

# Chapter 12. Use of hyperventilation in the acute management of severe pediatric traumatic brain injury

## I. RECOMMENDATIONS

*A. Standards.* There are insufficient data to support a treatment standard for this topic.

*B. Guidelines.* There are insufficient data to support a treatment guideline for this topic.

*C. Options.* Mild or prophylactic hyperventilation ( $P_{aCO_2} < 35$  mm Hg) in children should be avoided.

Mild hyperventilation ( $P_{aCO_2}$  30–35 mm Hg) may be considered for longer periods for intracranial hypertension refractory to sedation and analgesia, neuromuscular blockade, cerebrospinal fluid drainage, and hyperosmolar therapy.

Aggressive hyperventilation ( $P_{aCO_2} < 30$  mm Hg) may be considered as a second tier option in the setting of refractory hypertension. Cerebral blood flow (CBF), jugular venous oxygen saturation, or brain tissue oxygen monitoring is suggested to help identify cerebral ischemia in this setting.

Aggressive hyperventilation therapy titrated to clinical effect may be necessary for brief periods in cases of cerebral herniation or acute neurologic deterioration.

*D. Indications from the Adult Guidelines.* The adult guidelines recommended (1) at the level of a treatment standard that in the absence of increased intracranial pressure (ICP), chronic prolonged hyperventilation therapy ( $P_{aCO_2}$  of  $\leq 25$  mm Hg) should be avoided after severe TBI. At the level of a treatment guideline, it was recommended that prophylactic hyperventilation ( $P_{aCO_2} \leq 35$  mm Hg) therapy during the first 24 hrs after severe TBI should be avoided because it can compromise cerebral perfusion during a time when CBF is reduced.

It was recommended as a treatment option that hyperventilation therapy may be necessary for brief periods when there is acute neurologic deterioration or for longer periods if there is intracranial hypertension refractory to sedation, paraly-

sis, cerebrospinal fluid drainage, and osmotic diuretics. Jugular venous oxygen saturation, arterial jugular venous oxygen content differences, brain tissue oxygen monitoring, and CBF monitoring may help to identify cerebral ischemia if hyperventilation, resulting in  $P_{aCO_2}$  values  $< 30$  mm Hg, is necessary.

## II. OVERVIEW

Aggressive hyperventilation therapy has been used in the management of severe pediatric TBI for the rapid reduction of ICP since the 1970s. In an uncontrolled study, Bruce et al. (2) used a protocol that included aggressive hyperventilation and reported very good outcomes. This approach was based on the assumption that hyperemia was common after pediatric TBI. Hyperventilation therapy also was thought to benefit the injured brain through a variety of mechanisms including reduction of brain acidosis (3), improvement of cerebral metabolism (4), restoration of blood pressure autoregulation of cerebral blood flow (5), and increasing perfusion to ischemic brain regions (local inverse steal) (6).

More recent pediatric studies have shown that hyperemia is uncommon and also have raised concerns about the safety of hyperventilation therapy. Study of the effect of hyperventilation in children has focused on assessment of cerebral physiologic variables. The effect of hyperventilation therapy on outcome in infants and children with severe TBI has not been directly compared with other therapies such as hyperosmolar agents, barbiturates, hypothermia, or early decompressive craniectomy.

Hyperventilation reduces ICP by inducing hypocapnia. This leads to cerebral vasoconstriction and a reduction in CBF. This is accompanied by a reduction in cerebral blood volume, resulting in a decrease in ICP. However, hyperventilation

is associated with a risk of iatrogenic ischemia. In an experimental model, Mui-zelaar et al. (7) reported that the vasoconstrictor effect of hyperventilation was sustained for a period of  $< 24$  hrs. Chronic hyperventilation depletes brain tissue interstitial bicarbonate buffering and causes cerebral circulation to become hyper-responsive to subsequent increases in  $P_{aCO_2}$ . In addition, the respiratory alkalosis that accompanies hyperventilation causes a left shift of the hemoglobin-oxygen dissociation curve, which may impair delivery of oxygen to tissue.

The assumption of benefit from hyperventilation recently has been challenged. Recent clinical studies in mixed adult and pediatric populations also have demonstrated that hyperventilation may decrease cerebral oxygenation and may induce brain ischemia (8–11). After TBI, the CBF response to changes in  $P_{aCO_2}$  can be unpredictable and should be specifically monitored.

## III. PROCESS

We searched Medline and Healthstar from 1966 to 2001 by using the search strategy for this question (see Appendix A) and supplemented the results with literature recommended by peers or identified from reference lists. Of 20 potentially relevant studies, two were used as evidence for this question (Table 1).

