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CRITICAL CARE

REVIEW

Pro/con debate: Should PaCO2 be tightly controlled in all patients with acute brain injuries?

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Abstract

You are the attending intensivist in a neurointensive care unit caring for a woman five days post-rupture of a cerebral aneurysm (World Federation of Neurological Surgeons Grade 4 and Fisher Grade 3). She is intubated for airway protection and mild hypoxemia related to an aspiration event at the time of aneurysm rupture, but is breathing spontaneously on the ventilator. Your patient is spontaneously hyperventilating with high tidal volumes despite minimal support and has developed significant hypocapnia. She has not yet developed the acute respiratory distress syndrome. You debate whether to tightly control her partial pressure of arterial carbon dioxide, weighing the known risks of acute hypocapnia in other forms of brain injury against the potential loss of clinical neuromonitoring associated with deep sedation and neuromuscular blockade in this patient who is at high risk of delayed ischemia from vasospasm. You are also aware of the potential implications of tidal volume control if this patient were to develop the acute respiratory distress syndrome and the effect of permissive hypercapnia on her intracranial pressure. In this paper we provide a detailed and balanced examination of the issues pertaining to this clinical scenario, including suggestions for clinical management of ventilation, sedation and neuromonitoring. Until more definitive clinical trial evidence is available to guide practice, clinicians are forced to carefully weigh the potential benefits of tight carbon dioxide control against the potential risks in each individual patient based on the clinical issues at hand.

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Clinical scenario

You are the attending intensivist in a neurointensive care unit. A 45-year-old woman is five days post-rupture of a cerebral aneurysm (World Federation of Neurological Surgeons Grade 4 and Fisher Grade 3). She is intubated and receiving mechanical ventilation for airway protection and mild hypoxemia presumed to be secondary to an aspiration event at the time of aneurysm rupture. She does not meet criteria for acute respiratory distress syndrome (ARDS) [1]. She currently localizes and opens eyes only to painful stimuli. The intracranial pressure is normal (9 mmHg) as measured by an externalized ventricular drain. She is spontaneously hyperventilating with high tidal volumes despite minimal ventilatory support, and has developed significant hypocapnia (partial pressure of arterial carbon dioxide (PaCO2) 25 mmHg) over the past 12 hours.

You know that hypocapnia is associated with poor neurological outcomes in other brain injuries, but recognize that controlling PaCO2 would require sedation and paralysis, thus precluding frequent neurological monitoring should she develop delayed cerebral ischemia from vasospasm. You estimate her risk of delayed cerebral ischemia to be 30%. In addition, you know that if she were to develop ARDS, provision of tidal volume limited ventilation is associated with improved mortality, but permissive hypercapnia may put her at risk for intracranial hypertension.

You ask yourself if the benefits of aggressively managing this patient's PaCO2 outweigh the risks of sedation, paralysis and possibly a delay in diagnosing cerebral vasospasm and delayed ischemia.

Introduction

Neurological injuries are one of the most common reasons for initiating mechanical ventilation in the ICU [2]. Provision of mechanical ventilation to brain-injured patients is complex. These patients are likely to be less forgiving of changes in arterial partial pressure of carbon dioxide (PaCO2) and the hemodynamic compromise associated with positive pressure ventilation.

Induced hyperventilation with hypocapnia is frequently observed in patients with brain injury who receive

mechanical ventilation [3]. Historically, induced hypocapnia has been utilized as a method to treat acute elevations in intracranial pressure (ICP) or to decrease cerebral hyperemia following traumatic brain injury. However, acute hypocapnia can also reduce brain perfusion sufficiently to induce brain ischemia and neuronal injury. Indeed, hypocapnia has been independently associated with worse outcomes in a variety of brain injuries [4-7]. In a randomized controlled clinical trial of patients with traumatic brain injury (TBI), those receiving moderate prophylactic hyperventilation, as compared with those with mild hyperventilation, had worse outcomes [8].

Patients with acute brain injuries may have spontaneous hyperventilation leading to hypocapnia and respiratory alkalosis. Although the effects of spontaneous hypocapnia on brain perfusion are not different to those in patients with induced hypocapnia, it is unclear whether controlling PaCO2 to protect cerebral perfusion offsets the potential complications of the requirement for sedation and neuromuscular blockade. In the absence of data demonstrating how to weigh these competing risks, clinicians are faced with a dilemma.

In this article we will explore the advantages and disadvantages of controlling hypocapnia in brain injury, in the context of the aforementioned scenario of a patient with an aneurysmal subarachnoid hemorrhage who is now spontaneously hyperventilating. For the rest of this article, we assume hypocapnia to mean hypocapnia with respiratory alkalosis, to differentiate it from compensatory hypocapnia found with metabolic acidosis or other metabolic derangements.

Background

Hypocapnia and cerebral hemodynamics

Arterial levels of carbon dioxide (PaCO2) are maintained through a balance between production and elimination of carbon dioxide. In the physiological state, low PaCO2 is usually the result of an increased rate of carbon dioxide elimination through increased alveolar minute ventilation (that is, hyperventilation).

