were made with associated analyses of biochemistries. In addition to these measurements, arterial and sagittal sinus blood samples and CSF samples were drawn every 30 minutes from the onset of hyperventilation and for 2 hours after the termination of hyperventilation.

Blood gases, pH, and bicarbonates were determined with the Instrumentation Laboratory IL 1303 blood gas analyzer and IL 282 Co-oximeter. Blood and CSF lactates and pyruvates were assayed fluorometrically with a Sigma Chemical Co. lactate dehydrogenase diagnostic assay kit 826-UV.

To separate the mechanical effects of hyperventilation from the biochemical effects of lowered Paco₂, 9 goats were hyperventilated with supplemental CO₂ added to the inspired air mixture. CO₂ was carefully titrated into the inspired air to maintain Paco₂ within the normal limits for goats. Otherwise, the experiments with supplemental CO₂ were carried out in exactly the same fashion as previously described.

Four goats were hyperventilated for 6 hours and 2 goats for 12 hours and allowed to recover. These animals were then observed for up to 15 days for any evidence of neurologic damage.

Statistical significance was evaluated by one-way analysis of variance and the Bonferroni multiple com-
The effects of hyperventilation and hyperventilation plus supplemental CO2 on the CBF of unanesthetized goats. C, control, prehyperventilation values; 0, time zero (20 minutes after the initiation of hyperventilation). Hyperventilation was terminated at 6 hours. *Significantly different from preceding value; \( p < 0.05 \), \( n = 30 \). Points are mean \( \pm \) SEM.

Table 1. Effects of Hyperventilation With or Without Supplemental Inspired CO2 on Regional Brain Blood Flow

<table>
<thead>
<tr>
<th></th>
<th>Cortex</th>
<th>Thalamus</th>
<th>Hypothalamus</th>
<th>Medulla</th>
<th>Cerebellum</th>
<th>Brainstem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>H</td>
<td>67±4</td>
<td>87±6</td>
<td>44±4</td>
<td>83±4</td>
<td>73±5</td>
</tr>
<tr>
<td></td>
<td>H + CO2</td>
<td>72±4</td>
<td>84±4</td>
<td>37±4</td>
<td>78±5</td>
<td>67±6</td>
</tr>
<tr>
<td>Time 0</td>
<td>H</td>
<td>41±5*</td>
<td>56±4*</td>
<td>32±3*</td>
<td>53±5*</td>
<td>48±4*</td>
</tr>
<tr>
<td></td>
<td>H + CO2</td>
<td>61±4*</td>
<td>89±6</td>
<td>35±4</td>
<td>77±4</td>
<td>61±5</td>
</tr>
<tr>
<td>6 hours</td>
<td>H</td>
<td>62±5</td>
<td>58±3*</td>
<td>41±3</td>
<td>75±6</td>
<td>69±4</td>
</tr>
<tr>
<td></td>
<td>H + CO2</td>
<td>67±3</td>
<td>79±5</td>
<td>33±2</td>
<td>72±8</td>
<td>61±6</td>
</tr>
<tr>
<td>8 hours</td>
<td>H</td>
<td>98±7†</td>
<td>108±9†</td>
<td>49±4</td>
<td>94±7†</td>
<td>116±11†</td>
</tr>
<tr>
<td></td>
<td>H + CO2</td>
<td>75±6</td>
<td>75±6</td>
<td>32±4</td>
<td>74±7</td>
<td>66±7</td>
</tr>
</tbody>
</table>

All data are mean \( \pm \) SEM ml/100 g/min; H, hyperventilation; H + CO2, hyperventilation with supplemental inspired CO2. Control values were obtained before initiation of hyperventilation; Time 0 values were obtained 20 minutes after initiation of hyperventilation; hyperventilation was terminated at 6 hours.

*Significantly lower or higher, respectively, than control values; \( p < 0.05 \), \( n = 30 \).
changed (Table 2). Sagittal sinus and arterial blood lactates also rose significantly with hyperventilation, while venous levels being slightly but significantly higher than arterial concentrations at each time (Table 2). However, arterial and venous pyruvates also rose, so the lactate:pyruvate ratios did not change significantly. The addition of supplemental inspired CO₂ during hyperventilation prevented both lactate and pyruvate changes in the CSF and the arterial and venous blood fluid compartments (data not shown).

The effects of prolonged hyperventilation on pH, Pco₂, Po₂, and HCO₃⁻ in the CSF and arterial and venous blood fluid spaces can be seen in Figure 3 and Table 3. As expected, hyperventilation caused significant decreases in Pco₂ and increases in pH in the arterial and sagittal blood and CSF compartments. However, the changes were less marked in sagittal sinus blood and CSF compared with arterial blood.

