Regional cerebrovascular and metabolic effects of hyperventilation after severe traumatic brain injury

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Object. Recently, concern has been raised that hyperventilation following severe traumatic brain injury (TBI) could lead to cerebral ischemia. In acute ischemic stroke, in which the baseline metabolic rate is normal, reduction in cerebral blood flow (CBF) below a threshold of 18 to 20 ml/100 g/min is associated with energy failure. In severe TBI, however, the metabolic rate of cerebral oxygen (CMRO₂) is low. The authors previously reported that moderate hyperventilation lowered global hemispheric CBF to 25 ml/100 g/min but did not alter CMRO₂. In the present study they sought to determine if hyperventilation lowers CBF below the ischemic threshold of 18 to 20 ml/100 g/min in any brain region and if those reductions cause energy failure (defined as a fall in CMRO₂).

Methods. Two groups of patients were studied. The moderate hyperventilation group (nine patients) underwent hyperventilation to PaCO₂ of 30 ± 2 mm Hg early after TBI, regardless of intracranial pressure (ICP). The severe hyperventilation group (four patients) underwent hyperventilation to PaCO₂ of 25 ± 2 mm Hg 1 to 5 days postinjury while ICP was elevated (20–30 mm Hg). The ICP, mean arterial blood pressure, and jugular venous O₂ content were monitored, and cerebral perfusion pressure was maintained at 70 mm Hg or higher by using vasopressors when needed. All data are given as the mean ± standard deviation unless specified otherwise. The moderate hyperventilation group was studied 11.2 ± 1.6 hours (range 8–14 hours) postinjury, the admission Glasgow Coma Scale (GCS) score was 5.6 ± 1.8, the mean age was 27 ± 9 years, and eight of the nine patients were men. In the severe hyperventilation group, the admission GCS score was 4.3 ± 1.5, the mean age was 31 ± 6 years, and all patients were men. Positron emission tomography measurements of regional CBF, cerebral blood volume, CMRO₂, and oxygen extraction fraction (OEF) were obtained before and during hyperventilation. In all 13 patients an automated search routine was used to identify 2.1-cm spherical nonoverlapping regions with CBF values below thresholds of 20, 15, and 10 ml/100 g/min during hyperventilation, and the change in CMRO₂ in those regions was determined. In the regions in which CBF was less than 20 ml/100 g/min during hyperventilation, it fell from 26 ± 6.2 to 13.7 ± 1 ml/100 g/min (p < 0.0001), OEF rose from 0.31 to 0.59 (p < 0.0001), and CMRO₂ was unchanged (1.14 ± 0.23 compared with 0.97 ± 0.23 ml/100 g/min; p = 0.8). In the regions in which CBF was less than 15 ml/100 g/min during hyperventilation, it fell from 23.3 ± 6.6 to 11.1 ± 1.2 ml/100 g/min (p < 0.0001), OEF rose from 0.31 to 0.63 (p < 0.0001), and CMRO₂ was unchanged (0.98 ± 0.19 compared with 0.97 ± 0.23 ml/100 g/min; p = 0.92). In the regions in which CBF was less than 10 ml/100 g/min during hyperventilation, it fell from 18.2 ± 4.5 to 8.1 ± 0 ml/100 g/min (p < 0.0001), OEF rose from 0.3 to 0.71 (p < 0.0001), and CMRO₂ was unchanged (0.78 ± 0.26 compared with 0.84 ± 0.32 ml/100 g/min; p = 0.64).

Conclusions. After severe TBI, brief hyperventilation produced large reductions in CBF but not energy failure, even in regions in which CBF fell below the threshold for energy failure defined in acute ischemia. Oxygen metabolism was preserved due to the low baseline metabolic rate and compensatory increases in OEF; thus, these reductions in CBF are unlikely to cause further brain injury.