Carbon dioxide is a potent vasodilator of the cerebral vasculature, and hypocapnia causes rapid arterial constriction and a reduction in cerebral blood flow (CBF). This reduction in CBF is related to changes in pH within the perivascular space of the small arterioles of the brain [9,10]. This effect is dramatic: some studies have reported decreases in cerebral perfusion as much as 3% for every 1 mmHg reduction in arterial PaCO2 [11]. Furthermore, in healthy volunteers, CBF can be reduced by over 30% with hyperventilation [10]. However, the acute reduction in CBF mediated by hypocapnia is short-lived. As the perivascular space is buffered, local pH drops towards normal and cerebral vasculature acclimatizes to a lower PaCO2. This buffering occurs within 6 to 12 hours after the onset of hypocapnia, with substantial restoration of CBF towards baseline observed as early as 30 minutes after onset of hypocapnia in both healthy volunteers and brain-injured patients [9,10].

Historical uses of induced hypocapnia

Induced hyperventilation with hypocapnia has been used for the acute treatment of intracranial hypertension and critically raised ICP. In patients with high ICP, reductions in CBF and the resultant decrease in intracranial blood volume can provide a lifesaving, albeit temporary, decrease in ICP and restoration of cerebral perfusion pressure. It is important to note that the extent to which ICP changes with decreasing CBF depends on the pressure-volume status of the cranial vault. Because the volume of the cranium is fixed, in the normal state any increases in the volume of intracranial brain or blood are accommodated by displacement of cerebrospinal fluid (CSF) into the thecal space, thus preventing life-threatening increases in ICP. In cases where intracranial compensatory reserve is low or exhausted (the CSF-filled ventricles are collapsed or obstructed), even small changes in cerebral blood volume may result in large changes in ICP, and hence the efficacy of acute induced hypocapnia in life-threatening intracranial hypertension [11].

Longer-term and prophylactic use of induced hypocapnia has been more controversial and its use has waxed and waned over the past four decades. Mild to moderate hypocapnia is commonly observed in brain-injured patients who receive mechanical ventilation both within [3] and outside of the hospital [12]. This occurs despite the current recommendation of major TBI treatment guidelines to maintain eucapnia and avoid chronic or prophylactic hyperventilation [13].

Pro: Tight control of PaCO2 is indicated in this patient with acute brain injury

Proponents of tight control of PaCO2 in brain injury contend that hypocapnia is associated with deleterious reductions in CBF, thus increasing the potential for cerebral ischemia in a vulnerable, acutely injured brain. There is a substantial amount of data demonstrating that hypocapnia induces cerebral ischemia and metabolic crisis [14-17]. Furthermore, there are data linking induced hypocapnia with poor clinical outcomes in a variety of acute brain injuries [4-6,8,18,19].

Hypocapnia decreases cerebral perfusion and induces cerebral ischemia

In contrast to patients with critical intracranial hypertension, hypocapnia in other patient populations is associated with a reduction in CBF. Reductions in CBF may put brain tissue at risk of ischemia and irreversible

infarction, and the acutely injured brain may be at increased risk as cerebral perfusion and metabolism is already compromised. Hypocapnia is one of the most common identifiable causes of jugular venous oxygenation desaturation [20-22], decreased brain tissue oxygen tension [23,24] and cerebral hypoperfusion evident on imaging studies [15,16].

Most existing data suggest that hypocapnia-induced decreases in brain perfusion lead to brain tissue ischemia. Although an acutely injured brain may be relatively protected from ischemia in the face of decreasing CBF by (1) lower metabolic requirements and (2) an increased oxygen extraction fraction [25,26], most studies have demonstrated that reduction in CBF during acute hypocapnia does induce brain tissue ischemia [15-17]. Coles and colleagues [15,16] reported that even brief periods of moderate hypocapnia (<34 mmHg) can result in a significant increase in the volume of critically hypoperfused tissue in the injured brain and, further, an increase in oxygen extraction fraction. It is interesting to note that observed increases in hypoperfused brain volume occurred despite improvements in ICP and cerebral perfusion pressure, as well as maintenance of jugular venous oxygen saturation (SjvO2) levels >50% in all patients, a level usually interpreted as indicative of adequate global delivery of cerebral oxygen [16]. Another study, using cerebral microdialysis in patients with TBI, found evidence of anaerobic metabolism (defined as an increase in concentrations of glutamate, lactate and an increased lactate:pyruvate ratio) with hyperventilation [17]. These findings suggest that hypocapnia-related cerebral hypoperfusion was sufficient to cause metabolic crisis and potential neuronal injury [17]. Finally, hypocapnia has also been associated with excitatory cellular responses that may lead to secondary brain injury [27,28], and worsen ischemia-reperfusion injury [29,30].