## IV. SCIENTIFIC FOUNDATION

Diffuse cerebral swelling is a common finding in pediatric patients with severe TBI (12, 13). Increased cerebral blood volume and CBF had been considered to be the unique cause of this diffuse swelling, and raised ICP in children and aggressive hyperventilation was advocated (14). In the classic study by Bruce et al. (2), 36 of 76 children with severe TBI were found to have diffuse cerebral swelling on CT scan. Six patients, ages 14–21

Table 1. Evidence table

References	Description of Study	Data Class	Conclusion
Skippen et al. (22), 1997	Prospective cohort, 23 children with isolated severe TBI, GCS <8. Ages 3 mos to 16 yrs, mean 11 yrs. Paco <sub>2</sub> was adjusted by minute ventilation to >35, 25–35, and <25 torr. Measured CBF, C(a–j)O <sub>2</sub> , CMRO <sub>2</sub> = C(a–j)O <sub>2</sub> × CBF. Follow-up GOS 6 mos post-ICU discharge.	II	Severe TBI produced modest decrease in CBF, larger decrease in cerebral oxygen consumption. Hyperemia was uncommon, but measured CBF rates were above metabolic requirements of most. As Paco <sub>2</sub> reduced, ICP decreased and CPP increased. However, in almost all patients, CBF decreased.
Stringer et al. (19), 1993	Nonrandomized selected series of case studies. Twelve patients referred for CBF measurement. Three were children with head trauma and coma, ages 1 mo, 6 yrs, and 8 yrs. Xenon-enhanced CT scans. Measured ICP, CPP, MAP, ETco <sub>2</sub> , XeCT, CBF.	II	Hyperventilation-induced ischemia occurs and affects both injured and apparently intact areas of brain tissue.

TBI, traumatic brain injury; GCS, Glasgow Coma Scale; CBF, cerebral blood flow; C(a–j) O<sub>2</sub>, cerebral arteriojugular venous oxygen content difference; CMRO, cerebral metabolic rate; ICU, intensive care unit; CT, computed tomography; ICP, intracranial pressure; CPP, coronary perfusion pressure; MAP, mean arterial pressure; ETco<sub>2</sub>, end-tidal CO<sub>2</sub>; XeCT, xenon-enhanced computed tomography.

years, were found to have CBF that was normal or above normal. In three patients, CBF decreased back to control levels after diffuse swelling had resolved. Consequently, aggressive hyperventilation (Paco<sub>2</sub> 23–25 mm Hg) was advocated and mannitol was discouraged.

There are now data to suggest that hyperemia is not as common as previously thought (15). In a series of 80 normal, unanesthetized children, CBF ranged from 40 mL·100 g<sup>-1</sup>·min<sup>-1</sup> in the first 6 months of life to a peak of 108 mL·100 g<sup>-1</sup>·min<sup>-1</sup> at age 3–4 yrs, declining to 71 mL·100 g<sup>-1</sup>·min<sup>-1</sup> after age 9 yrs. Similarly, Chiron et al. (16) demonstrated that CBF ranged from about 50 mL·100 g<sup>-1</sup>·min<sup>-1</sup> in normal neonates to a peak of 71 mL·100 g<sup>-1</sup>·min<sup>-1</sup> at 5 yrs. After age 19, CBF gradually decreased to adult levels. Thus, posttraumatic CBF may not be greater than normal in children. However, caution should be exercised in interpreting these studies because techniques used to measure CBF differed between reports.

Adelson et al. (17) studied 30 children with severe TBI, all <8 yrs of age. Seventy-seven percent had CBF <20 mL·100 g<sup>-1</sup>·min<sup>-1</sup> on admission. Children were treated with a protocol including mild (Pco<sub>2</sub> 32–35 mm Hg) hyperventilation and barbiturate coma (60%). CBF was highest at 24–48 hrs (59.6 ± 4.5 mL·100 g<sup>-1</sup>·min<sup>-1</sup>) and decreased (<50 mL·100 g<sup>-1</sup>·min<sup>-1</sup>) after 3 days. Any child with global CBF of 20 mL·100 g<sup>-1</sup>·min<sup>-1</sup> or less at any time had a poor outcome. CBF of >55 mL·100 g<sup>-1</sup>·min<sup>-1</sup> was associated with a higher proportion of children with a good outcome.

