Carbon Dioxide Management in TBI: From Theory to Practice

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21.1 Introduction

Hyperventilation is a double-edged sword strategy for controlling intracranial volumes and therefore reducing intracranial pressure (ICP) after acute brain damage. The effect of hyperventilation is due to perivascular alkalosis, producing vasoconstriction and, therefore, reduced cerebral blood flow (CBF). Although this effect is short-lasting, hyperventilation carries a potential risk of cerebral ischemia. Although all patients with severe traumatic brain injury (TBI) are treated with mechanical ventilation, the target of the partial pressure of carbon dioxide in arterial blood ($PaCO_2$) remains poorly defined and there is insufficient evidence to support any recommendation. Even the latest guidelines and consensus documents state that in patients with severe TBI, normocapnia should be maintained ($PaCO_2$ 35–45 mmHg) and that, with a low level of evidence, prolonged prophylactic profound hyperventilation is not recommended. A target $PaCO_2$ of ≈36–40 mmHg has been reported by clinicians and, in the presence of raised ICP, this is usually lowered to ≈30–35 mmHg. In this chapter, starting from physiological concepts, the evidence around $PaCO_2$ management in TBI will be reviewed and some data on current practice of use of hyperventilation in TBI will be presented.

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21.2 Cerebral Blood Flow and Cerebrovascular CO_2 Reactivity

Brain oxygen consumption is very high, i.e., about 3.5 ml per 100 g/min, which is equivalent to 20% of the oxygen consumption of the whole human body. This high metabolic energetic demand requires a fine-tuned CBF to avoid ischemic conditions, i.e., situations in which the metabolic demand is not fulfilled. Under normal conditions, the CBF is maintained at a constant flow rate of 50–60 ml per 100 g/min in young adults, and 50 ml of oxygen is drawn from 700 to 800 ml of blood per minute. The extraction rate of oxygen by the brain is very high: the arteriovenous blood difference of the brain is 6.3 ml per 100 ml of blood. Considering the high metabolic demand of the brain and the limited storage of substrates, it is necessary to maintain CBF levels within the normal range. Under physiological conditions, this is achieved through a variety of mechanisms, commonly referred to as autoregulation.

The CBF depends on the diameter of the cerebral arterioles (resistance vessels), increasing with vasodilation and decreasing with vasoconstriction. To maintain CBF constant, these vessels physiologically respond to changes in systemic blood pressure, blood viscosity, and metabolic requirements. CBF is functionally linked to regional brain metabolism as expressed in the Fick equation:

$$\mathrm{CMRO_2} = \mathrm{CBF} \times \mathrm{avDO_2}$$

where $CMRO_2$ is the cerebral metabolic rate of oxygen and $avDO_2$ is the cerebral arterio-venous oxygen difference. Metabolic activity generates CO_2 and the CO_2 reactivity relates to the response of the cerebral vessels, and consequently CBF, to local changes in CO_2.

$PaCO_2$ can be manipulated with ventilation. Changes in $PaCO_2$ will elicit movement of CO_2 across the blood-brain barrier, and consequent vascular changes. An increase in $PaCO_2$ will produce acidosis and consequently vasodilation. A reduction in $PaCO_2$ will produce alkalosis and vasoconstriction. This effect is short-lasting due to subsequent re-equilibration of the following reaction, catalyzed by carbonic anhydrase:

$$\mathrm{CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons HCO_3^- + H^+}$$

The data obtained from *in vitro* and *in vivo* studies suggest that the endothelium and smooth muscles, as well as perivascular nerve cells, neurons, and glia, may be involved in the CO_2 reactivity and this complex mechanism seems to be correlated to changes in perivascular pH. The effect of pH variation on smooth muscle tone can be direct, modifying intracellular calcium concentration, or mediated by a second messenger system, such as nitric oxide (NO), potassium and calcium, prostaglandins, and cyclic nucleotides. Prostaglandins are effective vasodilators that can activate adenylate cyclase and increase cyclic adenosine monophosphate (cAMP). NO produced by the NO synthase (NOS) family in cerebral vascular endothelial cells, perivascular nerves, neurons, and glial cells will increase the intracellular concentration of cyclic guanosine monophosphate, thereby causing vasodilation [1]. Cyclic nucleotides reduce the entry of calcium into vascular smooth muscle and cause vasodilation directly or in a permissible manner, thereby allowing hypercapnia to

exert its vasodilation effect. The opening of potassium channels decreases the influx of extracellular calcium into cells in an indirect way, thereby reducing the tension of the vascular smooth muscle. In a clinical setting, every mmHg change in $PaCO_2$ from 20 to 60 mmHg in patients with TBI produces a CBF change of ≈3% [2] Hypoventilation leading to hypercarbia causes vasodilation and an increase in CBF, while hyperventilation causes vasoconstriction and a decrease in CBF.