Association between induced hypocapnia and poor clinical outcomes

Hypocapnia has been independently associated with poor neurological outcome in patients with a variety of acute brain injuries. To date, only one randomized clinical trial has been conducted evaluating the impact of induced hyperventilation on clinical outcomes in patients with TBI [8]. In this study, individuals receiving severe induced hypocapnia (PaCO2 25 mmHg) had worse functional outcomes compared to control (PaCO2 35 mmHg) at three and six months. This difference continued out to 12 months follow-up, although it was not statistically significant.

A significant amount of observational data link hypocapnia with poor clinical outcomes [4-6,18,19]. These include several studies in which pre-hospital hypocapnia or hypocapnia on presentation was identified as an independent risk factor for poor outcome. Hypocapnia has been clearly linked to decreased brain tissue oxygen tension [23,24], and other observational data have linked duration of brain tissue oxygen tension below 15 mmHg with worse outcomes [31-33]. Although causal inferences from these observational studies are limited, the direction and strength of association are all consistent and also might suggest that the duration of hypocapnia required to induce significant injury to a vulnerable brain is very short.

Finally, associations between hypocapnia and poor clinical outcomes or neuropsychiatric deficits have also been observed during anesthesia, cardiac surgery and extracorporeal lung assist in patients without primary acute brain injury [34-38]. During general anesthesia of healthy individuals, the risk of transient psychomotor and cognitive dysfunction is increased with exposure to hypocapnia [34], and mitigated by higher PaCO2 levels during anesthesia [35]. In a study by Graziani and colleagues [38], lower intraoperative end-tidal carbon dioxide (EtCO2) values were independently associated with longer hospital length of stay. Further, poor neurological outcomes associated with low PaCO2 are not limited to adult populations [37,38].

Spontaneous hypocapnia

Spontaneous hyperventilation was observed in brain-injured patients over four decades ago [39], yet little is known about its effects on brain oxygenation and clinical outcomes. The exact mechanism for spontaneous hyperventilation in brain injury is unclear. Theories include loss of descending inhibitory signals to the medullary respiratory centers, increased stimulation of J-receptors in the lung as a result of pulmonary edema, increased reflex hypoxic respiratory drive and concurrent systemic inflammatory responses [40].

Although most of the published data linking cerebral ischemia to hypocapnia have been in the context of induced hyperventilation, there is little physiologic rationale to suggest that spontaneous hypocapnia may be any less harmful than induced hypocapnia. A recent prospective observational trial by Carrera and colleagues [14] evaluated spontaneous hypocapnia in a mixed population of patients with severe brain injury (Glasgow Coma Scale score <8), including TBI, subarachnoid hemorrhage and intracranial hemorrhage. They found hypocapnia to be significantly associated with an increased risk of brain tissue hypoxia (defined by brain tissue oxygen tension (PbtO2) <15 mmHg).

In summary, data suggest that both induced and spontaneous acute hypocapnia are associated with decreases in CBF, worsening brain tissue hypoxia, and worse clinical outcomes. These findings are consistent across available data from animal models, human observational

studies and, although limited, clinical trials. Although definitive controlled clinical trial data demonstrating benefit of tight PaCO2 control in spontaneously breathing patients is unavailable, proponents of such an approach argue that there is sufficiently strong rationale to tightly control and prevent acute hypocapnia in patients with acute brain injury.

Con: Tight control of PaCO2 is not indicated in this patient

As presented above, there is considerable data associating hypocapnia with deleterious effects on brain physiology and worse clinical outcomes. In light of these data, avoidance of hypocapnia in acutely brain-injured patients during controlled mechanical ventilation is appropriate given the possible harms.

A challenge arises, however, in intubated patients who are spontaneously breathing with high minute ventilation and resultant hypocapnia. There is little physiologic reason to suspect that the cerebrovascular effects of spontaneous hypocapnia would be different to those of induced hypocapnia. The control of PaCO2 in these patients, however, may require sedatives and opioids to blunt respiratory drive and ultimately neuromuscular blockade may be necessary to prevent spontaneous breathing or ventilator dyssynchrony. These measures are associated with several disadvantages, including (1) drug-related adverse effects (including both drug-specific effects as well as the risks of prolonged sedation in the ICU), and (2) a decrease in clinical neuromonitoring. There are no data demonstrating overall benefit to actively controlling PaCO2 in spontaneously breathing patients in this scenario, so it is important to weigh the potential benefits and risks of ventilatory control for each patient.

The risks of sedation and neuromuscular blockade

Although sedatives are integral in the care of critically ill patients, multiple adverse effects are associated with the use of these agents; hemodynamic instability is commonly observed with increased doses of sedatives, and may prolong the need for mechanical ventilation [41], increasing the risk of pneumonia [42]. Further, the use of such agents has been independently associated with an increased risk of ICU delirium [43] and posttraumatic stress disorder [44]. Indeed, strategies to limit and prevent accumulation of sedatives have been shown to decrease duration of mechanical ventilation, ICU length of stay and posttraumatic stress disorder in survivors of critical illness [44-47].