Hyperventilation with or without supplemental inspired CO₂ had no significant effect on ICP (Table 4), and termination of 6 hours of hyperventilation produced little change in the ICP. In addition, no significant changes were seen in heart rate or mean arterial blood pressure as a result of hyperventilation.

The large reductions in CBF due to prolonged hyperventilation did not seem to cause cerebral hypoxia or gross evidence of neurologic damage. Four goats hyperventilated for 6 hours and 2 goats for 12 hours recovered without any clinical signs of neurologic complications during 15 days after hyperventilation.

**Discussion**

The most notable observation made in our study was that prolonged mechanical hyperventilation of normal, unanesthetized goats did not result in a sustained reduction in CBF. Although CBF fell dramatically with the onset of hyperventilation, it returned to normal in approximately 6 hours (Figure 1). Termination of hyperventilation resulted in a large increase in CBF, which persisted for at least 2 hours. Analysis of regional CBF indicates that the regions studied behaved for the most part similarly to total CBF, suggesting that no intracerebral blood flow shunting took place (Table 1).

The reduction, recovery, and posthyperventilation increase in total and regional CBF were due almost entirely to hyperventilation-caused biochemical changes and not the result of any mechanical change associated with hyperventilation. The addition of CO₂ to the inspired air reversed almost all of the physiologic manifestations of hyperventilation except for a slight but significant drop in CBF immediately following the initiation of hyperventilation. This slight reduction in CBF may have been due to the effects of hyperventilation on CO. Other studies have shown that hyperventilation can cause significant decreases in CO and cerebral perfusion pressure if high inspiratory pressures are used.⁸⁻⁹ It is believed that ventilation with high inspiratory pressure diminishes venous return through compression of the vena cava within the thoracic cavity.

**Table 2. Hyperventilation and the Appearance of Lactates-Pyruvates in Arterial and Venous Blood and CSF**

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Arterial Blood</th>
<th>Sagittal Sinus Blood</th>
<th>CSF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lactate</td>
<td>Pyruvate</td>
<td>Ratio</td>
</tr>
<tr>
<td>Control</td>
<td>0.43±0.04</td>
<td>0.06±0.01</td>
<td>7.2±0.5</td>
</tr>
<tr>
<td>Time 0</td>
<td>0.58±0.07†</td>
<td>0.07±0.01†</td>
<td>8.3±0.2</td>
</tr>
<tr>
<td>30 min</td>
<td>0.66±0.07†</td>
<td>0.08±0.01†</td>
<td>8.3±0.2</td>
</tr>
<tr>
<td>180 min</td>
<td>0.54±0.04†</td>
<td>0.08±0.02†</td>
<td>6.8±1.0</td>
</tr>
<tr>
<td>360 min</td>
<td>0.52±0.04†</td>
<td>0.07±0.01†</td>
<td>7.4±0.2</td>
</tr>
<tr>
<td>390 min</td>
<td>0.46±0.06</td>
<td>0.06±0.01</td>
<td>7.7±0.3</td>
</tr>
<tr>
<td>480 min</td>
<td>0.40±0.04</td>
<td>0.06±0.01</td>
<td>6.7±0.4</td>
</tr>
</tbody>
</table>

Values are mean ± SEM mmol. CSF, cerebrospinal fluid. Hyperventilation continued from 0 to 360 minutes.
*CSF lactate:pyruvate values higher than arterial or venous values.
†Significantly higher than control values; p < 0.05, n = 21.
‡Significantly higher than control values and preceding values; p < 0.05, n = 21.
However, in our study CBF returned to normal shortly after the beginning of hyperventilation, suggesting that the elevated intrathoracic pressure was eventually offset by cerebral autoregulation and/or other cardiovascular compensatory adjustments.

On first inspection, one might expect that the changes in CBF seen as a result of hyperventilation and termination of prolonged hyperventilation should have caused fluctuations in ICP (Table 4). However, it is well known that under normal conditions, i.e., in the absence of edema or a large space-occupying mass, significant changes in CBF can be accommodated without influencing ICP due to the normal compression of the brain and expansion of the cranium. As a result, the ICP-volume relation is in effect a biphasic curve, with the lower portion relatively flat and the upper portion rather steep. In other words, the evidence that CBF varies inversely with pH is circumstantial and often contradictory. Raichle et al concluded that perivascular pH was probably the primary regulator of CBF following CO₂ changes. However, the evidence that CBF varies inversely with pH is circumstantial and often contradictory. Raichle et al observed that CBF in awake, hyperventilated men appeared to be inversely related to arterial pH and that the doubling of CBF seen in our study did not increase the cerebral blood volume beyond the critical volume necessary to cause an increase in ICP.

