Lessons from on high: arterial CO₂, not pH, is the key mediator of cerebrovascular function

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Background physiology

The cytoarchitecture of the brain renders it entirely dependent upon a constant perfusion to sustain normal cerebral function. Consequently, the cerebrovasculature is sensitive to a milieu of metabolic, autonomic and chemical inputs, which act to regulate cerebral perfusion and preserve brain function. The sensitivity of the cerebrovasculature during alterations in arterial blood gases is well defined, with notable cerebral vaso-reactivity to changes in arterial carbon dioxide (pCO₂) (Willie et al. 2015; Duffin et al. 2021). Hypo- and hypercapnia elicit cerebral vasoconstriction and dilatation, respectively, with a greater sensitivity observed in hypercapnia, compared with hypocapnia (Hoiland et al. 2019). These phenomena underlie the physiological basis for cerebrovascular reactivity (CVR).

Moreover, acute alterations in CO₂ have important implications with respect to pH, described by the Henderson–Hasselback equation (see below):

\[ \text{pH} = 6.1 + \log_{10} \left( \frac{[\text{HCO}_3^-]}{(0.03 \times P_{\text{CO}_2})} \right) \]

It is because of this influence that the body relies upon a bicarbonate buffer system, which describes the reverse equilibrium between body water and CO₂, carbonic acid (H₂CO₃), [H⁺] and bicarbonate ions (HCO₃⁻), with bidirectional influence of carbonic anhydrases. The CO₂–HCO₃⁻ relationship is the most important pH buffering system within the body, utilizing bicarbonate to mitigate large fluctuations in pH during acute fluctuations in CO₂ levels. As such, it can be assumed that any interventions which influence the capacity of the bicarbonate buffering system will influence the P_{CO₂}–[H⁺]/pH relationship.

The regulatory effect of CO₂ on cerebral blood flow manifests from the free diffusion and equilibration of CO₂ across the blood–brain barrier (BBB) where it manipulates the pH of the cerebrospinal fluid (CSF) and perivascular space (Yoon et al. 2012). This observation has been demonstrated both in reduced preparations of cerebral vessels and within animal models. Once across the BBB, the bicarbonate-buffer system, along with other mechanisms, mitigates large deviations from normal perivascular/CSF pH levels. Thus, pH is maintained within narrow limits throughout the central nervous system to support normal neural and glial cell function.

Prior publications have begun to delineate the effects of manipulating the bicarbonate buffering capacity, either pharmacologically or through environmental (high altitude) exposure, on CVR sensitivity. The goal is to better understand the interaction between P_{CO₂} and arterial [H⁺]/pH on cerebral blood flow regulation. This narrative has obvious translational significance for pathological conditions which affect acid–base regulation, either systemically or within the central nervous system.

Study background and key findings

In a recent publication in The Journal of Physiology, Caldwell et al. (2021b) sought to examine the effects of environmental and pharmacologically induced manipulation of acid–base status on cerebral blood flow regulation in healthy human participants.

Resting cerebral blood flow and CVR were measured across three distinct experimental conditions: (1) resting acid–base balance (control); (2) metabolic acidosis, by way of 2 days of low-dose oral acetazolamide (ACZ) ingestion; and (3) post-arterial pH normalisation using intravenous infusion of sodium bicarbonate (NaHCO₃⁻). Measurements were obtained at sea level (344 m) and following a sojourn to, and sustained residence at, high altitude (14–20 days at 5050 m).

Under each experimental condition, participants were exposed to a graded isoxic CO₂ challenge in the following sequence: −10, −5, +0, +5, +10, +15 mmHg. Participants were unable to tolerate +15 mmHg at high altitude and this challenge was subsequently removed from final comparisons. Accurate and precise manipulation of CO₂ was achieved using an end-tidal forcing system. Intracranial middle and posterior cerebral blood velocities were continuously monitored using transcranial Doppler ultrasound. Moreover, duplex ultrasound of the internal carotid and vertebral arteries were recorded at rest, providing a direct measurement of global cerebral blood flow. This standardized approach was used to measure CVR across both hypo- and hypercapnic ranges. Radial arterial blood draws were obtained at sea level and high altitude prior to each experimental condition. Furthermore, a radial artery catheter was inserted at high altitude allowing for repeated samples to be drawn across each stage of the graded CO₂ challenge.