Key Words • cerebral blood flow • positron emission tomography • hyperventilation • brain injury

The role of hyperventilation in the management of severe TBI is currently being reexamined. Hyperventilation transiently lowers ICP; however, it may do so at an unacceptable cost. Because hyperventilation reduces CBF, it could produce or exacerbate cerebral ischemia. Reports of reductions in CBF after severe TBI in the absence of hyperventilation act to magnify these concerns further. Measurement of CBF alone is not sufficient to assess the impact of hyperventilation on brain tissue because it does not take brain metabolism into account. Hyperventilation produces vasodilatation, which leads to a fall in CBF and CBV. The fall in CBF reduces O₂ delivery to cerebral tissues and the brain compensates by increasing OEF so that the amount of substrate available to neurons and glia is maintained. If the amount of O₂ that reaches the tissue remains adequate to meet metabolic needs, the CMRO₂ does not take brain metabolism into account. Hyperventilation produces vasodilatation, which leads to a fall in CBF and CBV. The fall in CBF reduces O₂ delivery to cerebral tissues and the brain compensates by increasing OEF so that the amount of substrate available to neurons and glia is maintained. If the amount of O₂ that reaches the tissue remains adequate to meet metabolic needs, the CMRO₂ does.
not change. Thus, the metabolic impact of hyperventilation depends on the initial CMRO$_2$, the fall in CBF, and the compensatory increase in OEF. When the baseline CMRO$_2$ is normal, the threshold for energy failure is reached when CBF falls below 20 ml/100 g/min.\textsuperscript{12} When the baseline metabolism is reduced, however, this threshold does not apply.\textsuperscript{14} The CBF threshold for energy failure after TBI is unknown.

The magnitude of reduction in CBF parallels the degree of hyperventilation. Thus, despite the initially low CMRO$_2$ in TBI,\textsuperscript{9,22} extreme hyperventilation may still reduce CBF to the point at which increased O$_2$ extraction can no longer compensate for reduced delivery and metabolic needs are no longer met. At this point energy production begins to fail and there is potential for tissue injury.

We previously reported that baseline global CMRO$_2$ was low (1.59 ± 0.44 ml/100 g/min) in patients with acute TBI, and that moderate hyperventilation to a PaCO$_2$ of 30 mm Hg lowered global CBF to 25.5 ± 8.7 ml/100 g/min, but did not alter global CMRO$_2$.\textsuperscript{6} suggesting that moderate hyperventilation is well tolerated by the brain. Concern persists, however, that there may be focal regions within the brain with even lower CBF that may be adversely affected by hyperventilation. Such regional variations in response to changes in CO$_2$ has been reported in head injury.\textsuperscript{15} In our previous study we did not address whether brain regions would be vulnerable under the extreme conditions of more severe hyperventilation when ICP is elevated.

The goal of the present study was to determine if there were regional reductions in CBF to less than 20 ml/100 g/min during hyperventilation and if these reductions were sufficient to result in a fall in CMRO$_2$, thus indicating that CBF fell below levels sufficient to meet metabolic needs. We measured regional CBF, CMRO$_2$, CBV, OEF, and jugular AVDO$_2$ in two groups of patients. The moderate hyperventilation group (nine patients) was studied during hyperventilation to a PaCO$_2$ of 30 ± 2 mm Hg less than 24 hours after TBI, regardless of ICP. The severe hyperventilation group (four patients) underwent hyperventilation to a PaCO$_2$ of 25 ± 2 mm Hg 1 to 5 days postinjury while ICP was elevated (20–30 mm Hg).

Clinical Material and Methods

Patient Population

In the moderate hyperventilation group, nine patients were studied an average of 11.2 ± 1.6 hours posttrauma. Eight were men and one was a woman; three were African American and six were caucasian. The mean age was 27 ± 9 years (range 18–42 years), and the median admission GCS score was 6, with a range of 3 to 8. One patient experienced prehospital hypotension and hypoxia before admission, three received mannitol in the emergency department, and none underwent hyperventilation. In one patient a subdural hematoma was evacuated before PET scanning. No patient in this subgroup had significant extracerebral injuries. Admission CT scans were classified according to the criteria of Marshall, et al.,\textsuperscript{17} as follows: diffuse Type 1 (one patient), diffuse Type 2 (three patients), diffuse Type 3 (three patients), diffuse Type 4 (one patient), and nonevacuated mass lesion (one patient).

