Effect of hyperventilation on regional cerebral blood flow in head-injured children

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Objectives: To study cerebral blood flow and cerebral oxygen consumption in severe head-injured children and also to assess the effect of hyperventilation on regional cerebral blood flow.

Design: Prospective cohort study.

Setting: Pediatric intensive care unit at a tertiary-level university children's hospital.

Patients: Twenty-three children with isolated severe brain injury, whose admission Glasgow Coma Scores were <8.

Interventions: Paco2 was adjusted by altering minute ventilation. Cerebral metabolic measurements were made at three levels of Paco2 (>35, 25 to 35, and <25 torr [>4.7, 3.3 to 4.7, and <3.3 kPa]) after allowing 15 mins for equilibrium.

Measurements and Main Results: Thirty-eight studies (each study consisting of three sets of measurements at different levels of Paco2) were performed on 23 patients. At each level of Paco2, the following measurements were made: xenon-enhanced computed tomography scans; cerebral blood flow; intracranial pressure; jugular venous bulb oxygen saturation; mean arterial pressure; and arterial oxygen saturation. Derived variables included: cerebral oxygen consumption; cerebral perfusion pressure; and oxygen extraction ratio. Cerebral blood flow decreased below normal after head injury (mean 49.6 ± 14.6 mL/min/100 g). Cerebral oxygen consumption decreased out of proportion to the decrease in cerebral blood flow; cerebral oxygen consumption was only a third of the normal range (mean 1.02 ± 0.59 mL/min/100 g). Neither cerebral blood flow nor cerebral oxygen consumption showed any relationship to time after injury, Glasgow Coma Score at the time of presentation, or intracranial pressure. The frequency of one or more regions of ischemia (defined as cerebral blood flow of <18 mL/min/100 g) was 28.9% during normocapnia. This value increased to 73.1% for Paco2 at <25 torr.

Conclusions: Severe head injury in children produced a modest decrease in cerebral blood flow but a much larger decrease in cerebral oxygen consumption. Absolute hyperemia was uncommon at any time, but measured cerebral blood flow rates were still above the metabolic requirements of most children. The clear relationship between the frequency of cerebral ischemia and hypocapnia, combined with the rarity of hyperemia, suggests that hyperventilation should be used with caution and monitored carefully in children with severe head injuries. (Crit Care Med 1997; 25:1402-1409)

Key Words: head injury; hyperventilation; cerebral blood flow; jugular venous oximetry; xenon computed tomography scan; cerebral ischemia
Volume and a consequent increase in intracranial pressure. Their recommendations of early elective hyperventilation and avoidance of mannitol are still widely cited, despite the fact that the recommendations were based on measurements in only six children (12). More recent studies (13, 14) have shown that the cerebral metabolic and vascular responses to head injury in children are less predictable than previously claimed and have also raised concerns about the safety of routine hyperventilation.

Hyperventilation causes cerebral vasoconstriction, probably in response to induced cerebrospinal fluid alkalosis (15). The effect wears off in a few hours, probably due to cerebrospinal fluid buffering (16). Global vasoreactivity is usually preserved, despite serious head injury (17), although regional reactivities may vary widely in a given patient (18). Questions about the risk of inducing cerebral ischemia were raised shortly after hyperventilation was introduced into clinical practice (19). There is some justification for these concerns: the only controlled trial of the therapy showed slower recovery times among the hyperventilated group (20), while other studies (6, 21) demonstrated clinically important regional ischemia during periods of hyperventilation. Consequently, early routine hyperventilation is not currently recommended in the adult literature (22).

In view of the limited pediatric information, our study had two objectives: a) to study the cerebral metabolic and vascular responses to severe head injury in children; and b) to assess the effect of hyperventilation on regional cerebral blood flow rates.

MATERIALS AND METHODS

Patient Population. We studied 23 children admitted to our pediatric intensive care unit with isolated head injuries and a Glasgow Coma Score of 3 or less. Patient characteristics are outlined in Table 1.