21.3 Effects of Hyperventilation on Intracranial Pressure and CBF

The changes in $PaCO_2$ modify the intracranial blood volume, and therefore the pressure of the intracranial compartment (ICP). The relationship between $PaCO_2$ and ICP is not linear. In experimental studies over wide ranges of $PaCO_2$, an S-shaped relationship has been described between ICP and $PaCO_2$ [3]. Stocchetti et al. [4] calculated that for each millimeter of mercury of change in $PaCO_2$ the blood volume changed by 0.72 ± 0.42 ml. Similarly, Yoshihara et al. [5] demonstrated that, in patients with severe TBI, a change in blood volume of 0.5 ml could produce an ICP change of 1 mmHg. However, it is still unclear if the effect of hyperventilation on ICP remains during prolonged hyperventilation. After 24 h, as the pH of the perivascular spaces normalizes, the vasoconstrictive effect is reduced.

One of the main concerns in hyperventilating patients with TBI to reduce raised ICP is the risk of ischemia-induced by CBF reduction. One of the first descriptions of the therapeutic use of hyperventilation to treat elevated ICP was published by Lundberg et al. [6] in 1959. These authors stated that hyperventilation did not cause ischemia thanks to compensatory mechanisms that act to maintain tissue oxygenation. In fact, in normal conditions, cerebral oxygen delivery exceeds the brain's oxygen consumption, and this mechanism leaves an important reserve that allows the brain to tolerate CBF reduction, as occurs in hyperventilation. One year later, in 1960, Meyer et al. [7] confirmed this hypothesis, demonstrating that in healthy volunteers, hyperventilation produced no change in the $CMRO_2$. In 2002, Coles et al. [8] demonstrated that moderate hypocapnia could significantly reduce global CBF and result in significant increases in the volume of critically hypoperfused tissue in the injured brain even when improved cerebral perfusion pressure (CPP) and ICP values were recorded. These authors used positron emission tomography (PET) to quantify regional CBF and metabolism in response to CO_2 changes in 33 patients with TBI. This effect was not limited to the first 24 h after brain injury and the authors suggested that even brief periods of hyperventilation may cause a harmful reduction in CBF when $PaCO_2$ is reduced below 33 mmHg. The immediate effect on CBF of hyperventilation is clear, but the consequences of it, and the link with ischemia, is somehow controversial. Diringer et al. [9], using PET during hyperventilation in 13 patients with severe TBI in the first 8–14 h after TBI, found that CBF decreased, oxygen extraction fraction increased, and $CMRO_2$ was unchanged, suggesting that low CBF can be explained in the setting of patients with severe TBI treated with sedatives, with a primary reduction in $CMRO_2$ and a secondary passive fall in CBF.

Similarly, Letarte et al. [10], using a microdialysis probe placed adjacent to injured brain in 8 patients with severe TBI, concluded that hyperventilation that lowered $PaCO_2$ by 10 mmHg for 30 min (baseline $PaCO_2$ 35 ± 2 mmHg) reduced local CBF by 20%, while the lactate/pyruvate ratio did not change.

Ischemia is defined as a mismatch between metabolic requirements and CBF. Hyperventilation causes a reduction in CBF, but it does not always seem to be associated with a reduction in oxygen and metabolic supply. Finally, in 2006, Marion [11] explained that these discrepancies in findings concerning low $PaCO_2$ levels could be due to a loss of integrity of local CO_2 autoregulation, which may be impaired after TBI, and suggested that in patients with raised ICP responding to short-term hyperventilation, it can be considered safe.