Several hallmark features of the physiological response to high altitude as well as ACZ ingestion were observed. Relative to sea level, high altitude resulted in profound reductions in P_{CO₂}, with consequent hyperventilatory induced reductions in P_{CO₂}, and resultant respiratory alkalosis. The ventilatorily induced increase in arterial pH was partially compensated by the renal system via increased secretion of HCO₃⁻ (i.e. compensatory metabolic acidosis). Consequently, this renal response would serve to reduce bicarbonate buffering capacity between sea level and high altitude. Across both locations, oral ingestion of ACZ over a 2-day period resulted in a significant metabolic acidosis. Importantly, intravenous infusion of NaHCO₃ restored arterial pH levels to that of control conditions. This was an important observation with respect to the aim of this study, as it demonstrates a complete restoration of the bicarbonate buffering capacity following pharmacologically induced reductions, at least in the blood.

As expected, exposure to high altitude altered resting cerebral haemodynamics.

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This observation is well described, driven by a loss of cerebral autoregulation at high altitude in tandem with hypoxic vasodilatation of cerebral vessels. These changes maintain cerebral oxygen delivery during incidences of reduced arterial oxygen concentration. The key finding of this study was that CVR sensitivity to changes in CO₂ was unchanged between experimental conditions at both sea level and high altitude, despite profound manipulation and restoration of arterial pH.

**Discussion and future considerations**

The strengths of this experimental design were that it allowed for a thorough examination of manipulating bicarbonate buffering capacity and the consequential effects for CVR both in an acute lab-setting and the setting of chronic environmental blood gas stressor. This work complements a recent publication by this research group examining the effects of acute metabolic alkalosis, and by extension an increase in bicarbonate buffering capacity, on CVR and resting cerebral haemodynamics in a laboratory setting (Caldwell et al. 2021a). In direct contrast, this study examined the consequences for reducing and subsequently restoring bicarbonate buffering capacity on CVR sensitivity and resting cerebral haemodynamics.

Several interesting talking points emerge. This current article supports the concept that CVR is a function of \( P_{CO_2} \) rather than the prevailing arterial \([H^+]/pH\) per se, providing support for a perivascular/CSF mediated vasoreactivity. An interesting follow-up to these findings could be to assess the relative contribution, if any, of endothelial cells during CVR assessment. Experimental hypercapnia could elicit changes in endothelium intracellular pH, and subsequent activation of the calcium-dependent endothelial nitric oxide synthase (eNOS) isoform. A repeat examination of CVR during metabolic acidosis, with concurrent eNOS antagonism (e.g. using \( N^\omega \)-nitro-L-arginine) would be instructive. This would help dissociate the relative contribution of \( P_{CO_2} \)-dependent endothelium derived vasodilatation on CVR sensitivity.

Furthermore, an interesting prospect would be to examine differential effects of multiple carbonic anhydrase inhibitors on CVR sensitivity. As suggested, CVR magnitude is driven primarily by the diffusion capacity of CO₂ across the BBB, where it exerts its influence on perivascular/CSF pH. Whilst routinely used as a prophylaxis during high altitude ascent, ACZ has a limited penetration rate within the CNS. In contrast, methazolamide, a sister carbonic anhydrase inhibitor, possesses the capacity to penetrate the BBB, and might be better positioned to manipulate acid–base regulation within the central nervous system. The central tenet of the authors’ research study could be re-visited in a study using different carbonic anhydrase inhibitor interventions. Finally, the authors highlighted an intolerance to CO₂ (+15 mmHg) at high altitude. This observation was likely a consequence of the reduced CNS buffering capacity to tolerate such a diffusion gradient of CO₂ across the BBB. This suggests an upper limit threshold of the pH buffering system at high altitude. Future studies could examine the extent of the limits of this buffering capacity, which is of particular interest at high altitude given the progressive and concomitant reductions in both CO₂ and bicarbonate with ascent to higher altitudes. An exciting prospect is whether a lower limit of CNS buffering capacity exists. A recent finding from this research group suggests that bicarbonate may independently induce an increase in cerebral blood flow, thereby highlighting an important function of bicarbonate beyond that of pH buffering (Caldwell et al. 2021a). Whether a minimal concentration of bicarbonate is essential to sustain cerebrovascular and neurological function is of interest, particularly in the context of high-altitude ascent where the adaptive renal response is to augment bicarbonate secretion.

The technically elegant study by Caldwell et al. (2021b) provides insight into the interaction between acid–base physiology and cerebrovascular regulation, showcasing \( P_{CO_2} \) as a key mediator in CBF regulation.

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