The study was approved by the Ethics Committee of the University of British Columbia. Written parental or guardian consent was obtained for all patients.

Patient Management. As far as possible, a standardized management protocol was used for each child. All patients were intubated and mechanically ventilated. Unless otherwise indicated, PaCO₂ was maintained at 35 to 40 torr (4.7 to 5.3 kPa). Intracranial pressure was continuously measured in all children using an intraventricular catheter that was usually inserted at the bedside under sedation and local anesthesia. The patient’s head was positioned carefully to avoid venous compression. Sedation was achieved with infusions of morphine and midazolam. Hyperthermia was treated with a cooling blanket. Paralysis was only used to prevent shivering due to the cooling blanket or for uncontrollable intracranial pressure. Phenytoin was used for seizure control where indicated. Early feeding was instituted via nasogastric tube or nasoduodenal tube. In addition, all patients were monitored with intra-arterial and jugular venous catheters.

If the intracranial pressure remained increased above 15 mm Hg for >5 mins, the intraventricular catheter was opened to drain for 5 mins. Osseous diuretic agents were administered if the pressure remained consistently increased despite free cerebrospinal fluid drainage. Mild hyperventilation was used if the pressure still remained high.

The management of children whose intracranial pressure increased, despite this protocol, was modified to suit the particular patient but generally consisted of the following treatments: a) paralysis and cooling to achieve a core temperature of <35°C; b) cautious hyperventilation aiming to keep the cerebral oxygen extraction ratio at <30%; c) cardiovascular support (23) using fluid boluses and inotropes, aiming to keep cerebral perfusion pressure at >50 mm Hg for patients <12 yrs of age and at >60 mm Hg for patients >12 yrs of age. More aggressive hyperventilation, combined with osmotic therapy and support of cerebral perfusion pressure, was instituted for acute emergencies, such as dilation of a pupil. This intervention was usually followed by an urgent computed tomography (CT) scan. Neither high-dose phenobarbitone therapy nor corticosteroids were used in any child.

Table 1. Patient (pt) characteristics

<table>
<thead>
<tr>
<th>No. of pts studied</th>
<th>23 (12 boys, 11 girls)</th>
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<tr>
<td>Mean age (yr)</td>
<td>11 (range 3 mos to 16 yrs)</td>
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<tr>
<td>Mechanism of injury</td>
<td>19 MVAs, 4 nonaccidental injuries</td>
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<tr>
<td>Postresuscitation GCS&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2 pts (1 bilateral fixed dilated pupils)</td>
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<tr>
<td>GCS 3</td>
<td>11 pts (1 unilateral fixed dilated pupil)</td>
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<tr>
<td>GCS 4</td>
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<tr>
<td>GCS 5</td>
<td>1 pt</td>
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<tr>
<td>GCS 6</td>
<td>7 pts</td>
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<td>GCS 7</td>
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<sup>a</sup> No patients were hypotensive before admission; <sup>b</sup> see Eisenberg et al (37).

Table 2. Outcome of 23 patients at 6 months

<table>
<thead>
<tr>
<th>Admission GCS</th>
<th>Good</th>
<th>Moderate</th>
<th>Severe</th>
<th>Vegetative</th>
<th>Dead</th>
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<tbody>
<tr>
<td>7</td>
<td>-</td>
<td>3</td>
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GCS, Glasgow Coma Score; —, no patients (0).
Study Design. Thirty-eight studies were performed on 23 patients. Eighteen of these studies were made within the first 24 hrs after injury. Each study consisted of a set of three cerebral blood flow studies at different levels of Paco₂. The initial scan was performed at a Paco₂ of 35 to 40 torr (4.7 to 5.3 kPa). Minute ventilation was then increased to produce a stepwise reduction in Paco₂ to 25 to 35 torr (3.3 to 4.7 kPa) and lastly to <25 torr (<3.3 kPa). Ventilator changes were initially monitored by measurement of end-tidal CO₂. At equilibrium, the true Paco₂ was checked by an arterial gas sample. Fifteen-minute equilibration periods were allowed after ventilator changes. At each level of Paco₂, measurements were made of cerebral blood flow, intracranial pressure, jugular venous bulb oxygen saturation, mean arterial pressure, and arterial oxygen saturation. Some patients were not stable enough to allow a full set of three cerebral blood flow studies. A final total of 96 measurements was made.

