No reduction in cerebral metabolism as a result of early moderate hyperventilation following severe traumatic brain injury

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Object. Hyperventilation has been used for many years in the management of patients with traumatic brain injury (TBI). Concern has been raised that hyperventilation could lead to cerebral ischemia; these concerns have been magnified by reports of reduced cerebral blood flow (CBF) early after severe TBI. The authors tested the hypothesis that moderate hyperventilation induced early after TBI would not produce a reduction in CBF severe enough to cause cerebral energy failure (CBF that is insufficient to meet metabolic needs).

Methods: Nine patients were studied a mean of 11.2 ± 1.6 hours (range 8–14 hours) after TBI occurred. The patients’ mean Glasgow Coma Scale score was 5.6 ± 1.8 and their mean age 27 ± 9 years; eight of the patients were male. Intracranial pressure (ICP), mean arterial blood pressure, and jugular venous oxygen content were monitored and cerebral perfusion pressure was maintained at a level higher than 70 mm Hg by using vasopressors when needed. Measurements of CBF, cerebral blood volume (CBV), cerebral metabolic rate for oxygen (CMRO2), oxygen extraction fraction (OEF), and cerebral venous oxygen content (CvO2) were made before and after 30 minutes of hyperventilation to a PaCO2 of 30 ± 2 mm Hg. Ten age-matched healthy volunteers were used as normocapnic controls.

Global CBF, CBV, and CvO2 did not differ between the two groups, but in the TBI patients CMRO2 and OEF were reduced (1.59 ± 0.44 ml/100 g/minute [p < 0.01] and 0.31 ± 0.06 [p < 0.0001], respectively). During hyperventilation, global CBF decreased to 25.5 ± 8.7 ml/100 g/minute (p < 0.0009), CBV fell to 2.8 ± 0.56 ml/100 g (p < 0.001), OEF rose to 0.45 ± 0.13 (p < 0.02), and CvO2 fell to 8.3 ± 3 vol% (p < 0.02); CMRO2 remained unchanged.

Conclusions. The authors conclude that early, brief, moderate hyperventilation does not impair global cerebral metabolism in patients with severe TBI and, thus, is unlikely to cause further neurological injury. Additional studies are needed to assess focal changes, the effects of more severe hyperventilation, and the effects of hyperventilation in the setting of increased ICP.

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

For many years the induction of aggressive hyperventilation has been a cornerstone in the management of patients with severe TBI. In a survey of 277 medical centers specializing in brain trauma, 83% used hyperventilation for the treatment of intracranial hypertension in the majority of patients.9 Recently, concern has been raised that hyperventilation, because it reduces CBF, could produce or exacerbate cerebral ischemia. This concern has been magnified by reports of reduced CBF during the first several hours following severe TBI.6,12 Additionally, the results of a prospective randomized controlled study suggested that outcome was improved when prophylactic hyperventilation was not used.10 The authors of recently developed head injury guidelines recommended that prophylactic mild hyperventilation should be avoided during the first 24 hours after TBI because of the risk of inducing ischemia.13 The guidelines also called for additional clinical trials to determine whether short-term hyperventilation during the first 24 hours after injury is deleterious.

It is important to recognize that measurement of CBF alone is not adequate to determine whether hyperventilation is deleterious. Under normal circumstances, hyperventilation produces a moderate reduction in PaCO2 via constriction of cerebral arterioles with a subsequent fall in
CBV. However, due to increased O₂ extraction, sufficient amounts of substrate still reach neurons and glia to meet their metabolic needs. Thus, because O₂ supply is still adequate, CMRO₂ remains normal. During extreme hyperventilation, however, CBF may fall to the point at which increased O₂ extraction can no longer compensate and substrate delivery is no longer adequate to meet metabolic needs. It is at this point that there is potential for tissue injury. Thus to assess whether hyperventilation leads to cerebral injury, its impact on CBF must be interpreted in relation to changes in OEF and CMRO₂.

