

Cerebral Autoregulation: The Role of CO₂ in Metabolic Homeostasis

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In this review the role of PaCO₂ in regulating cerebral blood flow and flow/metabolism coupling, as well as its impact on intracellular metabolic processes are discussed. Starting with a discussion of alpha-stat versus pH-stat ventilatory management, the apparently contradictory finding of exacerbation of ischemic injury by extracellular acidosis in some experimental models versus others in which neuroprotection is evidenced is discussed and contrasted with the conclusion that the relatively small degree of change in pH associated

with clinical changes in PaCO₂ is unlikely to directly impact ischemia/reperfusion processes. However, examples of susceptible patients in whom relatively small changes in PaCO₂ can produce adverse effects on cerebral perfusion are also illustrated re-emphasizing the necessity for individualization rather than generalization of care.

Keywords: PaCO₂; CBF; ischemia/reperfusion; intracranial hypertension.

Much of our understanding of cerebral autoregulation is derived from measurements of cerebral blood flow (CBF) that are static and discontinuous, but they do provide a theoretical model for understanding factors influencing CBF. *Cerebral autoregulation* refers to the ability of the brain to maintain a relatively constant CBF over a wide range of cerebral perfusion pressures (CPPs) from about 60 to 150 mm Hg—referred to as the *autoregulatory plateau*—and reflecting mechanoregulation.¹ A primary determinant of cerebral vascular tone, and thus CBF, involves changes in endothelial nitric oxide, which can vary in proportion to PaCO₂—referred to as *chemoregulation*. It is recognized that regional CBF can be modulated by alterations in local metabolic activity and PaCO₂ concentrations, reflecting the close coupling between metabolic processes and substrate delivery. This appears to be mediated by changes in nitric oxide synthase, possibly mediated by rapid changes in pH accompanying perturbations of PaCO₂; in fact, the most potent known

vascular modulator of CBF is PaCO₂. This has important clinical implications because changes in systemic PaCO₂, acting globally, can override local cerebral regulatory mechanisms.

PaCO₂ is a potent cerebral vasodilator and will directly increase CBF. This response is maintained during hypothermia, markedly influencing CBF and having the potential to disrupt cerebral autoregulation.² Murkin et al² and others have demonstrated that in contrast to pH-stat, alpha-stat maintains cerebral autoregulation and flow–metabolism coupling during hypothermic cardiopulmonary bypass (CPB), enabling the brain to adjust CBF in response to metabolic demands and maintaining CBF over a wide range of perfusion pressures. On the contrary, pH-stat overrides cerebral autoregulation, produces a pressure passive CBF, and disrupts flow–metabolism coupling,² and theoretically has the potential to produce an intracerebral “steal.”³ Consistent with this, in patients with moyamoya disease cerebral collateral vessels appear to retain their ability to constrict during hypocapnia but not to dilate during hypercapnia. In such patients, an observed association between a fall in regional CBF in the presence of global cerebral hyperemia during hypercapnia supports the concept of intracerebral steal associated with global cerebral vasodilatation.⁴

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Role of PaCO₂ During Cerebral Ischemia/Reperfusion

During ischemia and reperfusion, it has been demonstrated that PaCO₂ can influence cerebral metabolic processes. In immature rats during hypoxia-ischemia, CBF is better preserved during normocapnia and hypercapnia; the greater oxygen delivery promotes cerebral glucose usage and oxidative metabolism for optimal maintenance of tissue high-energy phosphate reserves.⁵ In head injury patients, even brief periods of hyperventilation can significantly increase extracellular concentrations of mediators of secondary brain injury in brain tissue adjacent to cerebral contusions or underlying subdural hematomas.⁶ Such hyperventilation-induced changes were much more common during the first 24 to 36 hours after injury than at 3 to 4 days.

