Hypocapnia – benefit versus harm

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Key Questions

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

2. What are the benefits of Hypocapnia in the injured Brain?

3. How might hypocapnia harm the injured Brain?

4. What are the effects of hypocapnia on other organs?

5. Can we use hypocapnia safely in our ABI patients?
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Cranial cavity represents a fixed volume
- total volume of the intracranial contents must remain constant

Increase in intracranial volume initially compensated
- by displacement from another compartment.

When intracranial content volume exceeds a threshold, ICP rises precipitously
- sustained ICP >20 mmHg may cause secondary brain injury
- impairing cerebral perfusion, direct pressure, or by brainstem herniation.

Hypocapnia lowers ICP by decreasing the Cerebral Blood Volume
'Munro-Kellie Doctrine'

- Normocapnia
- Hypocapnia

Intracranial Pressure vs. Intracranial Volume
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
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Critically Elevated ICP

Potentially lifesaving Intervention for critically raised ICP
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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 $S_O_2$ 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
## Classification of severity of Hypocapnia

<table>
<thead>
<tr>
<th>Target PaCO₂ range</th>
<th>Classification</th>
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<tbody>
<tr>
<td>&lt;26 mmHg (&lt;3.5 kPa)</td>
<td>Intensified forced hyperventilation</td>
</tr>
<tr>
<td>26–30 mmHg (3.5–3.9 kPa)</td>
<td>Forced hyperventilation</td>
</tr>
<tr>
<td>31–35 mmHg (4.0–4.7 kPa)</td>
<td>Moderate hyperventilation</td>
</tr>
<tr>
<td>36–45 mmHg (4.8–6.0 kPa)</td>
<td>Normoventilation</td>
</tr>
</tbody>
</table>

*Note: Modified from Neuman et al*
Majority of patients hyperventilated did not have raised ICP
Key Findings

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

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

• Over 90% of patients with PaCO$_2$ $\leq$ 30 mmHg received no monitoring of brain oxygenation.
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.
Effect of Hypocapnia on 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

- 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 reduces CBF but little effect on CBV
Buffering of CSF pH ablates effectiveness of hypocapnia,
  - CBF may return to baseline levels by 4 hours.

Difficult to further reduce CO₂ 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 CO₂ vs. CBF
Effect of sustained hypocapnia on ICP

Normocapnia

Hypocapnia

Muizelaar JP, J Neurosurg 1991
Hyperventilation following head injury: Effect on ischemic burden and cerebral oxidative metabolism*

Jonathan P. Coles, PhD; Tim D. Fryer, PhD; Martin R. Coleman, PhD; Peter Smielewski, PhD; Arun K. Gupta, FRCA; Pawan S. Minhas, FRCS; Franklin Aigbirhio, Dphil; Doris A. Chatfield, BSc; Guy B. Williams, PhD; Simon Boniface,† FRCP; T. Adrian Carpenter, PhD; John C. Clark, DSc; John D. Pickard, FRCS; David K. Menon, PhD

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 S0 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 physiological 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
Unilateral Carotid Artery Ligation
8% oxygen

7 day postnatal Rats

Extent of Cerebral Infarcts

Hypocapnia (PCO₂ 26 mmHg)

Normocapnia (PCO₂ 42 mmHg)

Mild Hypercapnia (PCO₂ 54 mmHg)

Hypercapnia (PCO₂ 69 mmHg)

CO₂ in Hypoxic-Ischemic Brain Injury

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ARDS and Acute Brain Injury

Tasker R, Intens Care Med 1998; 24: 616-9
Experimental Pulmonary Edema due to Intermittent Positive Pressure Ventilation with High Inflation Pressures. Protection by Positive End-Exspiratory Pressure

HERBERT H. WEBB and DONALD F. TIERNEY
VENTILATION WITH LOWER TIDAL VOLUMES AS COMPARED WITH TRADITIONAL TIDAL VOLUMES FOR ACUTE LUNG INJURY AND THE ACUTE RESPIRATORY DISTRESS SYNDROME

