

“Therapeutic Hypercapnia” after Ischemic Brain Injury

Is There a Potential for Neuroprotection?

COMMONLY held truths deserve a revisit from time to time. In this issue of ANESTHESIOLOGY, Zhou *et al.*¹ present data from laboratory studies suggesting carbon dioxide as a protective and therapeutic agent during early recovery from global cerebral ischemia. These are indeed unexpected results for the clinician, as mainstream teaching extols hypercapnia, to prevent secondary brain injury or potential fatal deterioration from uncontrolled intracranial hypertension.

The subject of the investigation of Zhou *et al.* is not novel. Increased arterial carbon dioxide levels have been associated with beneficial effects after experimental brain injury in the past.^{2–4} The effects of mild respiratory acidosis in prevention as well as recovery from organ system damage have previously been studied in the heart, lung, and immune systems,^{5–9} and permissive hypercapnia is part of today’s clinical practice of low tidal volume ventilation to improve the outcome of patients with acute lung injury.¹⁰ Interestingly, the current American Heart Association Guidelines recommend 12–15 breaths/min during cardiopulmonary resuscitation and stress the potential negative role of inadvertent hyperventilation on survival.

Acute hypocapnia is widely used to reduce intracranial pressure after traumatic brain injury, acute intracranial hemorrhage, and during brain tumor surgeries. However, there is mounting evidence that hypercapnia improves tissue perfusion and oxygenation. Preserved cerebral blood flow induced by hypercapnia in the presence of relative low-perfusion pressures could have beneficial effects after intraoperative global brain ischemia.

The obvious concerns regarding permissive hypercapnia in the context of acute brain injury are the consecutive cerebral vasodilatation, intracranial volume expansion, and increased intracranial pressure. Moreover, there is conflicting evidence surrounding arterial carbon dioxide and its molecular effects on the ischemic brain. Mild hypercapnia may exert some neuroprotection after cerebral ischemia, possibly *via* activation of the hypothalamic–pituitary–adrenal axis, exertion of antiinflammatory and antioxidant effects, and amelioration of secretion and function of various neurotransmitters. In contrast, severe hypercapnia may aggravate neuronal injury by extra- and intracellular acidification and/or impairment of cellular calcium homeostasis.^{4,11} Therefore, it

remains to be clarified whether certain levels of permissive hypercapnia may outweigh the potential benefits.

With their experimental study, Zhou *et al.* targeted two key questions. First, to clarify whether permissive hypercapnia during early reperfusion after transient global cerebral ischemia can improve both functional and histologic outcomes in rats; and second, to determine the differential outcome effects of three different PaCO₂ levels during reperfusion after the ischemic insult. Zhou *et al.* induced transient global cerebral ischemia in adult Wistar rats by bilateral occlusion of the common carotid arteries and controlled hypotension for 15 min. After the release of the carotid clamps, the animals were exposed for 2 h to defined concentrations of inhaled carbon dioxide to achieve PaCO₂ goals of mild, moderate, and severe hypercapnia (60–80, 80–100, and 100–120 mmHg, respectively). Physiologic variables including mean arterial pressure, arterial blood gases, and intracranial pressure (ICP) were measured during ischemia and early reperfusion. The animals were evaluated at 24 and 72 h of recovery for functional performance (neurologic deficit score). Subsequently (at 72 h), the brains were analyzed for histopathologic changes, protein expression, and tissue edema formation. Hypercapnia at all three levels tested increased the ICP and mean arterial pressure and decreased the arterial pH. Although changes in ICP and mean arterial pressure did not differ between different PaCO₂ levels, the extent of respiratory acidosis was clearly dose dependent (*e.g.*, after 30 min of mild, moderate, and severe hypercapnia, arterial pH was 7.21 ± 0.07, 7.13 ± 0.09, and 7.05 ± 0.1, respectively). Mild and moderate hypercapnia were associated with better neurologic deficit scores, fewer ultrastructural histopathologic changes, and reduced neuronal apoptosis compared with normocapnia. The neuroprotective effects were best with moderate hypercapnia (PaCO₂ = 80–100 mmHg). In contrast, no neuroprotection was observed with severe hypercapnia, and these animals showed more pronounced brain edema (brain water content) and expressed more aquaporin-4 protein. Zhou *et al.* conclude that the neuroprotective effects observed with mild and moderate hypercapnia

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($\text{PaCO}_2 = 60\text{--}100$ mmHg) involve modulation of apoptosis-regulating proteins. In contrast, the absence of neuroprotection with severe hypercapnia ($\text{PaCO}_2 = 100\text{--}120$ mmHg) could potentially be attributed to more pronounced brain edema formation.