Cerebral Blood Flow Measurements. Global and regional cerebral blood flows were measured by xenon-enhanced CT (24). After a baseline cranial CT study, three 5-mm axial images were chosen to maximize the sampling of the brain stem, cerebellum, basal ganglia, cortex, and any injured brain. A mixture of 28% xenon, 30% to 50% oxygen and nitrogen was administered over 3.5 mins using a gas delivery system and measurement console (Anzai, Yokogawa Electric Corporation, Tokyo, Japan). The first image was obtained 30 secs after starting gas inhalation. Further scans were performed each minute, for a total of 5 mins, to obtain images at the washin, plateau and washout phases of the study. The initial axial levels chosen were used for all repeat measurements. All patients were paralyzed and sedated throughout the study. All changes in Paco₂ were stepwise reductions.

Measurements of Arterial-Jugular Venous Oxygen Content Difference-Cerebral Metabolic Rate of Oxygen Consumption. Each child was monitored with an indwelling jugular venous bulb catheter inserted via a retrograde approach so that the tip was in the jugular bulb. The position was confirmed by a lateral cervical radiograph (25). There was no routine for selecting the side of catheter insertion. During measurement of cerebral blood flow, arterial and jugular venous bulb blood samples were drawn and sent to the laboratory for determination of oxygen saturation (by cooximeter) and oxygen partial pressure. The cross-brain arterial venous oxygen content difference (C(a-j)O₂, mL/100 mL) was calculated from Equation 2 (Appendix). The cerebral metabolic rate for oxygen (CMRO₂, mL/min/100 g) was then calculated from simultaneous measurements of C(a-j)O₂ and cerebral blood flow using Equation 1 (Appendix).

Other Calculated Variables. Cerebral perfusion pressure, CO₂ vasoactivity, and cerebral oxygen extraction ratio were also derived. Cerebral perfusion pressure was calculated as the difference between mean arterial pressure and intracranial pressure (Eq. 3, Appendix). CO₂ vasoactivity expresses the percentage change in cerebral blood flow per torr change in Paco₂ and was calculated using Equation 4 (Appendix).

The cerebral oxygen extraction ratio is calculated from Equation 5 (Appendix).

Choice of Normal Values. The interpretation of measured values depends on their comparison with accepted normal ranges. Unfortunately, the available information is limited and difficult to interpret. For instance, values cited for normal cerebral blood flow range from 106.4 ± 9.9 mL/min/100 g in un sedated children (26) to 31 mL/min/100 g in un sedated premature-born infants (27). We used data from Settgren et al. (28) for the normal values, which were based on the only large study of cerebral metabolism in anesthetized children (cerebral blood flow of 65.0 ± 16.2 mL/min/100 g, C(a-j)O₂ of 4.86 ± 1.61 mL/min/100 g, and CMRO₂ of 3.02 ± 1.0 mL/min/100 g). These values compare well with the normal values in the original work by Kety and Schmidt (29) on un sedated adults, and have also been used as the basis of comparison for two large studies (14, 30) of head-injured children.

Defining the lowest acceptable limit of cerebral blood flow is also difficult. It has been shown that regional cerebral flows of 8 to 16 mL/min/100 g are associated with loss of cellular function and absence of synaptic transmission (31). Cold (21) defined cerebral oligemia as a regional cerebral blood flow of 15 to 20 mL/min/100 g. In keeping with an earlier study by Bouma et al. (9), we defined cerebral ischemia as any regional cerebral blood flow of <18 mL/min/100 g.