The severe hyperventilation group consisted of four patients studied 76 ± 47 hours posttrauma. All were men; two were African American and two were caucasian. The mean age was 31 ± 6 years (range 24–38 years). The median admission GCS score was 5, with a range of 3 to 8. One patient with hypotension was identified in the emergency department and none underwent hyperventilation. Admission CT scans were classified according to Marshall, et al.,\textsuperscript{17} as follows: diffuse Type 2 (two patients), diffuse Type 3 (one patient), and nonevacuated mass lesion (one patient).

Patient Selection and Initial Stabilization

Patients were eligible for inclusion in this study if they had suffered a nonpenetrating head injury, had a GCS\textsuperscript{27} score of less than 9, were at least 18 years old, and were clinically stable. Pregnant patients were excluded. The group of patients treated with moderate hyperventilation was studied within 24 hours of injury and underwent hyperventilation to a PaCO$_2$ of 30 ± 2 mm Hg regardless of ICP. Patients with TBI were enrolled in the severe hyperventilation group up to 7 days postinjury only if their ICP was 20 to 30 mm Hg at the time of the PET study; they underwent hyperventilation to a PaCO$_2$ of 25 ± 2 mm Hg. Their age, race, sex, time of injury, presence of preadmission hypoxia or hypotension, and use of illegal drugs were recorded. The patients’ CT scans were classified according to the criteria of Marshall, et al.,\textsuperscript{17} by researchers who were blinded to the physiological, clinical, and PET data. The Human Studies Committee of Washington University approved the protocol. Global CBF and metabolic data from the first group were included in a previous report.\textsuperscript{9}

All patients were evaluated in the Emergency Department by physicians from the Neurosurgery and Trauma services and underwent standard resuscitation and trauma management procedures, including volume replacement and early intubation before CT scanning. Midazolam and/or etomidate were used as premedication for endotracheal intubation. A GCS score was obtained following stabilization. If elevated ICP was suspected, mannitol (1–1.5 g/kg) was administered. No patients received hyperventilation at this time.

After the initial screening and stabilization, patients were transferred immediately to the Neurology/Neurosurgery Intensive Care Unit and an ICP monitor (Camino implantable transducer; Integra LifeSciences, Plainsboro, NJ) and arterial catheter were inserted. After determining that ICP was below 25 mm Hg, ventilation was adjusted to ensure that PaCO$_2$ was 40 ± 4 mm Hg at least 30 minutes before the PET studies. Patients who later developed elevated ICP were treated with osmotic therapy (but not with hyperventilation) and were eligible for inclusion in the severe hyperventilation group. The CPP was maintained at greater than 70 mm Hg or higher with ICP control, volume replacement, and vasopressor agents (phénylphrine), if necessary. Jugular bulb catheters were placed on the side of the greatest CT scan abnormalities, or on the right side if no focal or symmetrical bilateral abnormalities were present. Positioning was confirmed using a lateral skull x-ray study.

Packed red blood cells were transfused if the hematocrit was below 25 to 30%. Coagulopathies were corrected with vitamin K, fresh-frozen plasma, or platelets as needed if the prothrombin time was more than 14 seconds or the platelet count was less than 100,000. Active hypothermia was not
Regional effects of hyperventilation in severe traumatic brain injury

used. A loading dose of 15 mg/kg of phenytoin was administered intravenously.

Positive Emission Tomography Studies

All patients were studied using a PET scanner (Siemens/CTI ECAT EXACT HR 47; Siemens, Erlangen, Germany) located in the Neurology/Neurosurgery Intensive Care Unit. Each scan was acquired in the two-dimensional mode, and images were reconstructed with filtered back-projection by using measured attenuation and scatter correction to a resolution of 4.3 mm full width at half maximum. The PET scanner was calibrated for conversion of PET counts to quantitative radiotracer concentrations as previously described. 22 Arterial blood was sampled and the arterial time–radioactivity curve was determined using a scintillation counter.