Why CBF adapted to the imposition of continuous hyperventilation is an intriguing question. Historically, many studies have focused on the role of hydrogen ions in the regulation of cerebrovascular resistance. From a recent review of the literature, Kuschinsky concluded that perfusor pH was probably the primary regulator of CBF following CO₂ changes. However, the evidence that CBF varies inversely with pH is circumstantial and often contradictory. Raichle et al observed that CBF in awake, hyperventilated men appeared to be inversely related to arterial pH and that both pH and CBF tended to return to normal with extended hyperventilation. On the other hand, Plum et al using anesthetized dogs, and Wollman et al with humans all found that CBF underwent no restoration to

Table 3. Effects of Hyperventilation on CSF, Arterial and Sagittal Sinus Blood Gases, and Bicarbonates

<table>
<thead>
<tr>
<th></th>
<th>Arterial blood</th>
<th>Sagittal sinus blood</th>
<th>CSF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CO₂</td>
<td>O₂</td>
<td>HCO₃⁻</td>
</tr>
<tr>
<td>Control</td>
<td>33 ± 1.4</td>
<td>11.4 ± 0.9</td>
<td>20.6 ± 1.2</td>
</tr>
<tr>
<td>Time 0</td>
<td>16 ± 0.8*</td>
<td>12.2 ± 1.0</td>
<td>17.2 ± 1.0*</td>
</tr>
<tr>
<td>30 min</td>
<td>16 ± 0.3*</td>
<td>12.3 ± 1.6</td>
<td>16.4 ± 0.6*</td>
</tr>
<tr>
<td>180 min</td>
<td>17 ± 0.4*</td>
<td>11.9 ± 1.0</td>
<td>16.1 ± 0.7*</td>
</tr>
<tr>
<td>360 min</td>
<td>17 ± 0.6*</td>
<td>11.6 ± 0.9</td>
<td>15.3 ± 0.7*</td>
</tr>
<tr>
<td>390 min</td>
<td>29 ± 1.2</td>
<td>11.2 ± 0.9</td>
<td>16.5 ± 0.5*</td>
</tr>
<tr>
<td>480 min</td>
<td>32 ± 1.1</td>
<td>11.0 ± 0.8</td>
<td>17.4 ± 0.6*</td>
</tr>
</tbody>
</table>

Values are mean ± SEM; CO₂, mm Hg; O₂, vol%; HCO₃⁻, meq/l. CSF, cerebrospinal fluid. Hyperventilation continued from 0 to 360 minutes.

*Significantly lower than control value; p < 0.05, n = 30.
†Significantly lower than control value and preceding value; p < 0.05, n = 30.
normal after several hours of hypocapnia although pH decreased.\textsuperscript{5,6,13,14} Unfortunately, data from our study does not clarify the issue. As can be seen in Figure 3, the pH of the arterial and venous blood and cisternal CSF compartments rose with the onset of hyperventilation and gradually approached prehyperventilation values by 6 hours. Likewise, CBF followed a similar course, but in an inverse fashion (Figure 1). With the termination of hyperventilation, pH fell to normal while CBF rose significantly above control levels and remained elevated for at least 2 hours after the termination of hyperventilation. The latter observations would seem to suggest that the course of CBF is independent of pH. However, it should be realized that concentrations of hydrogen ions in CSF in most instances probably do not reflect their respective concentrations in the cerebral perivascular fluid spaces.\textsuperscript{12} Without direct measurement of perivascular pH it is not possible to establish the relation between CBF and hydrogen ions during the course of prolonged hyperventilation. In addition, anesthesia may have some impact on the course of CBF during hypocapnia. It is of interest that in our study and that of Raichle et al\textsuperscript{3} in which anesthesia was not used, CBF was restored during hyperventilation, while those studies using an anesthetic failed to demonstrate a restoration.\textsuperscript{5,6,13,14}

Another salient observation made in our study was the substantial and immediate fall in CMRO\textsubscript{2} that occurred with the initiation of hyperventilation (Figure 2). Although early studies failed to detect a fall in CMRO\textsubscript{2} with hyperventilation, more recent work in both humans and animals has clearly shown a decrease in CMRO\textsubscript{2} with the onset of hypocapnia.\textsuperscript{15} The decreases in CMRO\textsubscript{2} seen in our study are considerably larger than those reported elsewhere. Most likely we were able to detect these changes where others failed because we used unanesthetized animals. A drop of nearly 40\% was observed in some goats. In addition to the large decreases, we also found that CMRO\textsubscript{2} rose in parallel with CBF when hyperventilation was terminated. The increase in CMRO\textsubscript{2} was probably a hypermetabolic response to the prolonged depressant effects of hyperventilation. However, it is of interest to note that CMRO\textsubscript{2} did not increase in proportion to CBF once hyperventilation was terminated. Ordinarily, blood flow is thought to be coupled with metabolism on a one-to-one basis under normal circumstances. Since our study was not designed to examine this problem, we can only speculate as to why hyperventilation caused an apparent uncoupling of CBF and CMRO\textsubscript{2}. Perhaps the profound change in tissue pH that must have occurred as a result of prolonged hyperventilation may have in some way temporarily disrupted the mechanism by which the cerebral vasculature adjusts to metabolic fluctuations. It is also possible that the extended period of tissue alkalosis may have disturbed the cerebral autoregulatory mechanism, rendering it incapable of coping with the significant increase in CO that occurred after termination of hyperventilation (Table 4).