Neuromuscular blockers also have adverse effects. Paralysis suppresses the cough reflex, resulting in retention of secretions and atelectasis, both of which increase the risk of pulmonary infections. Prolonged immobility may also increase the risk of venous thromboembolic events, peripheral nerve injuries, skin breakdown, stasis ulcers, and slowed gastric motility [48]. Neuromuscular blockade has also been shown to be a risk factor for critical illness myopathy and neuropathy [49].

Sedation prevents monitoring of clinical neurologic status

Despite the aforementioned drawbacks to the use of sedation and neuromuscular blockade, perhaps the most significant disadvantage to their use to control PaCO2 in acutely brain-injured patients is the loss of close clinical neuromonitoring. Although significant occult secondary brain injury may occur following acute brain injury, clinical examination remains an important component of monitoring patients in the ICU. Surrogate markers of brain physiology and metabolism may be monitored through alternative monitoring modalities (transcranial doppler sonography, brain tissue oximetry, jugular bulb oximetry and cerebral microdialysis) [50,51], but these modes are often restricted to a small area of sampled brain and thus may not reflect perfusion and metabolism of other areas of the brain.

The loss of clinical monitoring is particularly important to patients with subarachnoid hemorrhage because these patients are at significant risk of delayed cerebral ischemia from vasospasm, and as such close clinical monitoring is important for detecting early signs of ischemia to prevent irreversible cerebral infarction. Correlation of clinical and radiological evidence of cerebral vasospasm is vital as a significant proportion of patients will develop radiographic cerebral vasospasm without symptoms, and vice versa. Although other modalities of neuromonitoring can be used when clinical exams are unavailable (for example, brain tissue oxygenation in traumatic brain injury), these modalities lack optimal sensitivity or specificity when used as screening tests for cerebral vasospasm and delayed cerebral ischemia [52,53].

Ultra-short acting sedatives and opioids (for example, remifentanil) have become increasingly popular in certain centers caring for patients with acute brain injuries [54-56] because these agents potentially allow both control of PaCO2 and repeated rapid awakenings for neurological observation. Significant decreases in PaCO2 can occur as patients hyperventilate on emergence from sedation, only to normalize when anesthesia is re-induced following clinical examination. It is possible that these repeated periods of acute hypocapnia, with resultant decreases in cerebral blood flow, may be even more harmful to the brain than prolonged hypocapnia where plasma and CSF buffering partially normalize cerebral perfusion over several hours [9].

Finally, the pathophysiology leading to spontaneous hyperventilation following acute brain injury is not fully

understood. Indeed, this lack of a causal understanding confounds observations linking spontaneous hypocapnia and poor neurological outcome. It remains unclear whether poor outcomes observed are due to the hypocapnia or if the hypocapnia is simply related to the higher severity of illness or greater burden of brain injury.

In summary, in the setting of isolated hyperventilation with hypocapnia in a patient with brain injury, tight control of hypocapnia via controlled mechanical ventilation may not be indicated given the risks of sedation, neuromuscular blockade, the loss of clinical monitoring and the lack of demonstrable overall clinical benefit.

Lung protective ventilation and the risk of permissive hypercapnia

In the scenario presented at the beginning of this debate, our patient was spontaneously hyperventilating, but was also receiving mechanical ventilation because of an aspiration event. Though oxygenation may not have initially been an issue, this patient is at risk of developing ARDS. The development of ARDS following subarachnoid hemorrhage is common, and has been independently associated with worse outcomes [57]. Therefore, in cases of patients with subarachnoid hemorrhage and ARDS, perhaps the most compelling and evidence-based reason to control ventilation would be for protection against ventilator-induced lung injury by limiting tidal volumes, distending pressures and cyclical tidal recruitment, an approach that has been shown to decrease mortality in a general population of patients with ARDS [58].

In patients with subarachnoid hemorrhage, despite the high incidence of ARDS, only 30% of patients with ARDS received low tidal-volume ventilation [57]. A potential reason for this is the concern amongst healthcare providers that low-tidal volume ventilation could increase ICP through hypercapnia-related cerebral vasodilation. Lung-protective ventilation does not necessarily imply hypercapnia or respiratory acidosis. In two landmark ARDSnet studies, the mean PaCO2 of enrolled patients did not change appreciably over the first 72 hours, and respiratory acidosis was uncommon [58,59]. Another observational study also found that the use of lung-protective ventilation was not associated with differences in pH or PaCO2 in patients with ARDS following subarachnoid hemorrhage [57].

Secondly, it is important to realize that the impact of acute changes in PaCO2 will depend to a great degree on intracranial compliance, and the ability of the brain to accommodate a small increase in intracranial blood volume should it occur. Most patients with adequate compensatory reserve are able to accommodate small changes in PaCO2 with negligible effect on their ICP.

