Hypocapnia and the Injured Brain: More harm than Benefit

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Disclosures

- None
Key Questions

1. Why do we use hypocapnia in patients with Acute Brain Injury?

2. How often do we use hypocapnia in clinical practice?

3. What happens to cerebral blood flow and oxygen requirements in the injured brain?

4. How does hypocapnia reduce cerebral blood volume?

5. Can hypocapnia damage the brain and/or other organs?

6. Can we use hypocapnia safely in our ABI patients?
1. Rationale for use of Hypocapnia in ABI
Rationale for Hypocapnia

- Hypocapnia is induced in order to decrease the Cerebral Blood Volume

- Hypocapnia reduces ‘luxury perfusion’ of Injured Brain
  - Implicated in cerebral edema, esp. in Children

- Hypocapnia may cause ‘inverse steal’
  - shunt blood from uninjured to injured Brian
2. Frequency of use of Hypocapnia in ABI Patients
The use of hyperventilation therapy after traumatic brain injury in Europe: an analysis of the BrainIT database

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Abstract Objective: To assess the use of hyperventilation and the adherence to Brain Trauma Foundation-Guidelines (BTF-G) after traumatic brain injury (TBI). Setting: Twenty-two European centers are participating in the BrainIT initiative. Design: Retrospective analysis of monitoring data. Patients and participants: One hundred and fifty-one patients with a known time of trauma and at least one recorded arterial blood-gas (ABG) analysis. Measurements and results: A total number of 7,703 ABGs, representing 2,269 ventilation episodes (VE) were included in the analysis. Related minute-by-minute ICP data were taken from a 30 min time window around each ABG collection. Data are given as mean with standard deviation. (1) Patients without elevated intracranial pressure (ICP) (<20 mmHg) manifested a statistically significant higher P\(_{\text{CO}_2}\) (36 ± 5.7 mmHg) in comparison to patients with elevated ICP (≥20 mmHg; P\(_{\text{CO}_2}\) ≥ 34 ± 5.4 mmHg, P < 0.001). (2) Intensified forced hyperventilation (P\(_{\text{CO}_2}\) ≤ 25 mmHg) in the absence of elevated ICP was found in only 49 VE (2%). (3) Early prophylactic hyperventilation (<24 h after TBI; P\(_{\text{CO}_2}\) ≤ 35 mmHg, ICP < 20 mmHg) was used in 1,224 VE (54%). (4) During forced hyperventilation (P\(_{\text{CO}_2}\) ≤ 30 mmHg), simultaneous monitoring of brain tissue pO\(_2\) or S\(_{\text{O}_2}\) was used in only 204 VE (9%). Conclusion: While overall adherence to current BTF-G seems to be the rule, its recommendations on early prophylactic hyperventilation as well as the use of additional cerebral oxygenation monitoring during forced hyperventilation are not followed in this sample of European TBI centers.

Descriptors: Neurotrauma

Keywords Traumatic brain injury · Hyperventilation
PaCO₂ histogram of 7,703 blood gas analyses

Neuman et al, Intens Care Med 2008
Key Findings

• Early ‘prophylactic’ hyperventilation - i.e. hypocapnia in the first 24h - was used in 54% of episodes.

• The majority of patients with a diagnosis of raised ICP had significant hypocapnia - Hypocapnic for up to 50% of total ventilation time.

• Over 90% of patients with PaCO$_2$ ≤ 30 mmHg received no monitoring of brain oxygenation.

Hypocapnia as the ‘default’ setting in Neurocritical Care?
Incidence of hypo- and hypercarbia in severe traumatic brain injury before and after 2003 pediatric guidelines*

Rebecca Curry, MSII; Will Hollingworth, PhD; Richard G. Ellenbogen; Monica S. Vavilala, MD

Objective: To examine the incidence of severe hypocarbia (Paco₂ <30 mm Hg) in patients with severe pediatric traumatic brain injury before and after publication of the 2003 pediatric guidelines (PG).