A neurocritical care physician was present in the room throughout the study to monitor and treat patients. During the PET study every effort was made to maintain a constant physiological state; CPP was continuously monitored and maintained at 70 mm Hg or higher by using vasopressor agents (phenylephrine) when necessary. If sedation was required, only fentanyl was used so as not to interfere with measurements of CBF or CMRO 2 .

The CBF was measured using an adaptation of the Kety autoradiographic method with bolus injection of 15 O-labeled water. 13,19 Regional CBV was measured using a brief inhalation of 15 O-labeled carbon monoxide. 13,19 Regional CMRO 2 , regional OEF, and regional CvO 2 were calculated using the CBF and CBV measurements and inhalation of 15 O-labeled O 2 . 21,30 Simultaneous arterial and jugular venous blood samples were collected at the conclusion of the 15 O PET study. Jugular bulb samples were drawn slowly (2 ml/minute) to avoid extracerebral contamination. The O 2 content was measured using a co-oximeter (Instrument Laboratories, Lexington, MA), and AVDO 2 was calculated as the difference between arterial and jugular venous O 2 contents (CaO 2 – CvO 2 ).

At the time of each PET study additional data were collected, including MABP, ICP, arterial blood gas, GCS score, and body temperature. The CPP was calculated as the difference between the MABP and ICP. The CvO 2 was calculated as the CaO 2 × (1 – OEF).

After collection of baseline clinical, physiological, and PET data, the PaCO 2 was reduced to 30 ± 2 mm Hg (moderate hyperventilation group) or 25 ± 2 mm Hg (severe hyperventilation group) by increasing the respiratory rate. Expired CO 2 was continually monitored with an in-line end-tidal CO 2 monitor (Hewlett Packard Co., Palo Alto, CA), and confirmation that the target PaCO 2 had been reached was obtained with an arterial blood gas measurement. Once the PaCO 2 had been stable at the target for 10 minutes, 21 a second set of clinical, physiological, and PET data were collected. After completion of the second PET study, the ventilator was returned to its original settings and any elevations in ICP were treated with mannitol.

Regional Analysis of PET Images

Each patient’s PET images were aligned to one another by using Automated Image Registration software (supplied by Roger Woods, University of California at Los Angeles, California). An image mask was created that comprised the brain above the cavernous sinus, below the superior sagittal sinus, and excluded large vessels visible in the CBV image. An automated search routine was used to locate non-overlapping 2.14-cm-diameter spherical regions with the lowest CBF during hyperventilation. Based on our previous experience, 10 we chose this size region of interest to provide the best balance between spatial resolution and adequate regional PET counts to obtain accurate measurements. The CBF was calculated from the mean PET counts in the sphere. The region with the lowest CBF was identified first, the next lowest CBF second, and so on. Overlap was prevented by restricting the center of all subsequent regions to locations at least one diameter from the center of all previously identified regions.

For each patient, regional hemodynamic and metabolic values on all PET images were computed 26 for the regions of low CBF identified during hyperventilation. In all cases, calculations were performed using the mean PET counts within the sphere. Regions were then sorted on the basis of the CBF values during hyperventilation into those with CBFs of less than 20, less than 15, and less than 10 ml/min/100g. The mean hemodynamic and metabolic values for all regions in which CBF was below these thresholds during hyperventilation were determined for each patient. Thus, for each of the three threshold values of CBF during hyperventilation, each individual had a single averaged value for all regions that met these criteria for each of the PET measurements (CBF, CBV, OEF, and CMRO 2 ) both before and during hyperventilation.

Data Analysis

Changes in hemodynamic and metabolic measurements before and after hyperventilation were compared using paired t-tests. A probability value of less than 0.05 was required for statistical significance. All continuous data are presented as the mean ± standard deviation. The CBF and CMRO 2 are presented as milliliters per 100 grams per minute, and CBV as milliliters per 100 grams.