Statistics. All numbers are expressed as mean ± SD. The linear line of best fit through multiple data points was calculated by the least squares method. Comparisons between interval data were made by unpaired t-test. Comparisons between frequency data were

Figure 1. Simultaneous measurements of cerebral blood flow (CBF) (top, mean 49.6 ± 14.6 mL/min/100 g), arterial-jugular venous oxygen content difference (C(a-j)O₂) (middle, mean 2.30 ± 1.56 mL/min/100 g), and cerebral metabolic rate of oxygen consumption (CMRO₂) (bottom, mean 1.02 ± 0.59 mL/min/100 g) plotted against time after initial injury. All measurements were made at Paco₂ values of 35 to 40 torr (4.7 to 5.3 kPa).
Variation of Cerebral Blood Flow and Cerebral Metabolic Rate of Oxygen Consumption With Time After Injury. Researchers (3, 13) have corrected cerebral blood flow measurements to a normalized PaCO₂ of 34 torr (4.5 kPa), assuming a 3% vasoreactivity. We chose not to do this correction because of the wide variation in CO₂ vasoreactivity (mean 2.7%/mm Hg, range 1.1 to -2.3%/mm Hg) that we have discovered. In all figures, we have displayed uncorrected cerebral blood flow and CMRO₂ measurements made in the PaCO₂ range of 35 to 40 torr (4.7 to 5.3 kPa). Measurements made at lower PaCO₂ levels were only used to assess the change of cerebral blood flow with hyperventilation. Figure 1 shows how cerebral blood flow, C(a-j)O₂, and CMRO₂ vary with time after injury. There was no apparent trend between any of the variables and time. Linear regression lines were not computed for Figure 1 since the graphs represent pooled repeat measurements. Group mean values were calculated and are given in the figure legend. Although the mean global cerebral blood flow rate in our study was significantly lower than that rate reported by Settergren et al. (28) (49.6 ± 14.6 mL/min/100 g vs. 65.0 ± 16.2 mL/min/100 g, p < .05), the spread of values was generally within the lower range cited by Settergren et al. However, our values for C(a-j)O₂ (2.30 ± 1.56 mL/100 mL) and CMRO₂ (1.02 ± 0.59 mL/min/100 g) were reduced out of proportion to the reduction in cerebral blood flow. The C(a-j)O₂ and CMRO₂ values were both less than half those values reported by Settergren et al. (28) (4.86 ± 1.61 mL/100 mL and 3.02 ± 1.0 mL/min/100 g, respectively, both p < .001). The relationship between global cerebral blood flow and C(a-j)O₂ is demonstrated in Figure 2. The line of identity representing CMRO₂ = 1.0 mL/min/100 g (calculated by the Fick equation) is superimposed on the graph.

Variation of Cerebral Blood Flow With Glasgow Coma Scale, Intracranial Pressure, and Cerebral Perfusion Pressure. Cerebral blood flow, C(a-j)O₂,
and CMRO₂ were measured within 24 hrs of the initial head injury in 18 children. The results are plotted against admission Glasgow Coma Score (Fig. 3). There was no relationship between any of the variables and the patient's initial neurologic presentation. In addition, there was no relationship between cerebral blood flow and intracranial pressure or cerebral perfusion pressure measured at any time (Fig. 4).

**Variation of Cerebral Blood Flow With Paco₂ and Frequency of Regional Ischemia.** The response of global cerebral blood flow to variations in Paco₂ was preserved in most patients, despite head injury. Figure 5 (top) is a composite of all 38 sets of cerebral blood flow measurements made at different levels of Paco₂. The calculated CO₂ vasoreactivity was 2.7%/mm Hg, but the range varied from 7.1 to -2.3%/mm Hg. The frequency of regional cerebral ischemia increased significantly with hyperventilation. However, even during normocapnia, 28.9% of patients had one or more areas of regional cerebral blood flow at <18 mL/min/100 g. In addition, two patients developed global ischemia after hyperventilation. The frequency of global ischemia increased to 73.1% at a Paco₂ of <25 torr (3.3 kPa) (Fig. 5, bottom). Xenon-enhanced CT scanning provided clear visual evidence of the potential risks of unmonitored hyperventilation. In some patients, small changes in Paco₂ were accompanied by marked decreases in cerebral blood flow (Fig. 6).