Muizelaar et al. (18) studied 32 children with severe TBI (age 3–18 yrs). The average CBF was only 44 ± 22 mL·100 g<sup>-1</sup>·min<sup>-1</sup>, which is considerably lower than the average of 68 ± 4 mL·100 g<sup>-1</sup>·min<sup>-1</sup> found in four normal unanesthetized children. No correlation was found between CBF and ICP.

Although the effect of hyperventilation on long-term outcome has not been directly addressed in pediatric TBI, several reports have described the effects of hyperventilation on CBF and brain physiology. Stringer et al. (19) studied local CBF and vascular reactivity before and after hyperventilation in 12 patients including three children with severe TBI. Hyperventilation-induced blood flow reductions affected both injured and apparently intact areas of the brain and were not reflected by ICP measurement.

Sharples et al. (20) investigated CBF, arterial jugular venous oxygen difference, and cerebral metabolic rate in 21 children with TBI. No fundamental difference between adults and children in the pathophysiologic response of CBF to severe TBI was found. Absolute cerebral hyperemia was uncommon. Raised ICP was associated with low, rather than increased, CBF. Cerebral metabolic rate was initially normal in 81% of children with TBI. These data do not support the hypothesis that ICP increases as a result of excessive CBF in children with TBI. Based on this study, and on a subsequent study of cerebral vascular reactivity (21), the authors recommended maintaining a normal Paco<sub>2</sub>.

Skippen et al. (22) found that hyperemia was uncommon in children with

severe TBI. However, CBF rates remained above the metabolic requirements of most children studied. A modest decrease in CBF and a much larger decrease in cerebral oxygen consumption were found at baseline. As Paco<sub>2</sub> was reduced with hyperventilation, CBF was decreased in almost all patients despite decreased ICP and increased cerebral perfusion pressure. A clear relationship between hypocarbia and frequency of cerebral ischemia was seen. The frequency of regional ischemia (CBF <18 mL·100 g<sup>-1</sup>·min<sup>-1</sup>) was 28.9% during normocapnia and increased to 73.1% for Paco<sub>2</sub> <25 mm Hg.

The effect of hyperventilation therapy on outcome of infants and children with severe TBI has not been directly compared with other therapies such as hyperosmolar agents, barbiturates, hypothermia, or early decompressive craniectomy. Surprisingly, outcome data reported by Bruce et al. (2) in the late 1970s, when aggressive hyperventilation (Paco<sub>2</sub> 20–25 mm Hg) represented the cornerstone of therapy for pediatric TBI (5), has not been surpassed by contemporary protocols and only rarely equaled (23). Hyperventilation may have unique advantages as a therapy in severe pediatric TBI; however, it can only be supported as a second tier therapy based on the current evidence.

### Key Elements from the Adult Guidelines Relevant to Pediatric TBI

The adult guidelines (1) conclude that prophylactic hyperventilation (Paco<sub>2</sub> <35 mm Hg) therapy during the first 24 hrs after severe TBI should be avoided be-

cause it can compromise cerebral perfusion during a time when CBF is already reduced. The guidelines (1) strongly contend that chronic prolonged hyperventilation therapy ( $\text{Paco}_2 < 25$  mm Hg) should be avoided after severe TBI in the absence of increased ICP. It was emphasized that the preponderance of the physiologic literature concludes that hyperventilation during the first few days following severe TBI, whatever the threshold, is potentially deleterious in that it can promote cerebral ischemia.

Specifically, CBF during the first day after injury is less than half that of normal individuals (18, 24–31). During the first 24 hrs after injury, there is a direct correlation between CBF and Glasgow Coma Scale score or outcome (24, 29). Hyperventilation reduces CBF (22, 32–34) even further but does not consistently reduce ICP (35, 36) and may cause loss of autoregulation (37). Aggressive hyperventilation may cause arterial jugular venous oxygen and CBF to approach ischemic levels.

In a prospective randomized clinical trial by Muizelaar et al. (8), 77 severe TBI patients were randomized to a group treated with chronic prophylactic hyperventilation ( $\text{Paco}_2$  of  $25 \pm 2$  mm Hg) or to a group kept relatively normocapnic ( $\text{Paco}_2$  of  $35 \pm 2$  mm Hg). At 3 and 6 months after injury, patients with initial Glasgow Coma Scale motor scores of 4–5 in the hyperventilation group had a significantly worse outcome than did patients in the normocapnic group. Statistically significant differences between the two groups were not found at 1 yr after injury; this was attributed to a type II statistical error since substantially fewer patients were available for 1-yr follow-up.