Results

The results of the arterial and jugular bulb blood gas measurements before and during hyperventilation are presented in Fig. 1. In both groups PaCO 2 fell to the target level, and this was associated with a widening of the AVDO 2 and a fall in the CvO 2 . The GCS score, temperature, and hemodynamic, global cerebrovascular, and metabolic effects of hyperventilation are presented in Table 1.

The results of the regional analysis combined for both groups are presented in Fig. 2. During hyperventilation there was an average of 26.1 ± 21.2 regions per patient in which CBF was less than 20 ml/min/100g/min, 16.1 ± 16.3 regions per patient in which CBF was less than 15 ml/min/100g/min, and 5.9 ± 6.4 regions per patient in which CBF was less than 10 ml/min/100g/min. In all regions, as well as in regions where CBF was less than 20, 15, or 10 ml/min/100g/min during hyperventilation, CBF fell, OEF rose, and CMRO 2 did not change in regions where CBF was less than 20 (0.99 ± 0.12 compared with 1.1 ± 0.2 ml/min/100g/min), less than 15 (0.91 ± 0.19 compared with 0.97 ± 0.23 ml/min/100g/min), and less than 10 (0.90 ± 0.20 compared with 0.89 ± 0.21 ml/min/100g/min) during hyperventilation.
A recent study by M. N. Diringer et al. reported that global CMRO₂ did not change after hyperventilation to a PaCO₂ of 30 mm Hg in patients with severe TBI studied within 14 hours of injury. However, in the present study, we sought to assess the effects of more aggressive hyperventilation performed when ICP was elevated, and to determine if hyperventilation leads to regional changes in CBF that are severe enough to impair energy metabolism. We found that even with severe hyperventilation, CMRO₂ remained stable in all brain regions, including those where CBF fell to less than 10 ml/100 g/min.

Limited data indicate that global CMRO₂ is reduced and O₂ extraction is low in the first few hours after severe TBI. Typical CBF levels below approximately 20 ml/100 g/min are thought to represent ischemia severe enough to lead to neuronal death. This definition, however, assumes that the baseline metabolic rate is normal. When the metabolism is suppressed by another process, such as the administration of barbiturates, the CBF is lowered because of reduced metabolic demand and must fall even lower before O₂ delivery becomes inadequate to meet the low metabolic needs of the tissue.

**Discussion**

We recently reported that global CMRO₂ did not change after hyperventilation to a PaCO₂ of 30 mm Hg in patients with severe TBI studied within 14 hours of injury. In the present study, we sought to assess the effects of more aggressive hyperventilation performed when ICP was elevated, and to determine if hyperventilation leads to regional changes in CBF that are severe enough to impair energy metabolism. We found that even with severe hyperventilation, CMRO₂ remained stable in all brain regions, including those where CBF fell to less than 10 ml/100 g/min.

In the first few hours after severe TBI, the CBF is reduced in some patients. Typically, CBF levels below approximately 20 ml/100 g/min are thought to represent ischemia severe enough to lead to neuronal death. This definition, however, assumes that the baseline metabolic rate is normal. When the metabolism is suppressed by another process, such as the administration of barbiturates, the CBF is lowered because of reduced metabolic demand and must fall even lower before O₂ delivery becomes inadequate to meet the low metabolic needs of the tissue.