Studies of hyperventilation during the first 24 hours after severe TBI have been limited and have not assessed its impact on cerebral metabolism. Given the potential for severe hyperventilation to produce cerebral injury, we chose first to study the impact of a moderate degree of hyperventilation on cerebral metabolism. We tested the hypothesis that moderate hyperventilation would not produce a reduction in CBF potentially severe enough to cause cerebral energy failure (defined as CBF that is insufficient to meet metabolic needs) during the first 24 hours following severe TBI (GCS² score < 9). To do so we measured CBF, CMRO₂, OEF, and AVDO₂ before and after induction of hyperventilation to a PaCO₂ of 30 mm Hg in patients within 24 hours of severe TBI.

Clinical Material and Methods

Patient Selection and Initial Stabilization

Patients were eligible for inclusion in the study if they suffered nonpenetrating head injury, had a GCS score less than 9, were at least 18 years of age, were clinically stable, and could be studied within 24 hours after injury. Pregnant patients were excluded. Age, race, gender, time of injury, presence of prehospitalization hypoxia or hypotension, and use of illicit drugs were recorded. Computerized tomography scans were classified according to the criteria set forth by Marshall, et al. by researchers blinded to physiological, clinical, and PET data. The Human Studies Committee of Washington University approved the study.

All patients were evaluated in the emergency department by neurosurgery and trauma clinicians 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(s) for endotracheal intubation. The patient’s GCS score was obtained following stabilization. If elevated ICP was suspected, mannitol (1–1.5 g/kg) was administered. Hyperventilation was not induced in any patient at this point.

Following initial screening and stabilization, patients were transferred immediately to the NNICU where an ICP monitor (Camino implantable transducer; Camino NeuroCare, Inc., San Diego, CA) and arterial catheter were placed. After determination was made that ICP was lower than 25 mm Hg, ventilation was adjusted to assure that PaCO₂ was 40 ± 4 mm Hg at least 30 minutes before the patient underwent PET studies. Cerebral perfusion pressure was maintained at 70 mm Hg or higher by ICP control, volume replacement, and, if necessary, administration of vasopressors (phenylephrine). Jugular bulb catheters were placed on the side on which the largest abnormalities could be observed using CT scanning, or on the right side if no focal or symmetrical bilateral abnormalities were present. Position was confirmed using lateral skull x-ray films. If additional sedation was required, only fentanyl was used so as not to interfere with measurements of CBF or CMRO₂.

Packed red blood cells were transfused if the patient’s hematocrit level 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/mm³. Active hypothermia was not used. A loading dose of 15 mg/kg of phentoyin was administered intravenously.

Positron Emission Tomography Studies

All patients and healthy volunteers were studied using a PET scanner¹¹ (ECAT EXACT HR 47; Siemens/CTI, Knoxville, TN) located in the NNICU. Each scan was acquired in the two-dimensional mode and images were reconstructed with filtered back projection by using measured attenuation and scatter correction. The PET scanner was calibrated for conversion of PET counts to quantitative radionuclide concentrations, as previously described.¹⁸,²³ 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. Cerebral perfusion pressure was continuously monitored and maintained at 70 mm Hg or higher by using vasopressor agents (phenylephrine) when necessary. Fentanyl was administered to provide any additional sedation necessary during the PET study.

Cerebral blood flow was measured using an adaptation of the Kety autoradiographic method by using a bolus injection of ¹⁵O-labeled water.¹²,²⁵,³⁰ Cerebral blood volume was measured from a brief inhalation of ¹⁵O-labeled CO₂.¹⁶ The CMRO₂, OEF, and cerebral CvO₂ were calculated using the CBF and CBV measurements and inhalation of ¹⁵O-labeled O₂.¹⁶,¹⁹,²⁷,³⁰ Simultaneous arterial and jugular venous samples were collected at the conclusion of the PET O₁⁵O₂ study. Jugular bulb samples were drawn slowly (2 ml/minute) to avoid extracerebral contamination. Oxygen content was measured using a cooximeter (Instrument Laboratories, Lexington, MA) and AVDO₂ was calculated as the difference between arterial and venous O₂ contents (CaO₂ – CvO₂).