In summary, the high incidence of ARDS in patients with brain injuries should prompt all providers to be vigilant in screening for this disorder and institute lung protective mechanical ventilation wherever possible. The existing data suggest that most patients, even with relative sensitivity to PaCO2 increases, are able to tolerate lung-protective ventilation safely.

Conclusions and recommendations

In this scenario a patient developed hypocapnia as a result of spontaneous hyperventilation following an aneurysmal subarachnoid hemorrhage. The dilemma of whether to sedate this patient in order to take control of their ventilation and tightly control PaCO2 is founded on the competing interests of (1) control of ventilation and PaCO2 to optimize cerebral perfusion and (2) the loss of clinical monitoring with heavy sedation and neuromuscular blockade. When summed together, tight control of our patient's PaCO2 may not be indicated on its own.

As previously stated, however, patients with subarachnoid hemorrhage commonly develop ARDS. Such cases would thus be further complicated by the consideration of providing best practice lung-protective ventilation. Therefore, if we were to assume our patient went on to develop ARDS (while preserving normal ICP), our practice and suggestion would be to prioritize lung protective ventilation given the mortality benefit associated with this mechanical ventilation strategy in clinical trials and our belief that any changes in PaCO2 (which are unlikely) will usually be tolerated from a brain perfusion point of view. We would first review the brain imaging (to assess ventricular size, cerebral edema and effacement of sulci and basal cisterns) to ensure there is no radiographic evidence of limited compensatory reserve. Many such patients would have an externalized ventricular drain that would allow measurement of ICP, but in the absence of a drain, consideration should be made to insertion of an ICP monitor. If significant hypercapnia develops during lung-protective ventilation with evidence of high ICP or limited intracranial compensatory reserve, then we would first carefully address anything that may decrease CO_2 removal or respiratory system compliance (for example, remove any dead space in the ventilation circuit, drain large pleural effusions or ascites, and so on) and finally relax restriction of tidal volumes to reduce PaCO2.

As previously discussed, it is not clear that tight control of PaCO2 is beneficial to patients overall and it is unknown if the improvement of cerebral perfusion by avoidance of spontaneous hypocapnia outweighs the risks of sedation. In the absence of evidence to guide patient care, we would attempt to be highly selective and control PaCO2 only in patients who are at highest risk of

evolving brain ischemia (for example, vasospasm), and in whom a reduction in CBF might result in permanent neurological injury. The presented scenario is an example of such a case, as the reduction in CBF in the context of evolving vasospasm could lead to catastrophic and widespread cerebral infarction. Our practice in such patients is to sedate with short acting sedatives and opioids (propofol and remifentanil) to allow intermittent neurological observation. When interrupting sedation for neurological examinations, we typically interrupt sedatives first, and once the patient's level of arousal has improved we interrupt remifentanil immediately prior to neurological examination; we have observed that this approach limits swings in PaCO2 with emergence from sedation and resumption of the patient's spontaneous hyperventilation. These patients receive monitoring with end tidal CO_2 monitoring, frequent arterial blood gas monitoring, ICP monitoring and daily or bi-daily transcranial doppler for vasospasm surveillance.

The neurocritical care community is in need of research evaluating optimal ventilation strategies in patients with acute brain injuries. Discovery of the exact mechanism and pathophysiology of spontaneous hyperventilation in brain injury would be critical not only to understand its potential impact on patients, but also to identify opportunities to modify ventilation if this proves to be a harmful or maladaptive response. Future clinical research regarding PaCO2 control in patients with brain injuries should employ functional outcomes (such as modified Rankin score) as primary endpoints, as the question is not whether control of PaCO2 affects cerebrovascular dynamics, but whether the balance between risks of hypocapnia and sedation favors aggressive PaCO2 control by sedation and anesthesia.

Abbreviations
ARDS, acute respiratory distress syndrome; CBF, cerebral blood flow; CSF, cerebrospinal fluid; ICP, intracranial pressure; PaCO2, partial pressure of arterial carbon dioxide; TBI, traumatic brain injury.

Competing interests
The authors declare that they have no competing interests.

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Authors' contributions
JMS conceived the idea for the manuscript. JMS and SLG together drafted the manuscript and provided critical revisions.