**DISCUSSION**

We measured cerebral blood flow, C(a-j)O₂, and CMRO₂ in 23 children to assess their cerebral metabolic and vascular responses to head injury. In addition, we examined the relationship between cerebral blood flow and Paco₂ to study the frequency of cerebral ischemia during periods of hyperventilation.

The original work of Bruce et al. (10), which concluded that early cerebral hyperemia was common in head-injured children, was investigated by two large pediatric studies (13, 14). Muizelaar et al. (13) stated that early cerebral hyperemia was common in head-injured children when compared with a normal value of 44.1 mL/min/100 g. Conversely, Sharples et al. (14) found that cerebral hyperemia was very uncommon. However, Sharples et al. (14) used a reference normal value of 65 mL/min/100 g (28). Close examination of the two studies (13, 14) shows that cerebral blood flow measurements in both studies were clustered around a mean of about 50 mL/min/100 g. The subsequent interpretations were mainly influenced by the choice of different reference values.

After severe head injury, the relationship between cerebral perfusion pressure and cerebral blood flow is altered and probably varies widely in different children. However, if autoregulation remains intact and Paco₂ is constant, it is likely that an increase in cerebral perfusion pressure will cause a small increase in cerebral blood flow (33), as long as cerebral perfusion pressure is above the lower limit of autoregulation (34). As we reduced Paco₂, intracranial pressure decreased in every case. Since mean arterial pressure remained constant, this decrease in intracranial pressure produced an increase in cerebral perfusion pressure over the course of each study. However, in almost all cases, cerebral blood flow decreased predictably after hyperventilation (Fig. 5). The negative effect of hypocarbia on cerebral blood flow appeared to outweigh
Figure 6. Xenon-enhanced computed tomography flow images from a child 16 hrs after a motor vehicle accident. Admission Glasgow Coma Scale was 5. Top: Scan performed at PaCO₂ of 45 torr (6.0 kPa), intracranial pressure of 44 mm Hg, cerebral perfusion pressure of 54 mm Hg, and global cerebral blood flow of 59 mL/min/100 g. Bottom: Scan at same level, 15 mins after hyperventilation, shows clinically important cerebral ischemia. Scan performed at PaCO₂ of 30 torr (4.0 kPa), intracranial pressure of 15 mm Hg, cerebral perfusion pressure of 82 mm Hg, and global cerebral blood flow of 14 mL/min/100 g. Several local areas of this scan had regional cerebral blood flow rates of <10 mL/min/100 g.

The small increase that might have been expected from the increase in cerebral perfusion pressure.

The relationship between cerebral perfusion pressure and cerebral blood flow and their ultimate effect on intracranial pressure is complex and cannot be adequately characterized without a measure of cerebral blood volume. Although we did not calculate cerebral blood volume in this study, we found no evidence to support the original claim by Bruce et al. (11) that cerebral hyperemia is common in head-injured children or that hyperemia is a major contributor to increased intracranial pressure in the first few days after injury. Our patients' blood flow rates were close to those rates found in previous studies (13, 14), and were clustered in the lower range of normal cited by Settergren et al. (28), with a mean of 49.6 ± 14.6 mL/min/100 g. Absolute cerebral hyperemia was rare at any time after head injury. In addition, there was no correlation between cerebral blood flow and intracranial pressure, which might have been expected if vascular engorgement were a major contributor to increased intracranial pressure.