**Table 1**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Moderate HV Group</th>
<th>Severe HV Group</th>
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</thead>
<tbody>
<tr>
<td>ICP (mm Hg)</td>
<td>Baseline</td>
<td>During HV</td>
</tr>
<tr>
<td>14 ± 8</td>
<td>12 ± 8</td>
<td>24 ± 4</td>
</tr>
<tr>
<td>MABP (mm Hg)</td>
<td>95 ± 14</td>
<td>91 ± 14</td>
</tr>
<tr>
<td>CPP (mm Hg)</td>
<td>81 ± 11</td>
<td>79 ± 9</td>
</tr>
<tr>
<td>median GCS score (range)</td>
<td>5.0 (3–8)</td>
<td>4.5 (3–7)</td>
</tr>
<tr>
<td>temperature (°C)</td>
<td>37.7 ± 0.8</td>
<td>37.7 ± 1.0</td>
</tr>
<tr>
<td>global CBF (ml/100 g/min)</td>
<td>38.0 ± 12.9</td>
<td>25.4 ± 8.2†</td>
</tr>
<tr>
<td>global OEF</td>
<td>0.31 ± 0.06</td>
<td>0.45 ± 0.12†</td>
</tr>
<tr>
<td>global CMRO₂ (ml/100 g/min)</td>
<td>1.6 ± 0.4</td>
<td>1.5 ± 0.5</td>
</tr>
<tr>
<td>global CBV (ml/100 g)</td>
<td>3.1 ± 0.5</td>
<td>2.8 ± 0.5†</td>
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</tbody>
</table>

* Unless otherwise noted, values are given as the mean ± standard deviation. Abbreviation: HV = hyperventilation.
† p < 0.0001 at baseline compared with during HV.
values that we observed may be a primary reduction in CMRO₂ with a secondary passive fall in CBF; our findings of low CMRO₂ prior to hyperventilation are consistent with this hypothesis.

This observation has important implications for interpreting the effects of hyperventilation. It is well known that CBF falls and O₂ extraction rises during hyperventilation.20,28 When metabolic demands are low, however, even a CBF as low as 10 ml/100 g/min might be adequate to meet that demand. We applied progressively lower CBF thresholds to selected brain regions in order to determine if there was a level of CBF during hyperventilation that was associated with reduced CMRO₂. We found that even when CBF fell to less than 10 ml/100 g/min during hyperventilation, O₂ metabolism was preserved.

We studied hyperventilation under two clinical conditions. In the moderate hyperventilation group we assessed the empirical use of hyperventilation to a PaCO₂ of 30 ± 2 mm Hg 8 to 14 hours postinjury. We initially chose to study a moderate degree of hyperventilation because of concerns about patient safety. Once we established that there was no regional impact on CMRO₂, more aggressive hyperventilation was used, to a PaCO₂ of 25 mm Hg during conditions of elevated ICP. The desire to study patients with elevated ICP required a shift from assessment of patients as soon as possible after injury to their assessment during the period when they had intracranial hypertension. We believed it would be more useful to study hyperventilation under the conditions in which it is more likely to be administered.

Our data and those of others.19,20 indicate that CMRO₂ is low after TBI; however, the mechanisms responsible for what appears to be a primary reduction in CMRO₂ after TBI are unknown. One possible explanation for this finding is that the brain is unable to use O₂, effectively after TBI. Recent data indicate that brain mitochondria are unable to use O₂ efficiently after TBI, which could lead to a shift from aerobic to anaerobic metabolism. Increased glucose metabolism has been reported following head injury,3 and in vitro studies of specimens obtained from the brains of patients with TBI support this hypothesis.18

The main limitation of this study is the relatively small number of patients included. Thus, the generalizability of the findings may be limited. The tests are extremely complex to perform and require availability of many highly trained individuals. In addition, to assess patients during elevated ICP the baseline studies must be performed rapidly and with extreme caution to avoid further rises in ICP that could potentially adversely affect the patient. Both of these factors served to limit enrollment. Finally, few patients had large contusions or mass lesions; therefore further studies are needed in these subgroups of patients with TBI.

Conclusions

In patients with severe TBI, we found no evidence that early moderate hyperventilation to a PaCO₂ of 30 mm Hg or hyperventilation to 25 mm Hg during periods of elevated ICP produced global or regional cerebral ischemia. This finding was robust: even in regions where CBF during hyperventilation fell below the CBF threshold for energy failure defined during acute ischemia, there was no reduction in cerebral metabolism. This indicates that there was no critical limitation of O₂ availability in the tissues. Although these data indicate that transient hyperventilation may be safe, they do not necessarily mean that it is beneficial.

References