

# Chapter 13. Hyperventilation

## I. RECOMMENDATIONS

Strength of Recommendations: Weak.  
Quality of Evidence: Low, from one poor-quality study and one moderate-quality class III study.

### A. Level I

There are insufficient data to support a level I recommendation for this topic.

### B. Level II

There are insufficient data to support a level II recommendation for this topic.

### C. Level III

Avoidance of prophylactic severe hyperventilation to a  $Paco_2 < 30$  mm Hg may be considered in the initial 48 hrs after injury.

If hyperventilation is used in the management of refractory intracranial hypertension, advanced neuromonitoring for evaluation of cerebral ischemia may be considered.

## II. EVIDENCE TABLE (see Table 1)

## III. OVERVIEW

Hyperventilation has been used in the management of severe pediatric traumatic brain injury (TBI) for the rapid reduction of ICP since the 1970s. This approach was based on the assumption that hyperemia was common after pediatric TBI. Hyperventilation therapy was thought to benefit the injured brain primarily through an increase in perfusion to ischemic brain regions and a decrease in ICP. More recent pediatric studies have shown that hyperemia is uncommon and also have raised concerns about the safety of hyperventilation therapy (1–6).

Research on the effect of hyperventilation in children has focused on assessment of cerebral physiological 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 producing hypocapnia-induced cerebral vasoconstriction and a reduction in cerebral blood flow (CBF) and cerebral blood volume, resulting in a decrease in ICP. Recent clinical studies in mixed adult and pediatric populations have demonstrated that hyperventilation may decrease cerebral oxygenation and may induce brain ischemia (5, 7–9). In addition, after TBI, the CBF response to changes in  $Paco_2$  can be unpredictable. A study by Stringer et al (10) studied regional CBF using xenon computed tomography and vascular reactivity before and after hyperventilation in 12 patients including three children with severe TBI. Hyperventilation-induced CBF reductions affected both injured and apparently intact areas of the brain. The ischemic threshold was defined as a CBF of 23 mL/100 g/min in gray matter and this occurred in four of 12 patients after hyperventilation. Changes in ICP, cerebral perfusion pressure, and mean arterial pressure were variable in these patients after hyperventilation. The level of hyperventilation used in this study was profound with end-tidal  $CO_2$  values of 20–26 mm Hg before and 8–19 mm Hg after hyperventilation. In addition to reducing CBF, prophylactic hypocarbia after TBI has been shown experimentally to reduce the buffering capacity of cerebrospinal fluid (CSF), an effect that may be as or more important than its effect on CBF (5).

Despite a prior recommendation in the 2003 guidelines against prophylactic hyperventilation, it remains a commonly used therapy in children (11–13). For example, >40% of the children in the recent Canadian multicentered trial of hypothermia in severe pediatric TBI had  $Paco_2 < 30$  mm Hg (12). Similarly, in the study by Curry et al (11), 50% of patients with severe TBI had severe hypocarbia ( $Paco_2 < 30$  mm Hg) by arterial blood gas in the first 48 hrs of admission. This finding parallels another recent report that

mild hyperventilation was the most commonly used therapy, having been applied in >90% of patients in the data bank of >500 children with severe TBI from the United Kingdom and Ireland (14).

## IV. PROCESS

For this update, MEDLINE was searched from 1996 through 2010 (Appendix B for search strategy), and results were supplemented with literature recommended by peers or identified from reference lists. Of 15 potentially relevant studies, one was added to the existing table and used as evidence for this topic.

## V. SCIENTIFIC FOUNDATION

Two class III studies met the inclusion criteria for this topic and provide evidence to support the recommendations (11, 15). Neither represented a comparison of hyperventilation vs. normal ventilation or to any other therapy targeting control of ICP. Similarly, there were no reports in children specifically addressing the effects of varying levels of hyperventilation on ICP or outcome or studies of the transient application of hyperventilation in the setting of impending herniation or ICP crisis. Lastly, neither study had a standardized protocol to assess  $Paco_2$ , measuring it only intermittently.

One report described the effects of hyperventilation on CBF, brain physiology, and Glasgow Outcome Scale at 6 months (15). A study by Skippen et al (15) was carried out as a prospective nonrandomized, selected case series of 23 children (3 months to 16 yrs of age) with isolated severe TBI. CBF was measured by xenon computed tomography during  $Paco_2$  adjustments to >35, 25–35, and <25 mm Hg. The ischemic threshold was defined as CBF <18 mL/100 g/min. However, the ischemic threshold in children is not defined and may vary with age.  $CO_2$  reactivity of CBF was also assessed. Management included CSF drainage and hyperosmolar therapy but not steroids or barbiturates. As  $Paco_2$  was reduced with hyperventilation, CBF decreased in almost all patients despite decreased ICP and increased cerebral perfusion pressure. A relationship