Our patients showed a profound decrease in CMRO₂ after head injury. The group's mean value of 1.02 ± 0.59 mL/min/100 g was only a third of the normal value measured in anesthetized children (28). Although the cerebral blood flow rate was usually within the low normal range, this mean value still represented luxury perfusion because the measured blood flow rates were well above the metabolic requirements of most children. Both Muizelaar et al. (13) and Sharples et al. (14) noted a decrease in CMRO₂, but only to a level of about 2 mL/min/100 g. Muizelaar et al. (13) considered a CMRO₂ of <1.0 mL/min/100 g to be a reliable indicator of death. It is our unit's policy to avoid paralysis whenever possible. Consequently, all head-injured children are deeply sedated with morphine and midazolam infusions. This drug combination has been shown to reduce CMRO₂ by 25% (35) and probably contributed to the low values. However, our measured values of CMRO₂ are so much lower than previous studies that this observation requires further investigation.

Xenon-enhanced CT scanning has been shown to be a safe and accurate technique (6, 9). It provides visual and quantitative information about regional and global cerebral blood flow rates. However, the measurement of C(a-j)O₂ and subsequent calculations of CMRO₂ are open to considerable criticism. Cerebral venous drainage is not equally divided between the two jugular veins. Consequently, unilateral samples may not be a fair representation of the brain's metabolism (36). In addition, cerebral venous blood is diluted by flow from small emissary veins draining the face and scalp directly into the jugular bulb (29). When performed carefully, monitoring of jugular venous bulb oxygen saturation and calculation of the cerebral oxygen...
Controlled ventilation of patients with severe head injury has been accepted as the standard of care since 1971, when Gordon (19) demonstrated a more favorable outcome after intubation and hyperventilation. The assumption of benefit from hyperventilation has recently been challenged by several studies (17, 21). Our finding of a clear relationship between regional cerebral ischemia and hypocarbia supports the concerns raised in the pediatric literature that unmonitored hyperventilation in children with an acute brain injury may result in potentially dangerous reductions in cerebral blood flow (14). We agree with current adult recommendations (22) that hyperventilation should not be used as a routine therapy for patients of any age after a severe head injury.

Our approach to head-injury management produced results that are comparable with any in the literature. Good or moderate outcomes occurred in 52.2% of our patients, and the overall death rate was 4.3%. Although care for each child will inevitably vary, we believe that the basis of head-injury management should be obsessive attention to oxygenation and cerebral perfusion pressure, combined with core temperature and metabolic homeostasis (particularly control of serum concentrations of glucose and sodium). We also advocate careful monitoring of minute ventilation and end-tidal \( CO_2 \) levels to try and avoid episodes of inadvertent hyperventilation that can easily occur during patient transport. Additional therapies should only be added after careful prospective study.

Hyperventilation should be reserved as a last resort for the control of increased intracranial pressure and, whenever possible, should be monitored by calculation of the cerebral oxygen extraction ratio using a jugular venous bulb catheter and, ideally, a xenon-enhanced CT flow study. Hyperventilation has a part to play in the management of children with head injuries. However, hyperventilation should be used with caution and monitored carefully.

ACKNOWLEDGMENT

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REFERENCES


Appendix. Equations

\[ CMRO_2 = C(a-j)O_2 \times CBF \]  
\[ C(a-j)O_2 = 1.34 \times Hb(SaO_2 - SJVO_2) + 0.003(PaO_2 - PVo_2) \]  
\[ CPP = MAP - ICP \]  
\[ CO_R = \frac{100 \times (CBF_i - CBF_f)}{CBF_f} \]  
\[ OER = \frac{SaO_2 - SJVO_2}{SaO_2} \times 100 \]

CMRO_2, cerebral metabolic rate of oxygen consumption; C(a-j)O_2, arterial-jugular venous oxygen content difference; CBF, cerebral blood flow; Hb, hemoglobin; SaO_2, arterial oxygen saturation; SJVO_2, jugular venous bulb oxygen saturation; PVo_2, venous partial pressure of oxygen; CPP, cerebral perfusion pressure; MAP, mean arterial pressure; ICP, intracranial pressure; CO_R, CO_2 vasoreactivity; CBF_i, initial value of cerebral blood flow; CBF_f, final value of cerebral blood flow; PaCO_2, initial arterial partial pressure of CO_2; PaCO_2f, final arterial partial pressure of CO_2.