21.4 Current Recommendations

Only one randomized controlled trial (RCT) is available about hyperventilation in TBI. In this trial, Muizelaar et al. [12] randomized 113 patients into three groups: normal ventilation, defined as $PaCO_2$ 35 ± 2 mmHg; prophylactic hyperventilation, defined as $PaCO_2$ 25 ± 2 mmHg; and prophylactic hyperventilation + THAM (tris(hydroxymethyl)aminomethane), which was added to compensate for the loss of HCO_3^- buffer from cerebrospinal fluid (CSF) that is responsible for the short-lived effect of hyperventilation on cerebral vasoconstriction. Patients were stratified based on the motor component of the Glasgow Coma Scale (GCS; 1–3 and 4–5). The outcome was assessed using the Glasgow Outcome Scale (GOS) at 3, 6, and 12 months. For patients with the higher motor GCS (motor score 4–5), the 3 and 6 month GOS scores were lower in the hyperventilated patients than in the control or THAM group but the effect was not confirmed at 12 months. This discrepancy between 3–6- and 12-month outcome may be due to a too small sample size; a direct correlation between hyperventilation and worse outcome has not been demonstrated. Moreover, CBF was lower in the hyperventilation + THAM group than in the control and hyperventilation groups, indicating a prolongation of the hyperventilation effect. There was no evidence of cerebral ischemia in any of the three groups, using CBF or $avDO_2$ data. In addition, in this trial, hyperventilation was used as a prophylactic maneuver and not as a treatment strategy and the course of ICP was most stable in the hyperventilation + THAM group.

Putting all these elements together, the fourth edition of the Brain Trauma Foundation guidelines [13] states that, in patients with TBI, there is insufficient evidence to support a strong recommendation in $PaCO_2$ management. Prolonged prophylactic hyperventilation with $PaCO_2$ of 25 mmHg or less is not recommended, but the optimal $PaCO_2$ range in these patients is still uncertain.

The recent Seattle International Severe Traumatic Brain Injury Consensus Conference [14] recommended mild hyperventilation, i.e., a $PaCO_2$ 32–35 mmHg, as a tier-two treatment if ICP remains resistant to first-line treatments, such as analgesia and sedation, osmotherapy, CPP maintenance and CSF removal. The Seattle

Consensus did not support lower $PaCO_2$ levels and recommended against routine hyperventilation to below 30 mmHg. In the same direction, a recent consensus on ventilation [15] in acute brain damage suggests that hypercapnia should be avoided in patients with acute brain injury, aiming for a physiologic range of $PaCO_2$ of between 35 and 45 mmHg. Short term hyperventilation in patients with acute brain injury and brain herniation can be considered as a therapeutic option. No consensus was reached regarding hyperventilation as a therapeutic option in patients with ICP elevation.

21.5 From Guidelines to Clinical Practice

In 2008, Neumann et al. [16] published data obtained from BrainIT (The brain monitoring with information technology) dataset analyzing 7703 blood gas analyses from 151 patients with TBI across 17 centers in Europe. The mean $PaCO_2$ was 35.8 ± 5.6 mmHg and the $PaCO_2$ was distributed in the range of normoventilation ($PaCO_2$ 36–45 mmHg) and moderate hyperventilation ($PaCO_2$ 35–31 mmHg). Early prophylactic hyperventilation as well as the use of additional cerebral oxygenation monitoring during hyperventilation, suggested by the Brain Trauma Foundation guidelines at that time, were not followed by most of the centers.

In 2018, Huijben et al. [17] performed a survey on treatment strategies before starting the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) trial. The most frequently reported $PaCO_2$ target was 36–40 mmHg in case of controlled ICP < 20 mmHg (69%), and 30–35 mmHg in case of raised ICP (62%), underlining that, in clinical practice, hyperventilation is used as a therapeutic option in patients with intracranial hypertension.

Some information on current CO_2 management was obtained by the CENTER-TBI study, a longitudinal prospective collection of data from patients with TBI across 65 centers in Europe. The study was conducted between December 19, 2014, and December 17, 2017, and aimed to better describe the incidence, management, and outcomes of patients with TBI in Europe [18]. For each patient enrolled in CENTER-TBI, along with much other information, the daily highest and lowest $PaCO_2$ values were registered for the first 7 days of admission. In 1100 mechanically ventilated patients with TBI admitted to the ICU for whom more than 2 values were available, the mean daily lowest $PaCO_2$ was 35.22 mmHg (SD = 5.27), very similar to the BrainIT data. However, there was huge variability in the mean value of the lowest $PaCO_2$ across centers (ranging from 32.3 to 38.6 mmHg) (Fig. 21.1), highlighting important differences in the way that CO_2 is managed. In patients with ICP monitoring, the observed mean values were lower compared with patients without ICP monitoring, i.e., 34.7 vs. 36.8 mmHg. A total of 397 patients had at least one episode of $PaCO_2$ <30 mmHg. These data suggest that, with considerable inter-center variability, hyperventilation is still largely used in TBI patients. At this stage, we are still exploring the effects of these management differences.