In brain tissue slices, however, extracellular acidosis can inhibit neuronal function by diminishing long-term potentiation, a long-lasting increase in synaptic strength induced by high-frequency stimulation that may participate in learning and memory formation.⁷ Whereas some studies indicate a protective effect of CO₂ during ischemia and reperfusion,⁸ others have shown that acidosis may act in concert with hypoxia to cause adenosine triphosphate depletion⁹; acidosis may also have direct effects on glutamate transporters unrelated to effects on cellular adenosine triphosphate levels.¹⁰ pH effects on glutamate uptake may thus be an important factor affecting neuronal survival during incomplete ischemia.

More recent studies have identified a key role for acid-sensing ion channels in facilitating intracellular Ca²⁺ rise leading to ischemic injury.¹¹ This mechanism is consistent with previous studies demonstrating that during chemical hypoxia the elevation in [Ca²⁺]_i at perfusate pH 6.2 was twice that at perfusate pH 7.3.¹² Change in [Ca²⁺]_i was correlated with perfusate pH but not pHi. These results, which differ from previous studies showing acid inhibition of calcium influx in isolated neurons, suggest that low extracellular pH may exacerbate cellular injury during severe hypoxia or ischemia in the intact brain.

pH Management and Profound Hypothermia

The potential clinical relevance of the impact of pH management on ischemia/reperfusion may be most germane during surgery employing profound hypothermia, procedures for which pH management

(eg, alpha-stat vs pH-stat) remains controversial. In part because of the variable tissue responses during ischemia and reperfusion as described above, relatively lower extracellular pH (pH-stat) may be anticipated to be either potentially neuroprotective⁸ or neurotoxic⁹⁻¹² depending on particular tissue conditions. In general, however, it would appear that there is very little difference in clinical outcomes with either technique. This is likely because the perturbations in perfusate pH as a consequence of alpha-stat or pH-stat management—even with a 20°C reduction in temperature—would only average approximately 0.29 pH units, much less than the 1.1 pH unit perturbations implicated above.¹²

Use of alpha-stat versus pH-stat acid-base management strategy during pediatric cardiac operations with deep hypothermic CPB has not been consistently related to either improved or impaired early neurodevelopmental outcomes. This was demonstrated in a landmark study of 168 pediatric heart surgery patients randomized to alpha-stat or pH-stat and followed longitudinally.¹³ These investigators were unable to detect any significant differences in developmental outcomes aside from a small subgroup, the ventricular septal defect patients (n = 16), in whom the alpha-stat group had significantly better scores. Overall, in the absence of more definitive clinical outcome data, a combined pH strategy in which pH-stat is employed while cooling—thus using the benefits of cerebral vasodilatation to enhance rate and homogeneity of brain cooling—followed by alpha-stat from the interval immediately prior to cessation of circulation and during restoration of perfusion and rewarming—thus minimizing extracellular acidosis and aiming for preservation of cerebral flow–metabolism coupling during reperfusion and rewarming—would appear to be the best physiologic approach.

Cerebral Autoregulation and CO₂

CO₂-induced cerebral vasodilation can also reduce perfusion pressure, jeopardizing areas of the brain dependent on flow through critically stenosed vessels.³ In addition, because cerebral emboli are felt to account for a significant proportion of neurological deficits following CPB, unnecessary elevations of CBF have the potential to directly increase delivery of emboli into the cerebral circulation.

The cerebral autoregulatory plateau is a function of the close coupling between CBF and cerebral metabolic rate of oxygen (CMRO₂). Accordingly, as O₂ content is reduced (eg, normovolemic anemia),