At the time of each PET study, additional data were collected including MABP, ICP, arterial blood gas levels, GCS score, and body temperature. The CPP was calculated as the difference between the MABP and ICP.

Following collection of baseline clinical, physiological, and PET data, the ventilator was adjusted to reduce PaCO₂ to 30 ± 2 mm Hg by increasing the ventilator rate without any change in tidal volume. Expired CO₂ was continually monitored using an in-line end-tidal CO₂ monitor (Hewlett–Packard Co., Palo Alto, CA), and confirmation that the target PaCO₂ had been reached was obtained with arterial blood gas level measurement. Once the PaCO₂ had been stable at the target level for 10 minutes,³² a second set

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**Table 1**

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<th>Case No.</th>
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<th>Mannitol in ED</th>
<th>HV Before PET</th>
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<td>no</td>
<td>nonevac mass</td>
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</table>

* Diffuse type 1 = no visible pathological entity; diffuse type 2 = cisterns present, shift 0 to 5 mm, and/or lesion densities present; diffuse type 3 = cistern compressed or absent and no high-density lesions larger than 25 ml; diffuse type 4 = shift greater than 5 mm and no high-density lesions larger than 25 ml; ED = emergency department; HV = hyperventilation; nonevac = high-density lesion larger than 25 ml, not surgically evacuated; post-hosp = posthospitalization; prehosp = prehospitalization.

**Results**

Nine patients were studied an average of 11.2 ± 1.6 hours after trauma occurred (Table 1). The average GCS score was 5.6 ± 1.8. Eight patients were male and one was female; three patients were African American and six were Caucasian. The average age was 27 ± 9 years (range 18–42 years). One patient experienced prehospitalization hypotension and hypoxia and three received mannitol while in the emergency department; however, none underwent induced hyperventilation. A subdural hematoma was evacuated in one patient before the PET scan was obtained. None had significant extracerebral injuries. The healthy volunteers were an average age of 31 ± 8 years (range 19–39 years); three were female and seven were male; six were African American, three Caucasian, and one Asian American. In two patients only the CBF and CBV studies were usable because of technical reasons.

On the initial PET study, patients with TBI on average had an MABP of 95 ± 14 mm Hg, an ICP of 14 ± 8 mm Hg, a CPP of 81 ± 11 mm Hg (two patients were supported with phenylephrine), and a PaCO₂ of 38 ± 4 mm Hg (Table 2). The patients’ mean temperature was 37.8 ± 0.8°C. The CaO₂ was 14.6 ± 2.57 vol%, the CvO₂ in the jugular bulb samples was 12 ± 2 vol%, and the AVDO₂ was 3.04 ± 1.6 vol%. The patients with TBI had the following mean global values: CBF 38.4 ± 13.6 ml/100 g/minute, CBV 3.06 ± 0.57 ml/100 g, CMRO₂ 1.59 ± 0.44 ml/100 g/minute, OEF 0.31 ± 0.06, and CvO₂ 10.3 ± 2.6 vol% (Fig. 1).

In the control group CBF, CBV, and CvO₂ values did not differ from those of the TBI patients; however, OEF and CMRO₂ values were significantly higher (0.41 ± 0.06 and 2.85 ± 0.32 ml/100 g/minute, respectively; Fig. 1).

After 30 to 45 minutes of hyperventilation, arterial and jugular venous values changed as follows: PaCO₂ fell by 10.1 to 29.1 ± 1.3 mm Hg; AVDO₂ rose to 5.5 ± 2.1 vol%; CvO₂ fell to 9.6 ± 1.9 vol%. The CaO₂ was un-

**Table 2**

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<th>Case No.</th>
<th>Interval (hrs)</th>
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<th>ICP (mm Hg)</th>
<th>CPP (mm Hg)</th>
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* SD = standard deviation.
changed (Fig. 2). The second PET study was performed during 30 to 60 minutes of hyperventilation and indicated that CBF fell to 25.5 ± 8.7 ml/100 g/minute; CBV fell to 2.8 ± 0.56 ml/100 g; OEF rose to 0.45 ± 0.13; and CvO2 fell to 8.3 ± 3 vol%. The CMRO2 was unchanged (Fig. 3). The mean GCS score and patient temperature did not change between the two studies. Individual patient changes in OEF and CMRO2 are shown in Fig. 4. Before hyperventilation, there was a very close correlation between CBF and CMRO2 (r = 0.97). The correlation coefficient fell to 0.49 during hyperventilation (Fig. 5). The CvO2 values measured by PET and from jugular bulb samples did not differ.