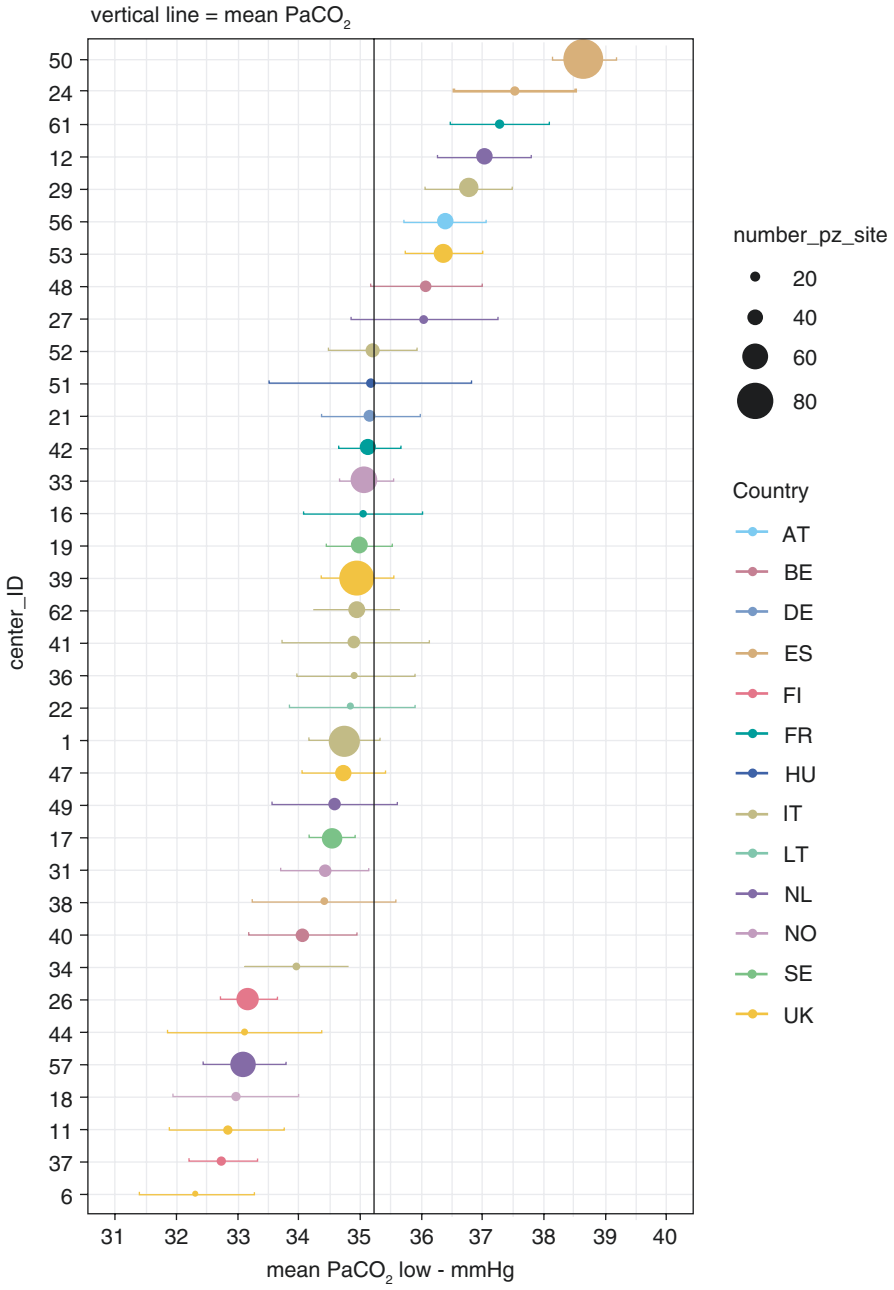

Fig. 21.1 Lowest mean $PaCO_2$ value in the CENTER-TBI trial [18]. Data from 1100 patients enrolled in 36 European centers participating in Center-TBI. For each center, the mean values of the lowest $PaCO_2$ values recorded daily in the first week are represented by a dot, with their respective confidence interval. The solid line is drawn in correspondence with the lowest mean $PaCO_2$. The mean daily lowest $PaCO_2$ from different centers ranged from 32.3 to 38.6 mmHg. This result seems to be linked more to the different management strategies of the individual centers, rather than being related to different national $PaCO_2$ management strategies

21.6 Conclusion

The relationship between CBF and $PaCO_2$ is well known. For 60 years, authors have discussed the risk of ischemia related to a reduction in CBF induced by hyperventilation but no strong evidence exists. Although hyperventilation induces a CBF reduction, it has not yet been demonstrated that this reduction always corresponds to an insufficient metabolic supply and therefore to ischemia.