Design: Retrospective cohort analysis.


Patients: Children <15 yrs of age with severe pediatric traumatic brain injury.

Interventions: None.

Measurements and Main Results: The pre-PG group (before August 1, 2003) included 375 patients and the post-PG group included 89 patients. Post PG guidelines, there was a trend toward earlier (45 vs. 32 mins; p = .05) and more frequent (7.1 vs. 8.4 samples; p = .06) Paco₂ sampling within 48 hrs of admission. Children 0–2 yrs had a longer time (75.0 mins) between admission and first Paco₂ sample than older children (44.3 mins; p < .01). The youngest children also had the highest incidence of severe hypocarbia on the first Paco₂ sample (31% vs. 19%; p = .02). Incidence of severe hypocarbia was high and did not decline (60% vs. 52%; p = .2) after the PG guidelines. However, over the 11 yrs, the odds of severe hypocarbia decreased (adjusted odds ratio 0.9; 95% confidence interval 0.84–0.96). During both periods, the incidence of severe hypocarbia was highest during the first 2 hrs after hospital admission. Intracranial pressure monitors were used more frequently post-PG. In 62 of 82 (77%) patients with severe hypocarbia in whom an intracranial pressure monitor was in place, the preceding intracranial pressure was <20 mm Hg. Severe hypocarbia independently predicted inpatient mortality (adjusted odds ratio 2.8; 95% confidence interval 1.3–5.9).

Conclusions: Although Paco₂ sampling was more frequent during the post-PG period and severe hypocarbia decreased during successive study years, the incidence of severe hypocarbia remained high during the first 48 hrs after hospital admission during the post-PG period. Time to Paco₂ sampling was longer in young children and associated with more severe hypocarbia. The presence of severe hypocarbia predicted mortality. (Pediatr Crit Care Med 2008; 9:141–146)

Key Words: hyperventilation; traumatic brain injury; outcome; children; Paco₂; hypoventilation
Hypocapnia in children with ABI

- Hypocapnia remains prominent in the management of ABI children.

- 2003 Pediatric Brain Trauma guidelines minimal impact.

- The youngest children (< 2y) had the highest incidence of severe hypocapnia.

- Severe hypocapnia was common in children without elevated ICP.
Hypocapnia in early ABI

- Hypocapnia seen in ABI patients even before ICU admission.

- 50% Michigan emergency physicians routinely employ prophylactic hyperventilation in patients with severe TBI.

- Accidental hyperventilation is also common.
  - Severe hypocapnia in 70% of patients transferred by helicopter to an US urban level I trauma center.

- 16% of intubated TBI patients en route to a Level I trauma center had PaCO₂ levels < 30 mmHg
  - 30% had levels of 30-35 mmHg.
3. Does Hypocapnia work?
**Mechanism of reduction of ICP**

- Hypocapnia is induced in order to lower ICP by decreasing the Cerebral Blood Volume

- Hypocapnia primarily affects Cerebral Blood Flow
  - It induces cerebral arterial vasoconstriction

- Hypocapnia effect pH mediated
  - Multiple mechanisms underlying effect, with NO centrally involved
  - ATP sensitive K+ channels also implicated

- CBF decreases by approximately 3% per mmHg change in PaCO2 (60 to 20 mmHg PCO2 range) in patients with TBI
• Effect of hypocapnia of CBV indirect
  – Predominantly acts to reduce arterial blood flow
  – 30% of CBF resides in the arteries
  – Hypocapnia has little effect on cerebral veins

• Effect of hypocapnia on CBF disproportionately greater than effect on CBV
  – 30% reduction in CBF results in 7% reduction in CBV

• More severe hypocapnia further reduced CBF but little effect on CBV.
Discredited concepts regarding Hypocapnia