Together, these results suggest a potential role for “therapeutic hypercapnia” after global cerebral ischemia. However, much experimental work is necessary to further elucidate the neuroprotective mechanisms of hypercapnia and acidosis before a clinical application should be considered.

There are many strengths to the study design for which the authors deserve praise, namely the applied injury model (reversible global ischemia followed by reperfusion) has translational relevance particularly for the perioperative period. The electrical brain activity was monitored (by electroencephalogram) during the insult to ensure isoelectricity, thus confirming an equal insult for all animals included in the analysis. The neurologic deficits of the rats were evaluated by a blinded observer, 1 and 3 days after the insult, thereby allowing a link between functional deficit and structural injury in a short-term outcome model. Finally, ICP was measured in each animal during ischemia and early reperfusion. This allows for observation of the effects of the three different levels of induced hypercapnia on the cranial vault and provides important information for an adequate discussion of the observed data. The ICP increased with induced hypercapnia during reperfusion, but the ICP increase was not different between the three hypercapnia levels tested although the neuroprotective effects were present only with mild and moderate hypercapnia. The ICP quickly returned to baseline in all groups after normocapnia was restored. The brain wet-to-dry ratios, as well as the aquaporin-4 protein expression, were determined as markers of cerebral edema. The tests demonstrated that only severe hypercapnia was associated with increased brain edema compared with normocapnia in the control group. Thus, these findings suggest that mild-to-moderate hypercapnia is neuroprotective in this experimental model. However, a PaCO_2 level more than 100 mmHg leads to more pronounced cerebral edema, and thus it is potentially harmful to the recovering brain. The results are in concert with those from other groups, who showed deleterious effects for the same level of hypercapnia in a model of hypoxia-ischemia in neonatal rats.⁴

The most obvious shortcomings of the study are the relative short observational period to which outcomes were followed (3 days) and the lack of analysis for any particular mechanisms to explain the findings.

In humans, recovery from stroke is evaluated at weeks and even months after the insult. If the rodent equivalent of a human year is nearly 3 weeks, then the evaluation for clinical improvement after an intervention should also be at a minimum of 3 weeks, or longer. Future experimental studies on the effects of “therapeutic hypercapnia” as a potential neuroprotectant after cerebral ischemia that involve rodents, therefore, need to look at functional and structural changes weeks and even months after the insult. Despite the potential ben-

eficial effects, permissive hypercapnia in the context of brain injury obviously carries significant risks, which could be deleterious as shown in the work of Zhou *et al.* (increased ICP and worsened brain edema) and previously by other groups.⁴ Unless a clear long-term benefit can be shown and the safety margin has been tested, “therapeutic hypercapnia” is not ready for clinical use after cerebral ischemia.

In addition, it is of paramount importance to identify the mechanism of the observed neuroprotection. This will allow targeted modulations of future interventions. Further understanding of the differential roles of carbon dioxide, respiratory acidosis, changes in brain tissue perfusion, and effects on systemic hemodynamics—all components of hypercapnia—need to be explored in future studies. For example, it is conceivable that improved cerebral blood flow, induced by hypercapnia, may have improved neuronal survival and functional outcome in the experiments of Zhou *et al.* Alternatively, mild-to-moderate arterial respiratory acidosis immediately after injury may have provided neuroprotection *via* delay in the functional recovery of neurons and reduced sensitivity to excitotoxic injury and depolarization, thereby improving energy balance and ameliorating intracellular calcium load during the critical period of reperfusion.³

In fact, Zhou *et al.* observed less neuronal cell death 72 h after the insult. In contrast, severe respiratory acidosis immediately after insult may aggravate injury through the activation of acid-sensitive ion channels.¹² This is one possible explanation for the absence of functional benefit and neuroprotection in the severe hypercapnia group in the study of Zhou *et al.*, as opposed to explaining the detriment purely through increased brain edema formation.

Other important questions relate to the therapeutic window. For example, how effective is therapeutic hypercapnia when instituted with delay after the ischemic insult (*i.e.*, in nonperioperative stroke) particularly concerning the potential role of changes in tissue pH, as discussed, or how effective is hypercapnia if it is maintained for longer than 2 h? Finally, experimental observations in rodents must be translated to other, preferentially gyrencephalic species before any consideration for clinical application of a particular intervention can reasonably be initiated.

At this point, Zhou *et al.* have clearly attracted our attention to hypercapnia and its potential benefits after cerebral ischemia. As anesthesiologists, we are particularly interested in its potential role for the perioperative environment. To date, the relationship between arterial carbon dioxide and prognosis as well as long-term survival after cerebral ischemia-reperfusion injury remains uncertain. “Therapeutic hypercapnia” carries promise for the treatment of patients after ischemic brain injury. However, further experimental efforts are necessary to justify its clinical use.

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