Despite these rather large reductions in CMRO\textsubscript{2}, there was no physical evidence of cerebral hypoxia. Hyperventilation of unanesthetized goats for up to 12 hours produced no observable deleterious neurologic effects after treatment. However, during hyperventilation blood and CSF lactate levels increased (Table 2). Early studies attributed the rise in brain tissue, CSF, and cerebral venous blood lactate to be the result of cerebral hypoxia caused by the large decreases in CBF.\textsuperscript{20} Indeed, the evidence in support of this hypothesis is very impressive. The EEG changes seen during hyperventilation are similar to those observed during global cerebral ischemia, whereas hyperbaric hyperventilation with 100\% O\textsubscript{2} results in a normal EEG.\textsuperscript{21,22} CSF lactate:pyruvate ratio has been shown to increase in some studies.\textsuperscript{20,21,24} Likewise, brain tissue NADH: NAD\textsuperscript{+} ratios may increase during hyperventilation.\textsuperscript{25} Finally, it has been reported that the rate of cerebral glucose utilization in humans increases during hypocarbia.\textsuperscript{15}

Although these data are persuasive, more recent work has thrown the meaning of these observations into question and seriously undermines the hypothesis that severe hypocarbia produces cerebral hypoxia. Young and Yagel and Kogure et al have recently reported that hyperventilation causes significant decreases in CMRO\textsubscript{2} with little or no change in cerebral tissue glucose, glycogen, phosphonucleotides, and phosphocreatine.\textsuperscript{19,26} Though these authors did observe elevated cerebral lactates and pyruvates, they were unanimous in their opinion that these increases were due to accelerated glycolysis and not hypoxia. In our study, CSF and cerebral venous and arterial blood lactate increased, but pyruvate levels also increased, resulting in no significant change in their ratio at any time (Table 2). As discussed by Kogure et al, the NADH:NAD\textsuperscript{+} ratio can be increased by alkalosis or by stagnation of electron flow if the metabolic impairment is in the mitochondrial system.\textsuperscript{19} It has been demonstrated that the enzyme phosphofructokinase is extremely sensitive to pH, and a change of as little as 0.2 unit in the presence of normal oxygen levels can stimulate this enzyme, leading to accelerated glycolysis and lactate production.\textsuperscript{27} In addition, infusion of bicarbonate into normal animals produces a lactacidemia similar to that seen in hyperventilated animals.\textsuperscript{28}

In conclusion: Continuous hyperventilation of normal, unanesthetized goats produced only transient reductions in CBF and CMRO\textsubscript{2}, which returned to normal within 6 hours. In addition, goats subjected to 12 hours of hyperventilation showed no ill effects for several days after treatment. We conclude from these studies that hyperventilation has only a temporary effect on CBF and that it does not seem to cause any lasting ill effects in normal animals.

Because the effects of hyperventilation on CBF appear to be only temporary, one wonders whether this form of intervention has any real therapeutic value. Raichle and Plum, after reviewing the pertinent literature, have concluded that hyperventilation is ineffective in the treatment of stroke, intracranial hypertension, and cerebral edema.\textsuperscript{2} Christensen found
hyperventilation to be of no help in resolving the outcome of patients suffering from a variety of head injuries and, in fact, hyperventilation may have been deleterious with regard to pulmonary infections and esophageal ulceration.\textsuperscript{29}

Although the goats employed in our study were healthy and free of vascular disease, it would seem that the use of hyperventilation may be a questionable therapeutic adjunct in many cases. Indeed, the posthyperventilation rebound in CBF might prove dangerous in some clinical settings. Clearly, more laboratory work with impaired animals must be conducted to determine whether hyperventilation actually improves survival.

References


Key Words • cerebral blood flow • cerebral metabolism • hyperventilation • CO\(_2\) • CSF
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Stroke. 1987;18:649-655
doi: 10.1161/01.STR.18.3.649

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1987 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

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