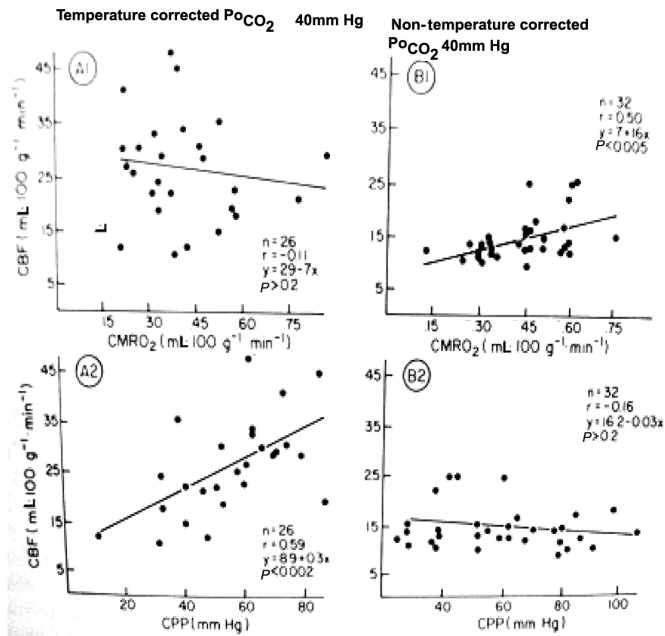


Figure 1. Panel A1 shows cerebral blood flow (CBF) versus cerebral metabolic rate for oxygen (CMRO₂), illustrating uncoupling of cerebral flow and metabolism during pH-stat management; panel B1 shows CBF versus CMRO₂, demonstrating intact cerebral flow–metabolism coupling during alpha-stat management; panel A2 shows CBF versus cerebral perfusion pressure (CPP), demonstrating pressure-passive CBF during pH-stat management; panel B2 shows CBF versus CPP, showing preservation of cerebral pressure autoregulation during alpha-stat management.

there will be a corresponding increase in CBF. Conversely, as CMRO₂ is reduced (eg, anesthesia, hypothermia), there is a proportionate decrease in CBF. This implies that in the presence of intact cerebral autoregulatory mechanisms there are in fact a family of autoregulatory curves corresponding to varying levels of cerebral substrate delivery and cerebral metabolic demand.

One of the fundamental misunderstandings of pH management during hypothermic CPB involves the so-called “extension” of the limits of cerebral autoregulation ascribed to alpha-stat management. This is derived from studies showing that during hypothermic CPB ($\approx 28^\circ\text{C}$ nasopharyngeal temperature) with alpha-stat there is no change in CBF over a wide range of perfusion pressures lower than those encountered in the awake normothermic state, as shown in Figure 1(B2).^{2,14}

As shown in Figure 2, rather than a fundamental change in cerebral physiology inherent in an apparent

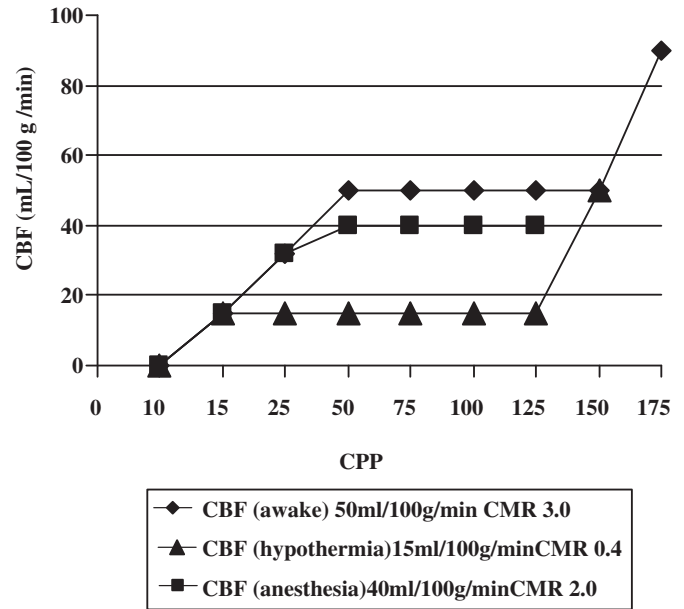


Figure 2. A series of cerebral autoregulatory curves defined by varying cerebral metabolic rates (CMR) showing cerebral blood flow (CBF) as a function of cerebral perfusion pressure (CPP) and reflecting the influence of intact cerebral flow–metabolism coupling. The lower CPP limit of each cerebral autoregulation curve is determined by and varies with the metabolic rate of brain tissue.