Table 1. Evidence table

Reference	Study Description	Data Class, Quality, and Reasons	Results and Conclusion
Study from previous guidelines Skippen et al, 1997 (15)	Design: case series N = 23 Age: mean 11 yrs (range, 3 months to 16 yrs) Protocol: CBF measured by xenon-enhanced computed tomography during partial pressure of arterial carbon dioxide adjustments to >35, 25–35, and <25 mm Hg Outcome: ischemic threshold defined as <18 mL/100 g/min; Glasgow Outcome Scale score at 6 months	Class III Poor quality: no control for confounders	Areas of CBF below ischemic threshold 28.9%, 59.4%, and 73.1%, respectively (not compared statistically) Mean vasoreactivity 2.7% change in CBF per mm Hg change in arterial carbon dioxide (range, –2.3% to 7.1%) 52.2% had good or moderate outcome; 43.5% were severe or vegetative; 4.3% died (no analysis)
New study Curry et al, 2008 (11)	Design: retrospective cohort study (trauma registry) before and after 2003 pediatric Brain Trauma Foundation guidelines N = 464 Age: mean 8.0 yrs (range, 0–14 yrs) Protocol: all children had controlled mechanical ventilation Outcome: incidence of severe hypocarbia (arterial carbon dioxide <30 mm Hg) during the initial 48 hrs and risk of inpatient mortality Analysis: chi square and logistic regression	Class III Moderate quality: unclear if outcome assessment methods unbiased; otherwise met all criteria	Severe hypocarbia 60% patients before and 52% after ( $p = .19$ ) Severe hypocarbia on initial measurement was more common in infants ( $\leq 2$ yrs) vs. older children (30.8% vs. 19.3%, respectively, $p = .02$ ) Incidence of severe hypocarbia in the first 48 hrs was similar between age groups (58.9% for infants vs. 58.0% for older children; $p = .91$ ) Mortality adjusted odds ratio (95% confidence interval) of 1.44 (0.56–3.73) for 1 episode, 4.18 (1.58–11.03) for 2 episodes of severe hypocarbia, and 3.93 (1.61–9.62) for $\geq 3$ episodes

CBF, cerebral blood flow.

between the level of hypocarbia and frequency of cerebral ischemia was observed. The frequency of regional ischemia was 28.9% during normocapnia and increased to 59.4% and 73.1% for  $\text{Paco}_2$  25–35 mm Hg and <25 mm Hg, respectively. However, no statistical analysis was done. Fifty-two percent had a good or moderate outcome, 43.5% were severely disabled or vegetative, and 4.3% died. Again, no analysis was conducted.

A second report examined the association between hypocarbia and outcome at hospital discharge in a large pediatric series of severe TBI victims who were all mechanically ventilated (11). A study by Curry et al (11) was carried out as a retrospective cohort study of 464 patients <15 yrs of age with an admission Glasgow Coma Scale score <9 and a head Abbreviated Injury Score  $\geq 3$  with a  $\text{Paco}_2$  recorded in the first 48 hrs of admission for the years 2000–2005. The authors examined the incidence of severe hypocarbia ( $\text{Paco}_2$  <30 mm Hg) and its relationship with neurologic outcome before

(375 patients) and after (89 patients) the publication of the 2003 pediatric TBI guidelines (16). They found a nonsignificant change in the incidence of severe hypocarbia from 60% of patients before to 52% after ( $p = .19$ ). Patients with one documented episode of severe hypocarbia, controlling for emergency department Glasgow Coma Scale score, lowest emergency department systolic blood pressure, Injury Severity Score,  $\text{Paco}_2$  sampling frequency, and year of admission, had an adjusted odds ratio (95% confidence interval) for mortality of 1.44 (0.56–3.73) for one episode of severe hypocarbia, 4.18 (1.58–11.03) for two episodes, and 3.93 (1.61–9.62) for three or more episodes compared with patients with mild or no hypocarbia. These findings, although retrospective, show a strong association of severe hypocarbia with poor outcomes. However, there might be other contributors to hypocarbia such as marked reduction in metabolic rates or acidosis from systemic shock. Thus, the exact contribution of induced hyperventilation to

poor outcome cannot be clearly defined from this study.

## VI. INFORMATION FROM OTHER SOURCES

### A. Indications From the Adult Guidelines

The most recent adult guidelines (17) had one level II recommendation: “prophylactic hyperventilation ( $\text{Paco}_2$  of 25 mm Hg or less) is not recommended.” The authors also had several level III recommendations: 1) “hyperventilation is recommended as a temporizing measure for the reduction of elevated ICP”; 2) “hyperventilation should be avoided during the first 24 hrs after injury when CBF is often critically reduced”; and 3) “if hyperventilation is used, jugular venous oxygenation saturation or brain tissue oxygen tension measurements are recommended to monitor oxygen delivery.”

## VII. SUMMARY

Despite a lack of published evidence supporting the use of hyperventilation in the management of pediatric patients with severe TBI, it continues to be used commonly worldwide. No randomized controlled trial has been carried out to study the impact of hyperventilation on any aspect of the management of severe TBI in children such as in the setting of refractory intracranial hypertension or herniation. The limited evidence, however, supports that prophylactic severe hyperventilation to a  $Paco_2 < 30$  mm Hg should be avoided in the initial 48 hrs after injury. Arguing against the use of prophylactic hyperventilation, published evidence discussed in this report indicates that the use of hyperventilation is associated with CBF reductions and that prolonged and or significant hypocarbia is associated with poor outcome in pediatric patients with severe TBI. As a result, advanced neuromonitoring for evaluation of cerebral ischemia may be considered if hyperventilation is to be used in the management of refractory intracranial hypertension.

## VIII. KEY ISSUES FOR FUTURE INVESTIGATION

- In the setting of refractory intracranial hypertension or brain herniation, studies are needed to determine the efficacy of hyperventilation in comparison to other second-tier therapies.
- Studies are needed to determine the optimal monitoring technique in patients treated with hyperventilation, including assessments of markers of cerebral ischemia, such as CBF, brain tissue oxygen

tension, jugular venous oxygenation saturation, transcranial Doppler, near-infrared spectroscopy, serum biomarkers of brain injury, or other advanced neuromonitoring.

- The effects of hyperventilation on long-term outcome should be addressed.

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