In clinical practice, because of the lack of strong recommendation, the management of $PaCO_2$ is variable among centers, and hyperventilation is still commonly used, especially in patients with raised ICP. The correlation between $PaCO_2$ levels and outcome is still under exploration and further studies are required to better characterize ventilator strategies in patients with TBI and their effect on outcomes.

References

1. Stocchetti N, Maas AIR, Chieregato A, van der Plas AA. Hyperventilation in head injury. Chest. 2005;127:1812–27.
2. Cold GE. Cerebral blood flow in acute head injury. The regulation of cerebral blood flow and metabolism during the acute phase of head injury, and its significance for therapy. Acta Neurochir Suppl. 1990;49:1–64.
3. Reivich M. Arterial PCO_2 and cerebral hemodynamics. Am J Phys. 1964;206:25–35.
4. Stocchetti N, Mattioli C, Paparella A, et al. Bedside assessment of CO2 reactivity in head injury: changes in CBF estimated by changes in ICP and cerebral extraction of oxygen. J Neurotrauma. 1993;10:187.
5. Yoshihara M, Bandoh K, Marmarou A. Cerebrovascular carbon dioxide reactivity assessed by intracranial pressure dynamics in severely head injured patients. J Neurosurg. 1995;82:386–93.
6. Lundberg N, Kjallquist A, Bien C. Reduction of increased intracranial pressure by hyperventilation. A therapeutic aid in neurological surgery. Acta Psychiatr Scand Suppl. 1959;34:1–64.
7. Meyer JS. Metabolic and electroencephalographic effects of hyperventilation. Arch Neurol. 1960;3:539.
8. Coles JP, Minhas PS, Fryer TD, et al. Effect of hyperventilation on cerebral blood flow in traumatic head injury: clinical relevance and monitoring correlates. Crit Care Med. 2002;30:1950–9.
9. Diringer MN, Yundt K, Videen TO, Adams RE, Zazulia AR, Deibert E, et al. No reduction in cerebral metabolism as a result of early moderate hyperventilation following severe traumatic brain injury. J Neurosurg. 2000;92:7–13.
10. Letarte PB, Puccio AM, Brown SD, Marion DW. Effect of hypocapnea on CBF and extracellular intermediates of secondary brain injury. Acta Neurochir Suppl. 1999;75:45–7.
11. Marion DW. Does hyperventilation cause secondary brain injury? Crit Care Med. 2006;34:1284–5.
12. Muizelaar JP, Marmarou A, Ward JD, Kontos HA, Choi SC, Becker DP, et al. Adverse effects of prolonged hyperventilation in patients with severe head injury: a randomized clinical trial. J Neurosurg. 1991;75:731–9.
13. Carney N, Totten AM, O'Reilly C, et al. Guidelines for the management of severe traumatic brain injury, fourth edition. Neurosurgery. 2017;80:6–15.
14. Hawryluk GWJ, Aguilera S, Buki A, et al. A management algorithm for patients with intracranial pressure monitoring: the Seattle International Severe Traumatic Brain Injury Consensus Conference (SIBICC). Intensive Care Med. 2019;46:919–29.
15. Robba C, Poole D, McNett M, et al. Mechanical ventilation in patients with acute brain injury: recommendations of the European Society of Intensive Care Medicine consensus. Intensive Care Med. 2020;46:2397–410.

16. Neumann JO, Chambers IR, Citerio G, Enblad P, Gregson BA, Howells T, et al. The use of hyperventilation therapy after traumatic brain injury in Europe: an analysis of the BrainIT database. Intensive Care Med. 2008;34:1676.
17. Huijben JA, Wiegers EJA, Lingsma HF, Citerio G, Maas AIR, Menon DK, et al. Changing care pathways and between-center practice variations in intensive care for traumatic brain injury across Europe: a CENTER-TBI analysis. Intensive Care Med. 2020;46:995–1004.
18. Steyerberg EW, Wiegers E, Sewalt C, Buki A, Citerio G, De Keyser V, et al. Case-mix, care pathways, and outcomes in patients with traumatic brain injury in CENTER-TBI: a European prospective, multicentre, longitudinal, cohort study. Lancet Neurol. 2019;18:923–34.