- ‘Luxury perfusion’ of Injured Brain rare
  - CBF and Cerebral \( \text{O}_2 \) delivery \emph{reduced} following ABI
    esp in first 24 hours
  - Regional perfusion often severely reduced
  - Neuronal ischemia prominent in non-survivors

- ‘Inverse steal’ not seen
  - Responsiveness to \( \text{CO}_2 \) preserved in injured Brain
Ischemic Thresholds and $\text{CMRO}_2$

• ‘Mitochondrial dysfunction’ Hypothesis
  – Concept that injured brain may require less $\text{O}_2$ due to injury induced mitochondrial dysfunction
  – Reduced $\text{O}_2$ requirements as reason for reduced CBF in ABI
  – Potentially possible to further reduce perfusion without Injury

• Used to justify reduction of CBF below ‘ischemic’ thresholds

• Difficulty titrating hypocapnia safely to avoid regional ischemia on basis of global indices
Hypocapnia increases $\text{CMRO}_2$

- Hypocapnia can *increase* $\text{CMRO}_2$ in TBI

- Hypocapnia may increase neuronal excitability
  - increases cerebral glucose utilization
  - prolongs seizure activity
  - Increases production of cytotoxic excitatory amino acids

- Alkalosis inhibits the negative feed-back whereby low pH reduces cellular metabolism
Effects of hypocapnia on CBF via CSF pH

- Buffering of CSF pH occurs within 6-24 Hours
- Buffering within 4 hours of sustained hypocapnia in Volunteers
  - Raichle ME et al, Arch Neurol 1970
  - Rebound hyperaemia occurs on restoration of Normocapnia

Hypocapnia depletes CSF bicarbonate

- Larger swings in CSF pH and CBF with CO₂ changes
  - Tasker RC et al PCCM 2005
Mechanism of rebound Hyperemia
Key points re sustained Hypocapnia

- Buffering of CSF pH ablates effectiveness of hypocapnia,
  - CBF may return to baseline levels by 4 h.

- Difficult to further reduce CO\textsubscript{2} to decrease ICP acutely.
  - e.g. incipient herniation

- Rebound intracranial hypertension must be anticipated following restoration of normocapnia.

- Buffering capacity of CSF reduced with sustained hypcapnia
  - Increases slope of the relationship between CO\textsubscript{2} vs. CBF
4. Evidence for harmful effects of Hypocapnia
Hypocapnia causes Brain Ischemia

- Hypocapnia demonstrated to cause regional Ischemia
  - In Adults and Children with TBI

- Hypocapnia reduces SjO2 and increases lactate following resuscitation after Cardiac Arrest

- In experimental studies, hypocapnia
  - reduces regional CBF and local cortical tissue PO2,
  - reduces cerebral oxyhemoglobin and oxidised cytochrome aa3
  - increases cerebral deoxyhemoglobin
Hyperventilation following head injury: Effect on ischemic burden and cerebral oxidative metabolism

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**Objective:** To determine whether hyperventilation exacerbates cerebral ischemia and compromises oxygen metabolism (CMRO₂) following closed head injury.

**Design:** A prospective interventional study.

**Setting:** A specialist neurocritical care unit.

**Patients:** Ten healthy volunteers and 30 patients within 10 days of closed head injury.

**Interventions:** Subjects underwent oxygen-15 positron emission tomography imaging of cerebral blood flow, cerebral blood volume, CMRO₂, and oxygen extraction fraction. In patients, positron emission tomography studies, somatosensory evoked potentials, and jugular venous saturation (SjO₂) measurements were obtained at Paco₂ levels of 36 ± 3 and 29 ± 2 torr.

