

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.

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

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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, remifentanyl) 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 hypocapnia

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 CO₂ 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 remifentanyl) 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 remifentanyl 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 CO₂ 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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