Discussion

We report the cerebrovascular and metabolic effects of brief, moderate hyperventilation induced within 14 hours of severe TBI. The demographics and CT scan abnormalities in our patients were typical of those in other patients with TBI. Their initial PET studies were notable in that their global CBF did not differ from that of healthy volunteers and cerebral metabolism was suppressed in the setting of reduced O2 extraction. Hyperventilation to a PaCO2 of 30 mm Hg produced a fall in CBF and a rise in OEF, but had no effect on CMRO2, indicating that it had not adversely affected cerebral metabolic function.

Ischemia Following TBI

Ever since the description of ischemic neuronal changes found during postmortem examination of patients who died of severe head injury, further definition of the role of ischemia in TBI has been sought. Although the results of initial studies indicated that CBF was normal, casting doubt on the role of ischemia, investigators in subsequent studies that focused on the first few hours after severe TBI reported low CBF. These findings were interpreted to indicate that ischemia was common in the early hours after TBI and led to reassessment of the role of hyperventilation in the management of TBI. Although addressing the question of the presence of ischemia was not the primary intent of this report, our data provide additional insight into this issue. However, to understand their implications, the approach used to define ischemia must be discussed.

Defining Ischemia by Relationships Among CBF, CMRO2, and OEF

Classically, CBF below approximately 20 ml/100 g/minute is considered to represent ischemia and, if prolonged, leads to neuronal death. The often unstated assumption of this definition is that the metabolic rate is normal. Thus, although this definition may be appropriate in the setting of acute cerebral ischemic stroke or global hypoperfusion, it is not necessarily always valid, for example, in the newborn or following administration of barbiturate medications. Similarly, it may not be valid in cases of TBI.

Although limited in number, measurements obtained using jugular bulb catheters during the first few hours after severe TBI indicate that CMRO2 is low. When coupled with low CBF, low CMRO2 may be a consequence of inadequate supply of substrate, as in ischemia, or be the primary event in head injury with a secondary passive fall in CBF. The key to determining which is the primary event (fall in CBF or fall in CMRO2) is the OEF, which will be high if the primary event is a reduction in CBF and normal or low if the primary event is a reduction in CMRO2. Our findings of low CMRO2 and low OEF support the hypothesis that, in severe TBI, there is a primary reduction in CMRO2 and a secondary fall in CBF, hence not ischemia.

The interpretation of the effects of hyperventilation is somewhat more complex. The normal response to hyperventilation is a reduction in CBF and a rise in OEF, thus it looks like “misery perfusion” (Fig. 6). This pattern is consistently seen in healthy humans, without causing...
permanent injury.26,29 Theoretically, hyperventilation will cause damage when the reduction in CBF is so severe that the increase in OEF can no longer supply the metabolic needs of the tissue, at which point CMRO2 will fall. Our findings of a stable CMRO2 are consistent with those seen in healthy humans26 and do not indicate that this degree of hyperventilation had potential for causing further injury to this group of patients.