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References

1. The ARDS Definition Task Force: **Acute respiratory distress syndrome: the Berlin definition.** *JAMA* 2012, **307:**2526-2533.
2. Pelosi P, Ferguson ND, Frutos-Vivar F, Anzueto A, Putensen C, Raymondos K, Apezteguia C, Desmery P, Hurtado J, Abroug F, Elizalde J, Tomicic V, Cakar N, Gonzalez M, Arabi Y, Moreno R, Esteban A: **Management and outcome of mechanically ventilated neurologic patients.** *Crit Care Med* 2011, **39:**1482-1492.
3. Neumann JO, Chambers IR, Citerio G, Enblad P, Gregson BA, Howells T, Mattern J, Nilsson P, Piper I, Ragauskas A, Sahuquillo J, Yau YH, Kiening K: **The use of hyperventilation therapy after traumatic brain injury in Europe: an analysis of the BrainIT database.** *Intensive Care Med* 2008, **34:**1676-1682.
4. Rout MW, Lane DJ, Wollner L: **Prognosis in acute cerebrovascular accidents in relation to respiratory pattern and blood gas tensions.** *BMJ* 1971, **3:**7-9.
5. Warner KJ, Cuschieri J, Copass MK, Jurkovich GJ, Bulger EM: **The impact of prehospital ventilation on outcome after severe traumatic brain injury.** *J Trauma* 2007, **62:**1330-1336; discussion 1336-1338.
6. Davis DP, Idris AH, Sise MJ, Kennedy F, Eastman AB, Velky T, Vilke GM, Hoyt DB: **Early ventilation and outcome in patients with moderate to severe traumatic brain injury.** *Crit Care Med* 2006, **34:**1202-1208.
7. Caulfield EV, Dutton RP, Floccare DJ, Stansbury LG, Scalea TM: **Prehospital hypocapnia and poor outcome after severe traumatic brain injury.** *J Trauma* 2009, **66:**1577-1582.
8. Muizelaar JP, Marmarou A, Ward JD, Kontos HA, Choi SC, Becker DP, Gruemer H, Young HF: **Adverse effects of prolonged hyperventilation in patients with severe head injury: a randomized clinical trial.** *J Neurosurg* 1991, **75:**731-739.
9. Raichle ME, Posner JB, Plum F: **Cerebral blood flow during and after hyperventilation.** *Arch Neurol* 1970, **23:**394-403.
10. Fortune JB, Feustel PJ, deLuna C, Graca L, Hasselbarth J, Kupinski AM: **Cerebral blood flow and blood volume in response to O2 and CO2 changes in normal humans.** *J Trauma* 1995, **39:**463-471; discussion 471-462.
11. Curley G, Kavanagh BP, Laffey JG: **Hypocapnia and the injured brain: more harm than benefit.** *Crit Care Med* 2010, **38:**1348-1359.
12. Davis DP, Heister R, Poste JC, Hoyt DB, Ochs M, Dunford JV: **Ventilation patterns in patients with severe traumatic brain injury following paramedic rapid sequence intubation.** *NeurocritCare* 2005, **2:**165-171.
13. Bratton SL, Chestnut RM, Ghajar J, McConnell Hammond FF, Harris OA, Hartl R, Manley GT, Nemecek A, Newell DW, Rosenthal G, Schouten J, Shutter L, Timmons SD, Ullman JS, Videtta W, Wilberger JE, Wright DW: **Guidelines for the management of severe traumatic brain injury. XIV. Hyperventilation.** *J Neurotrauma* 2007, **24 Suppl 1:**S87-90.
14. Carrera E, Schmidt JM, Fernandez L, Kurtz P, Merkow M, Stuart M, Lee K, Claassen J, Sander Connolly E, Mayer SA, Badjatia N: **Spontaneous hyperventilation and brain tissue hypoxia in patients with severe brain injury.** *J Neurol Neurosurg Psychiatry* 2010, **81:**793-797.
15. Coles JP, Fryer TD, Coleman MR, Smielewski P, Gupta AK, Minhas PS, Aigbirhio F, Chatfield DA, Williams GB, Boniface S, Carpenter TA, Clark JC, Pickard JD, Menon DK: **Hyperventilation following head injury: effect on ischemic burden and cerebral oxidative metabolism.** *Crit Care Med* 2007, **35:**568-578.
16. Coles JP, Minhas PS, Fryer TD, Smielewski P, Aigbirihio F, Donovan T, Downey SP, Williams G, Chatfield D, Matthews JC, Gupta AK, Carpenter TA, Clark JC, Pickard JD, Menon DK: **Effect of hyperventilation on cerebral blood flow in traumatic head injury: clinical relevance and monitoring correlates.** *Crit Care Med* 2002, **30:**1950-1959.
17. Marion DW, Puccio A, Wisniewski SR, Kochanek P, Dixon CE, Bullian L, Carlier P: **Effect of hyperventilation on extracellular concentrations of glutamate, lactate, pyruvate, and local cerebral blood flow in patients with severe traumatic brain injury.** *Crit Care Med* 2002, **30:**2619-2625.
18. North JB, Jennett S: **Abnormal breathing patterns associated with acute brain damage.** *Arch Neurol* 1974, **31:**338-344.
19. Davis DP, Dunford JV, Poste JC, Ochs M, Holbrook T, Fortlage D, Size MJ, Kennedy F, Hoyt DB: **The impact of hypoxia and hyperventilation on outcome after paramedic rapid sequence intubation of severely head-injured patients.** *J Trauma* 2004, **57:**1-8.
20. Schneider GH, von Helden A, Lanksch WR, Unterberg A: **Continuous monitoring of jugular bulb oxygen saturation in comatose patients--therapeutic implications.** *Acta Neurochir (Wien)* 1995, **134:**71-75.
21. Sheinberg M, Kanter MJ, Robertson CS, Contant CF, Narayan RK, Grossman RG: **Continuous monitoring of jugular venous oxygen saturation in head-**