THE ACUTE RESPIRATORY DISTRESS SYNDROME NETWORK

![Graph showing the proportion of patients over days after randomization for different tidal volume groups. The graph compares lower tidal volumes and traditional tidal volumes with survival and discharge outcomes.](Image)
Hypocapnia increases Lung Permeability

Laffey et al, Am J Resp Crit Care Med 2000
Hypocapnia and the injured brain: More harm than benefit

Gerard Curley, MB, FCARCSI; Brian P. Kavanagh, MD, FRCPC; John G. Laffey, MD, MA, BSc, FCARCSI

Table 3. Deleterious pulmonary effects of hypocapnia

- Reduced lung compliance (150)
  - Dysfunctional surfactant production (151)
  - Lamellar body depletion (155)
- Increased airway resistance
  - Increased bronchial tone (75, 197, 198)
  - Bronchial release of tachykinins (199)
- Direct parenchymal lung injury (152, 153)
  - Increased pulmonary capillary permeability (113)
  - Increased tracheal mucosal permeability (200)
  - Increased stretch induced lung injury (153, 154)
- Reduced systemic oxygenation
  - Reduced ventilation/perfusion matching (160)
  - Increased intrapulmonary shunt (160)
  - Reduced hypoxic vasoconstriction (201)
  - Increased ventilation heterogeneity (77, 160)
Hypocapnia and the injured brain: More harm than benefit

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Table 4. Deleterious cardiovascular effects of hypocapnia

<table>
<thead>
<tr>
<th>Reduced myocardial oxygen supply</th>
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<tbody>
<tr>
<td>Reduced coronary flow (161, 164)</td>
</tr>
<tr>
<td>Decreased collateral flow (163)</td>
</tr>
<tr>
<td>Increased coronary vascular resistance (162, 166)</td>
</tr>
<tr>
<td>Increased coronary artery spasm (167, 177)</td>
</tr>
<tr>
<td>Increased hemoglobin oxygen affinity (202)</td>
</tr>
<tr>
<td>Increased coronary microvascular leak (165)</td>
</tr>
<tr>
<td>Increased platelet number (203)</td>
</tr>
<tr>
<td>Increased platelet aggregation (174)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Increased myocardial oxygen demand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased heart rate (173)</td>
</tr>
<tr>
<td>Increased $O_2$ extraction (164, 170)</td>
</tr>
<tr>
<td>Increased (later decreased) contractility (169, 171)</td>
</tr>
<tr>
<td>Increased intracellular $Ca^{2+}$ (169)</td>
</tr>
<tr>
<td>Increased systemic vascular resistance (141)</td>
</tr>
<tr>
<td>Myocardial ischemia (164, 167, 204)</td>
</tr>
<tr>
<td>Increased myocardial reperfusion injury (112)</td>
</tr>
<tr>
<td>Ventricular and atrial arrhythmias (176–178)</td>
</tr>
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‘Moderate/Titrated’ Hypocapnia

- Moderate hypocapnia ($\text{PCO}_2$ 28 mmHg) may temporarily improve cerebral autoregulation in head injured patients
  - more severe hypocapnia ($\text{PCO}_2$ 23 mmHg) impairs autoregulation
  - Duration of effect short-lived

- Significant *regional* differences in oxygenation seen in the injured Brain.

- No generic ‘safe’ threshold for hypocapnia in ABI
‘Titration’ Hypocapnia

• 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

• Titration of hypocapnia to CMRO2
  – Confounded by effect of Hypocapnia in CMRO2?

• Significant *regional* differences in oxygenation seen in the injured
  – Regional monitors of brain oxygenation near penumbra of focal lesion
Using Hypocapnia in the Injured Brain

- 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
“Poison is in everything, and no thing is without poison. The dosage makes it either a poison or a remedy.”

Paracelsus (Philippus Theophrastus Aureolus Bombastus von Hohenheim), 16th century.
LUNG-SAFE

Large observational study to UNderstand the Global impact of Severe Acute respiratory FailurE

A multicentre, prospective, observational, 4-week inception cohort study

Northern Hemisphere: Feb-Mar 2014
Southern Hemisphere: Jun-Aug 2014

Join us!
http://www.esicm.org/research/lung-safe
lung-safe@esicm.org