Comparison With Previous Studies

At first glance it may be difficult to reconcile our findings with those of previous reports. However, the explanation may be found by exploring the circumstances and timing of the studies. Histological examinations of patients who died following severe TBI reveal that ischemic brain damage is common.10 However, whether the ischemic damage occurred at the time of injury or was a result of secondary reductions in CBF, either spontaneous or iatrogenic, has not been clearly determined. Additionally, because the autopsies were performed in patients who died of their head injuries, there was likely a selection bias toward those patients with devastating terminal injuries. Marion, et al.,14 reported a low mean hemispheric CBF (27 ± 14 ml/100 g/minute) 1 to 4 hours after injury that rose to 44 ± 10 ml/100 g/minute by 5 to 24 hours postinjury. Bouma, et al.,3 reported a similar pattern, with a mean CBF for the first 6 hours postinjury of 22.5 ± 5 ml/100 g/minute and a subsequent rise in CBF peaking 36 to 42 hours postinjury. In ultra-early studies performed 3.1 ± 2.1 hours postinjury, Bouma, et al.,6 found a global or regional CBF lower than 18 ml/100 g/minute in 11 of 35 patients. All these studies focused on patients in whom CBF measurements were obtained closer to the time of injury than the patients in our series; the earliest timeframe in which we studied a patient was 8 hours.

Previous studies of patients with TBI suggested that hyperventilation might produce ischemia. Enevoldsen, et al.,4 noted an increase in the number of oligemic areas (CBF < 20 ml/100 g/minute) that occurred primarily in patients with low global CBF before experiencing hyperventilation. Because cerebral metabolism was not measured in that study, however, it was not possible to determine if the fall in CBF resulted in ischemia. Obrist, et al.,22 identified a subset of TBI patients with a higher CMRO2 and a lower CBF. In that subgroup, severe hyperventila-

tion to PaCO2 of 23 mm Hg produced a fall in CBF, a rise in AVDO2, and a fall in CMRO2, (3.3–1.9 ml/100 g/minute). Unfortunately, these patients were studied under a wide range of clinical conditions up to several days after TBI, and lesser degrees of hyperventilation were not assessed.

In a recent study it was suggested that glucose metabolism is increased after head injury4 and that mitochondrial function may be impaired in patients with TBI. The very close relationship between CBF and CMRO2 that we found does not support the concept that glucose delivery is the limiting factor in brain metabolism in TBI. In addition, had hyperventilation critically reduced glucose delivery to the brain, then the CMRO2, which depends on two-carbon molecules derived from the metabolism of glucose, would have fallen.

Limitations of the Study

The lack of ultra-early studies is the major limitation of
our study. This is due, in large part, to the techniques that were used. Whereas xenon-CT CBF studies can be performed in the emergency department at the time of presentation, PET studies require patient stabilization, placement of arterial and jugular venous lines and ICP monitors, and transportation to the NNICU. This limitation, however, primarily affects our ability to detect ultra-early ischemia. The question of whether hyperventilation induces ischemia becomes more relevant somewhat later after TBI, when increased ICP becomes more of a problem.

A second limitation is the lack of assessment of the regional impact of hyperventilation, especially around areas of contusion or hematoma. This again is due to the complex techniques required to study CMRO₂ by using the PET technique. Calculating regional CMRO₂ requires superimposition of three PET images; CBF, CBV, and OEF.⁶⁻¹⁹ Because these images are collected sequentially, any patient movement will complicate the alignment. Any misalignment can result in artifactual changes in CMRO₂, especially at the edges of the brain where contusions are likely to occur. Furthermore, the statistical quality is less than that in single CBF and CBV images due to the mathematical operations performed when combining the three images. This leads to a greater increase in variability (decreased signal/noise ratio) in the CMRO₂ and OEF images compared with the CBF and CBV images. Although on visual inspection we did not see regions of reduced CMRO₂ that appeared artifactual, we have not yet developed an objective, operator-independent means of performing this analysis. Therefore, at present, we are not confident about regional measurements of CMRO₂ and have chosen only to report global values. With additional work, we hope to develop an objective means of making this assessment.

Conclusions

In patients studied 8 to 14 hours after severe TBI, we found no evidence that moderate hyperventilation to a PaCO₂ of 30 mm Hg produced global cerebral ischemia. Although we can infer from these data that transient moderate hyperventilation may be safe, there is no indication that it is beneficial or that there may not be adverse effects. Further studies will be needed to assess focal changes, more severe hyperventilation, and the its effects on CBF and CMRO₂, in the setting of increased ICP.

References

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