## V. SUMMARY

Hyperemia may not be as common in severe pediatric TBI as previously reported. Hyperventilation can reduce CBF to potentially ischemic levels. Additionally, the cerebrovascular response to hyperventilation can be extremely variable following TBI. Studies in children with severe TBI raise the concern that the toxicity of hyperventilation may be similar to the toxicity that has been demonstrated in adults and related to adverse outcome. Unfortunately, the precise relationship between hyperventilation and outcome has not been studied in children with severe TBI.

## VI. KEY ISSUES FOR FUTURE INVESTIGATION

- Studies to identify subgroups of patients who might benefit from hyperventilation are needed.
- Studies are needed to address the timing and duration of the optimal use of hyperventilation.
- Studies to determine the optimal monitoring technique of patients undergoing hyperventilation are lacking.
- Studies are needed to address the influence of age on the response to hyperventilation
- The effects on long-term outcome should be addressed in all aspects of research on hyperventilation. Hyperemia may not be as common in severe pediatric traumatic brain injury as previously reported.

## REFERENCES

1. Bullock R, Chesnut RM, Clifton G, et al: Guidelines for the management of severe traumatic brain injury. *J Neurotrauma* 2000; 17:451–553
2. Bruce D, Raphaely R, Goldberg A, et al: Pathophysiology, treatment and outcome following severe head injury in children. *Childs Brain* 1979; 5:174–191
3. Gordon E, Rossanda M: The importance of cerebrospinal fluid acid base status in the treatment of unconscious patients with brain lesions. *Acta Anesthesiol Scand* 1968; 12: 51–73
4. Obrist WD, Clifton GL, Robertson CS, et al: Cerebral metabolic changes induced by hyperventilation in acute head injury. In: *Cerebral Vascular Disease 6*. Meyer JS, et al. (Eds). Elsevier Science, 1987, pp 251–255, 241–253
5. Raphaely RC, Swedlow DB, Downes JJ, et al: Management of severe pediatric head trauma. *Pediatr Clin North Am* 1980; 27: 715–727
6. Darby JM, Yonas H, Marion DW, et al: Local “inverse steal” induced by hyperventilation in head injury. *Neurosurgery* 1988; 23: 84–88
7. Muizelaar JP, Vanderpoel HG, Li Z, et al: Pial arteriolar diameter and  $\text{CO}_2$  reactivity during prolonged hyperventilation in the rabbit. *J Neurosurg* 1988; 69:923–927
8. Muizelaar JP, Marmarou A, Ward JD, et al: Adverse effects of prolonged hyperventilation in patients with severe head injury: A randomized clinical trial. *J Neurosurg* 1991; 75: 731–739
9. Schneider GH, von Helden A, Lanksch WR et al: Continuous monitoring of jugular bulb oxygen saturation in comatose patients—Therapeutic implications. *Acta Neurochir* 1995; 134:71–75
10. von Helden A, Schneider GH, Unterberg A, et

- al: Monitoring of jugular venous oxygen saturation in comatose patients with subarachnoid haemorrhage and intracerebral hematomas. *Acta Neurochir* 1993; 59:102–106
11. Kiening KL, Hartl R, Unterberg AW, et al: Brain tissue  $\text{pO}_2$  monitoring in comatose patients: Implications for therapy. *Neurol Res* 1997; 19:233–240
12. Aldrich EF, Eisenberg HM, Saydjari C, et al: Diffuse brain swelling in severely head-injured children. *Neurosurgery* 1992; 76: 450–454
13. Lang DA, Teasdale GM, MacPherson P, et al: Diffuse brain swelling after head injury: More often malignant in adults than children? *J Neurosurg* 1994; 80:675–680
14. Schut L, Bruce DA: Recent advances in the treatment of head injuries. *Pediatr Ann* 1976; 10:81–104
15. Zwienerberg M, Muizelaar JP: Severe pediatric head injury: The role of hyperemia revisited. *J Neurotrauma* 1999; 16:937–943
16. Chiron C, Raynaud C, Maziere B, et al: Changes in regional cerebral blood flow during brain maturation in children and adolescents. *J Nucl Med* 1992; 33:696–703
17. Adelson PD, Clyde B, Kochanek P, et al: Cerebrovascular response in infants and young children following severe traumatic brain injury: A preliminary report. *Pediatr Neurosurg* 1997; 26:200–207
18. Muizelaar JP, Marmarou A, DeSalles AA, et al: Cerebral blood flow and metabolism in severely head injured children: Part 1: Relationship with GCS score, outcome, ICP and PVI. *J Neurosurg* 1989; 71:63–71
19. Stringer WA, Hasso AN, Thompson JR, et al: Hyperventilation-induced cerebral ischemia in patients with acute brain lesions: Demonstration by Xenon-enhanced CT. *AJNR* 1993; 14:475–484
20. Sharples PM, Stuart AG, Matthews DSF, et al: Cerebral blood flow and metabolism in children with severe head injury. Part I: Relation to age, Glasgow Coma Score, outcome, intracranial pressure, and time after injury. *J Neurol Neurosurg Psychiatry* 1995; 58:145–152
21. Sharples PM, Matthews DSF, Eyre JA: Cerebral blood flow and metabolism in children with severe head injuries. Part 2: Cerebrovascular resistance and its determinants. *J Neurol Neurosurg Psychiatry* 1995; 58:153–159
22. Skippen P, Seear M, Poskitt K, et al: Effect of hyperventilation on regional cerebral blood flow in head-injured children. *Crit Care Med* 1997; 25:1402–1409
23. Peterson B, Khanna S, Fisher B, et al: Prolonged hypernatremia controls elevated intracranial pressure in head-injured pediatric patients. *Crit Care Med* 2000; 28:1136–1143
24. Bouma GJ, Muizelaar JP, Choi SC, et al: Cerebral circulation and metabolism after severe traumatic brain injury: The elusive bulb of ischemia. *J Neurosurg* 1991; 75:685–693
25. Bouma GJ, Muizelaar JP, Stringer WA, et al: Ultra early evaluation of regional cerebral blood flow in severely head injured patients