**Measurements and Main Results:** We estimated the volume of ischemic brain and examined the efficiency of coupling between oxygen delivery and utilization using the SD of the oxygen extraction fraction distribution. We correlated CMRO₂ to cerebral electrophysiology and examined the effects of hyperventilation on the amplitude of the cortical somatosensory evoked potential response. Patients showed higher ischemic brain volume than controls (17 ± 22 vs. 2 ± 3 mL; p ≤ .05), with worse matching of oxygen delivery to demand (p < .001). Hyperventilation consistently reduced cerebral blood flow (p < .001) and resulted in increases in oxygen extraction fraction and ischemic brain volume (17 ± 22 vs. 88 ± 66 mL; p < .0001), which were undetected by SjO₂ monitoring. Mean CMRO₂ was slightly increased following hyperventilation, but responses were extremely variable, with 28% of patients demonstrating a decrease in CMRO₂ that exceeded 95% prediction intervals for zero change in one or more regions. CMRO₂ correlated with cerebral electrophysiology, and cortical somatosensory evoked potential amplitudes were significantly increased by hyperventilation.

**Conclusions:** The acute cerebral blood flow reduction and increase in CMRO₂ secondary to hyperventilation represent physiologic challenges to the traumatized brain. These challenges exhaust physiologic reserves in a proportion of brain regions in many subjects and compromise oxidative metabolism. Such ischemia is underestimated by common bedside monitoring tools and may represent a significant mechanism of avoidable neuronal injury following head trauma. (Crit Care Med 2007; 35:568–578)

**Key Words:** ischemia; hyperventilation; positron emission tomography; trauma; head injury.
Adverse effects of prolonged hyperventilation in patients with severe head injury: a randomized clinical trial

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There is still controversy over whether or not patients should be hyperventilated after traumatic brain injury, and a randomized trial has never been conducted. The theoretical advantages of hyperventilation are cerebral vasoconstriction for intracranial pressure (ICP) control and reversal of brain and cerebrospinal fluid (CSF) acidosis. Possible disadvantages include cerebral vasoconstriction to such an extent that cerebral ischemia ensues, and only a short-lived effect on CSF pH with a loss of HCO₃⁻ buffer from CSF. The latter disadvantage might be overcome by the addition of the buffer tromethamine (THAM), which has shown some promise in experimental and clinical use. Accordingly, a trial was performed with patients randomly assigned to receive normal ventilation (PaCO₂ 35 ± 2 mm Hg [mean ± standard deviation]; control group), hyperventilation (PaCO₂ 25 ± 2 mm Hg; HV group), or hyperventilation plus THAM (PaCO₂ 25 ± 2 mm Hg; HV + THAM group). Stratification into subgroups of patients with motor scores of 1–3 and 4–5 took place. Outcome was assessed according to the Glasgow Outcome Scale at 3, 6, and 12 months. There were 41 patients in the control group, 36 in the HV group, and 36 in the HV + THAM group. The mean Glasgow Coma Scale score for each group was 5.7 ± 1.7, 5.6 ± 1.7, and 5.9 ± 1.7, respectively; this score and other indicators of severity of injury were not significantly different. A 100% follow-up review was obtained. At 3 and 6 months after injury the number of patients with a favorable outcome (good or moderately disabled) was significantly (p < 0.05) lower in the hyperventilated patients than in the control and HV + THAM groups. This occurred only in patients with a motor score of 4–5. At 12 months posttrauma this difference was not significant (p = 0.13). Biochemical data indicated that hyperventilation could not sustain alkalization in the CSF, although THAM could. Accordingly, cerebral blood flow (CBF) was lower in the HV + THAM group than in the control and HV groups, but neither CBF nor arteriovenous differences in oxygen data indicated the occurrence of cerebral ischemia in any of the three groups. Although mean ICP could be kept well below 25 mm Hg in all three groups, the course of ICP was most stable in the HV + THAM group. It is concluded that prophylactic hyperventilation is deleterious in head-injured patients with motor scores of 4–5. When sustained hyperventilation becomes necessary for ICP control, its deleterious effect may be overcome by the addition of THAM.