injured patients. *J Neurosurg* 1992, **76:**212-217.
22. von Helden A, Schneider GH, Unterberg A, Lanksch WR: **Monitoring of jugular venous oxygen saturation in comatose patients with subarachnoid haemorrhage and intracerebral haematomas.** *Acta Neurochir Suppl (Wien)* 1993, **59:**102-106.
23. Imberti R, Bellinzona G, Langer M: **Cerebral tissue PO2 and SjvO2 changes during moderate hyperventilation in patients with severe traumatic brain injury.** *J Neurosurg* 2002, **96:**97-102.
24. Schneider GH, Sarrafzadeh AS, Kiening KL, Bardt TF, Unterberg AW, Lanksch WR: **Influence of hyperventilation on brain tissue-PO2, PCO2, and pH in patients with intracranial hypertension.** *Acta Neurochir Suppl* 1998, **71:**62-65.
25. Diringer MN, Yundt K, Videen TO, Adams RE, Zazulia AR, Deibert E, Aiyagari V, Dacey RG Jr, Grubb RL Jr, Powers WJ: **No reduction in cerebral metabolism as a result of early moderate hyperventilation following severe traumatic brain injury.** *J Neurosurg* 2000, **92:**7-13.
26. Diringer MN, Videen TO, Yundt K, Zazulia AR, Aiyagari V, Dacey RG, Grubb RL, Powers WJ: **Regional cerebrovascular and metabolic effects of hyperventilation after severe traumatic brain injury.** *J Neurosurg* 2002, **96:**103-108.
27. Graham EM, Apostolou M, Mishra OP, Delivoria-Papadopoulos M: **Modification of the N-methyl-D-aspartate (NMDA) receptor in the brain of newborn piglets following hyperventilation induced ischemia.** *Neurosci Lett* 1996, **218:**29-32.
28. Pastuszko P, Wilson DF: **Activation of tyrosine hydroxylase in striatum of newborn piglets in response to hypocapnic ischemia and recovery.** *Adv Exp Med Biol* 1997, **411:**65-73.
29. Vannucci RC, Towfighi J, Heitjan DF, Brucklacher RM: **Carbon dioxide protects the perinatal brain from hypoxic-ischemic damage: an experimental study in the immature rat.** *Pediatrics* 1995, **95:**868-874.
30. Vannucci RC, Brucklacher RM, Vannucci SJ: **Effect of carbon dioxide on cerebral metabolism during hypoxia-ischemia in the immature rat.** *Pediatr Res* 1997, **42:**24-29.
31. Bratton SL, Chestnut RM, Ghajar J, McConnell Hammond FF, Harris OA, Hartl R, Manley GT, Nemecek A, Newell DW, Rosenthal G, Schouten J, Shutter L, Timmons SD, Ullman JS, Videtta W, Wilberger JE, Wright DW: **Guidelines for the management of severe traumatic brain injury. X. Brain oxygen monitoring and thresholds.** *J Neurotrauma* 2007, **24 Suppl 1:**S65-70.
32. van den Brink WA, van Santbrink H, Steyerberg EW, Avezaat CJ, Suazo JA, Hogesteeger C, Jansen WJ, Kloos LM, Vermeulen J, Maas AI: **Brain oxygen tension in severe head injury.** *Neurosurgery* 2000, **46:**868-876; discussion 876-868.
33. Valadka AB, Gopinath SP, Contant CF, Uzura M, Robertson CS: **Relationship of brain tissue PO2 to outcome after severe head injury.** *Crit Care Med* 1998, **26:**1576-1581.
34. Wollman SB, Orkin LR: **Postoperative human reaction time and hypocarbia during anaesthesia.** *Br J Anaesth* 1968, **40:**920-926.
35. Hovorka J: **Carbon dioxide homeostasis and recovery after general anaesthesia.** *Acta Anaesthesiol Scand* 1982, **26:**498-504.
36. Wax DB, Lin HM, Hossain S, Porter SB: **Intraoperative carbon dioxide management and outcomes.** *Eur J Anaesthesiol* 2010, **27:**819-823.
37. du Plessis AJ, Jonas RA, Wypij D, Hickey PR, Riviello J, Wessel DL, Roth SJ, Burrows FA, Walter G, Farrell DM, Walsh AZ, Plumb CA, del Nido P, Burke RP, Castaneda AR, Mayer JE Jr, Newburger JW: **Perioperative effects of alpha-stat versus pH-stat strategies for deep hypothermic cardiopulmonary bypass in infants.** *J Thorac Cardiovasc Surg* 1997, **114:**991-1000; discussion 1000-1001.
38. Graziani LJ, Gringlas M, Baumgart S: **Cerebrovascular complications and neurodevelopmental sequelae of neonatal ECMO.** *Clin Perinatol* 1997, **24:**655-675.
39. Leitch AG, McLennan JE, Balkenhol S, Loudon RG, McLaurin RL: **Mechanisms of hyperventilation in head injury: case report and review.** *Neurosurgery* 1979, **5:**701-707.