- using xenon enhanced computed tomography. *J Neurosurg* 1992; 77:360–368
26. Cruz J: Low clinical ischemic threshold for cerebral blood flow in severe acute brain trauma. Case report. *J Neurosurg* 1994; 80:143–147
  27. Fieschi C, Battistini N, Beduschi A, et al: Regional cerebral blood flow and intraventricular pressure in acute head injuries. *J Neurol Neurosurg Psychiatry* 1974; 37:1378–1388
  28. Jaggi JL, Obrist WD, Gennarelli TA, et al: Relationship of early cerebral blood flow and metabolism to outcome in acute head injury. *J Neurosurg* 1990; 72:176–182
  29. Marion DW, Darby J, Yonas H: Acute regional cerebral blood flow changes caused by severe head injuries. *J Neurosurg* 1991; 74:407–414
  30. Robertson CS, Clifton GL, Groosman RG, et al: Alterations in cerebral availability of metabolic substrates after severe head injury. *J Trauma* 1988; 28:1523–1532
  31. Schroder ML, Muizelaar JP, Kuta AJ: Documented reversal of global ischemia immediately after removal of an acute subdural hematoma. *Neurosurgery* 1994; 80:324–327
  32. Dahl B, Bergholt B, Cold GE, et al: CO<sub>2</sub> and indomethacin vasoreactivity in patients with head injury. *Acta Neurochir* 1996; 138:265–273
  33. Fortune JB, Feustel PJ, Graca L, et al: Effect of hyperventilation, mannitol, and ventriculostomy drainage on cerebral blood flow after head injury. *J Trauma* 1995; 39:1091–1099
  34. Sioutos PJ, Orozco JA, Carter LP, et al: Continuous regional cerebral cortical blood flow monitoring in head injured patients. *Neurosurgery* 1995; 36:943–950
  35. Crockard HA, Coppel DL, Morrow WF: Evaluation of hyperventilation in treatment of head injuries. *BMJ* 1973; 4:634–640
  36. Obrist WD, Langfitt TW, Jaggi JL, et al: Cerebral blood flow and metabolism in comatose patients with acute head injury. *J Neurosurg* 1984; 61:241–253
  37. Cold GE, Christensen MS, Schmidt K: Effects of two levels of induced hypocapnia on cerebral autoregulation in the acute phase of head injury coma. *Acta Anaesthesiol Scand* 1981; 25:397–401

## APPENDIX: LITERATURE SEARCH STRATEGIES

### SEARCHED MEDLINE AND HEALTHSTAR FROM 1966 TO 2001

#### Chapter 12. Hyperventilation

1. exp craniocerebral trauma/
2. head injur\$.tw.
3. brain injur\$.tw.
4. 1 or 2 or 3
5. brain ischemia/ or “cerebral ischemia”.mp.
6. 4 and 5
7. limit 6 to (newborn infant <birth to 1 month> or infant <1 to 23 months> or preschool child <2 to 5 years> or child <6 to 12 years> or adolescence <13 to 18 years>)