“extension” of the limits of cerebral autoregulation, however, this lower CPP reflects that the autoregulatory plateau actually consists of a series of parallel identities that are operative at different conditions of cerebral metabolism. In other words, during anesthesia, and particularly during hypothermia, cerebral metabolism is reduced, thus requiring a lesser substrate delivery (CBF). This proportionately lowered CBF can be delivered at a lower CPP that is still within limits of physiologic CBF. We had previously demonstrated this phenomenon using transcranial Doppler for instantaneous assessment of CBF velocity during alpha-stat or pH-stat management over a range of differing perfusion pressures.¹⁵ In that study, by using each patient as his or her own control, it was confirmed that there is no significant change in CBF velocity and thus CBF over a wide range of perfusion pressures during alpha-stat but that with pH-stat CBF velocity and thus CBF varies in proportion to changes in CPP.

An important consideration in the context of CPB is that CPP is the difference between cerebral inflow pressure, mean arterial pressure (MAP), and outflow pressure, generally considered as intracranial pressure (ICP) in cases of head injury or cerebral ischemia. Clinically, it is often assumed that because there is no evidence for elevation of ICP during CPB in adults, CPP is equivalent to MAP. However, the influence of transient cerebral venous outflow obstruction, a potential consequence of verticalization of the heart or other restriction to superior vena cava outflow, may occur during cardiac surgery.¹⁶ For determination of appropriate cerebral perfusion intraoperatively, therefore, it has been long advocated that both MAP and pressure in superior vena cava be continuously displayed or some form of neuromonitoring for cerebral ischemia be instituted.¹⁷ The recent introduction of near-infrared spectroscopy for measurement of cerebral oxygen saturation has been effective in detecting such otherwise clinically silent compromise of CPP because of venous outflow obstruction¹⁸ and has also been associated with generally improved clinical outcomes in a large randomized prospective trial in coronary bypass patients.¹⁹

Noncardiac Clinical Implications

Increasingly, mild hypothermia is being considered for patients with severe acute ischemic stroke. Experimental evidence and clinical experience show that hypothermia protects the brain from cerebral injury. Recent insights into the mechanisms of cerebral ischemia and reperfusion are suggestive of why hypothermia may be an ideal modality for stroke therapy.²⁰ Therapeutic hypothermia is likely to undergo phase III clinical trials in various clinical settings. Whereas some animal models have demonstrated an apparently salutary effect of pH-stat ventilatory management on cerebral ischemic injury during mild hypothermia,²¹ others have demonstrated a steeper fall in regional CBF after ischemia in the pH-stat group, suggesting that the autoregulatory response of the collateral pathways may have been reduced in this group—not inconsistent with intracerebral steal.²² A recent small unpublished clinical trial indicated a demonstrably adverse effect of pH-stat ventilation in a series of comatose patients in whom moderate hypothermia was induced for massive cerebral ischemic injury.

In 3 of 8 patients during onset of pH-stat ventilatory management, there was a significant increase in ICP (>20 mm Hg) coincident with acute ipsilateral

pupillary dilatation because of attendant cerebral hyperperfusion. CBF during pH-stat increased nearly 2-fold in comparison with alpha-stat management. This was reversed by restoration of alpha-stat ventilation. Of clinical note is the fact that the difference in PaCO₂ between interventions was approximately 7 to 10 mm Hg between alpha-stat and pH-stat ventilation—within routine clinical limits but illustrative of the potentially profound influence of relatively minor fluctuations in PaCO₂ on CBF and ICP in a susceptible population through interference with cerebral autoregulatory processes (personal communication).

In summary, careful consideration of pH management is of fundamental importance in clinical ventilatory care given the critical role of PaCO₂ in both regulating CBF and preserving cerebral autoregulatory responses. Relatively mild perturbations may profoundly influence neuronal integrity during ischemia/reperfusion injury in susceptible patients in various clinical settings. In general, ventilatory pH management should be directed toward maintaining eucapnia, with preference for alpha-stat management during most hypothermic procedures.

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