40. Leitch AG, McLennan JE, Balkenhol S, McLaurin RL, Loudon RG: **Ventilatory response to transient hyperoxia in head injury hyperventilation.** *J Appl Physiol* 1980, **49:**52-58.
41. Kollef MH, Levy NT, Ahrens TS, Schaiff R, Prentice D, Sherman G: **The use of continuous i.v. sedation is associated with prolongation of mechanical ventilation.** *Chest* 1998, **114:**541-548.
42. Rello J, Diaz E, Roque M, Valles J: **Risk factors for developing pneumonia within 48 hours of intubation.** *Am J Respir Crit Care Med* 1999, **159:**1742-1746.
43. Pandharipande P, Shintani A, Peterson J, Pun BT, Wilkinson GR, Dittus RS, Bernard GR, Ely EW: **Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients.** *Anesthesiology* 2006, **104:**21-26.
44. Girard TD, Shintani AK, Jackson JC, Gordon SM, Pun BT, Henderson MS, Dittus RS, Bernard GR, Ely EW: **Risk factors for post-traumatic stress disorder symptoms following critical illness requiring mechanical ventilation: a prospective cohort study.** *Crit Care* 2007, **11:**R28.
45. Kress JP, Pohlman AS, O'Connor MF, Hall JB: **Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation.** *N Engl J Med* 2000, **342:**1471-1477.
46. Kress JP, Gehlbach B, Lacy M, Pliskin N, Pohlman AS, Hall JB: **The long-term psychological effects of daily sedative interruption on critically ill patients.** *Am J Respir Crit Care Med* 2003, **168:**1457-1461.
47. Girard TD, Kress JP, Fuchs BD, Thomason JW, Schweickert WD, Pun BT, Taichman DB, Dunn JG, Pohlman AS, Kinniry PA, Jackson JC, Canonico AE, Light RW, Shintani AK, Thompson JL, Gordon SM, Hall JB, Dittus RS, Bernard GR, Ely EW: **Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial.** *Lancet* 2008, **371:**126-134.
48. Sharpe MD: **The use of muscle relaxants in the intensive care unit.** *Can J Anaesth* 1992, **39:**949-962.
49. Maramattom BV, Wijdicks EFM: **Acute neuromuscular weakness in the intensive care unit.** *Crit Care Med* 2006, **34:**2835-2841.
50. Bhatia A, Gupta AK: **Neuromonitoring in the intensive care unit. I. Intracranial pressure and cerebral blood flow monitoring.** *Intensive Care Med* 2007, **33:**1263-1271.
51. Bhatia A, Gupta AK: **Neuromonitoring in the intensive care unit. II. Cerebral oxygenation monitoring and microdialysis.** *Intensive Care Med* 2007, **33:**1322-1328.
52. Heran NS, Hentschel SJ, Toyota BD: **Jugular bulb oximetry for prediction of vasospasm following subarachnoid hemorrhage.** *Can J Neurol Sci* 2004, **31:**80-86.
53. Marshall SA, Nyquist P, Ziai WC: **The role of transcranial Doppler ultrasonography in the diagnosis and management of vasospasm after aneurysmal subarachnoid hemorrhage.** *Neurosurg Clin N Am* 2010, **21:**291-303.
54. Egerod I, Jensen MB, Herling SF, Welling KL: **Effect of an analgo-sedation protocol for neurointensive patients: a two-phase interventional non-randomized pilot study.** *Crit Care* 2010, **14:**R71.
55. Karabinis A, Mandragos K, Stergiopoulos S, Komnos A, Soukup J, Speelberg B, Kirkham AJ: **Safety and efficacy of analgesia-based sedation with remifentanil versus standard hypnotic-based regimens in intensive care unit patients with brain injuries: a randomised, controlled trial [ISRCTN50308308].** *Crit Care* 2004, **8:**R268-280.
56. Pace MC, Cicciarella G, Barbato E, Maisto M, Passavanti MB, Gazzerro G, Barbarisi M, Aurilio C: **Severe traumatic brain injury: management and prognosis.** *Minerva Anestesiol* 2006, **72:**235-242.
57. Kahn JM, Caldwell EC, Deem S, Newell DW, Heckbert SR, Rubenfeld GD: **Acute lung injury in patients with subarachnoid hemorrhage: incidence, risk factors, and outcome.** *Crit Care Med* 2006, **34:**196-202.
58. The Acute Respiratory Distress Syndrome N: **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.** *N Engl J Med* 2000, **342:**1301-1308.
59. Brower RG, Lanken PN, MacIntyre N, Matthay MA, Morris A, Ancukiewicz M, Schoenfeld D, Thompson BT: **Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome.** *N Engl J Med* 2004, **351:**327-336.

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