KEY WORDS: head injury · hyperventilation · tromethamine · outcome · cerebral blood flow · intracranial pressure
Table 5. Severe hypocarbia (SH) during the first 48 hrs after emergency department (ED) admission and mortality

<table>
<thead>
<tr>
<th>Predictor</th>
<th>AOR (95% CI) death</th>
</tr>
</thead>
<tbody>
<tr>
<td>ED GCS</td>
<td>0.56 (0.35–0.90)</td>
</tr>
<tr>
<td>Lowest ED SBP</td>
<td>0.97 (0.96–0.98)</td>
</tr>
<tr>
<td>ISS</td>
<td>1.07 (1.04–1.11)</td>
</tr>
<tr>
<td>Paco₂ sampling frequency</td>
<td>1.09 (1.02–1.17)</td>
</tr>
<tr>
<td>Year</td>
<td>0.87 (0.77–0.97)</td>
</tr>
<tr>
<td>SH episodes</td>
<td>Reference group</td>
</tr>
<tr>
<td>0</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.44 (0.56–3.73)</td>
</tr>
<tr>
<td>2</td>
<td>4.18 (1.58–11.03)</td>
</tr>
<tr>
<td>≥3</td>
<td>3.93 (1.61–9.62)</td>
</tr>
</tbody>
</table>

AOR, adjusted odds ratio; CI, confidence interval; GCS, Glasgow Coma Scale score; SBP, systolic blood pressure; ISS, Injury Severity Score.
Pre-Hospital Hypocapnia worsens Outcome

• Severe hypocapnia (end expired CO2 < 30 mmHg) reported in 70% of patients transferred by helicopter to an US urban level I trauma center.

• Warner et al. reported that 16% of intubated TBI patients en route to a Level I trauma center had PaCO2 levels < 30 mmHg, while 30% had levels of 30-35 mmHg.

• Pre-hospital hypocapnia worsens outcome in TBI.
Curley et al, Crit Care Med, 2010
5. Can hypocapnia be titrated to effect?
‘Moderate’ Hypocapnia

• Potential for harm minimized where hypocapnia used for short intervals for specific indications
  – Normocapnia restored as soon as feasible

• Moderate hypocapnia (PCO2 28mmHg) may temporarily improve cerebral autoregulation in head injured patients
  – more severe hypocapnia (PCO2 23 mmHg) impairs autoregulation
  – Duration of effect short-lived

• Even brief moderate hypocapnia produces critical reductions in Brain tissue PO2 in 20% patients with TBI

• No generic ‘safe’ threshold for hypocapnia in ABI
Proposed that hypocapnia be titrated to indices of Cerebral Oxygenation in individual patients.

20% TBI patients with increased ICP may have excess CBF based on SjO2 measurements
- ‘optimized’ hyperventilation proposed for these patients

Significant regional differences in oxygenation seen in the injured Brain.
- Regional monitors of brain oxygenation near penumbra of focal lesions

Limitations of global indicators of cerebral oxygenation clear

Titration of hypocapnia to CMRO2
- Confounded by effect of Hypocapnia in CMRO2?
6. Summary and Conclusions
Significant **regional** differences in oxygenation seen in the injured Brain.

- No ‘safe’ threshold level of hypocapnia

Presence of significant regional heterogeneity renders global indices of perfusion inadequate.

Regional brain tissue PO2 monitoring may enhance potential utility of titrated hypocapnia

Potential for direct injury for Hypocapnia remains
Current Clinical Role of Hypocapnia

- Strong rationale for use of hypocapnia in setting of imminent Brain herniation
  - Actual evidence limited

- Intra-operative use to facilitate access or acutely reduce brain bulk.

- Avoid accidental Hypocapnia

- Prophylactic hypocapnia has no Clinical role

- Where Hypocapnia is used in ABI patients
  - Clear rationale is required
  - Restrict to short term use while definitive measures instituted.
  - Restore normocapnia as soon as is feasible