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REVIEW

Ventilatory and cerebrovascular regulation and integration at high-altitude

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Abstract
Ascent to high-altitude elicits compensatory physiological adaptations in order to improve oxygenation throughout the body. The brain is particularly vulnerable to the hypoxemia of terrestrial altitude exposure. Herein we review the ventilatory and cerebrovascular changes at altitude and how they are both implicated in the maintenance of oxygen delivery to the brain. Further, the interdependence of ventilation and cerebral blood flow at altitude is discussed. Following the acute hypoxic ventilatory response, acclimatization leads to progressive increases in ventilation, and a partial mitigation of hypoxemia. Simultaneously, cerebral blood flow increases during initial exposure to altitude when hypoxemia is the greatest. Following ventilatory acclimatization to altitude, and an increase in hemoglobin concentration—which both underscore improvements in arterial oxygen content over time at altitude—cerebral blood flow progressively decreases back to sea-level values. The complimentary nature of these responses (ventilatory, hematological and cerebral) lead to a tightly maintained cerebral oxygen delivery while at altitude. Despite this general maintenance of global cerebral oxygen delivery, the manner in which this occurs reflects integration of these physiological responses. Indeed, ventilation directly influences cerebral blood flow by determining the prevailing blood gas and acid/base stimuli at altitude, but cerebral blood flow may also influence ventilation by altering central chemoreceptor stimulation via central CO_2 washout. The causes and consequences of the integration of ventilatory and cerebral blood flow regulation at high altitude are outlined.

Keywords Cerebral blood flow · Ventilation · High-altitude · Acclimatization

Introduction

The reduced barometric pressure associated with ascent to high-altitude necessitates compensatory adaptations to mitigate hypoxia-related decrements in physiological functioning. Of the multitude of physiological adaptations that occur, hyperventilation and further ventilatory acclimatization stand alone as the most important [1, 2] (Fig. 1). This response reduces the drop in the partial pressure of arterial oxygen (PaO_2) that would occur without any alteration in ventilation (V_E), while ventilatory acclimatization further and progressively increases PaO_2 over time at altitude. Slower hematological changes leading to increased hemoglobin mass and concentration (Hb) are also important in partially mitigating the drop in arterial oxygen content (CaO_2) associated with altitude. The importance of these two changes is clearly visible in the equation below, whereby PaO_2 primarily influences CaO_2 via its impact on arterial oxyhemoglobin saturation (SaO_2), and (Hb) impacts CaO_2 through O_2 binding—both SaO_2 and (Hb) are directly proportional to CaO_2 (Eq. 1):

$$CaO_2\left(mL \cdot dL^{-1}\right) = 1.34 \times [Hb]\left(g \cdot dL^{-1}\right) \times SaO_2(\%) + 0.003 \times PaO_2(mmHg) \quad (1)$$

where 1.34 is the oxygen binding capacity of hemoglobin, and 0.003 is the solubility of O_2 in blood. Given the brain's inordinate metabolism for its comparatively small mass and limited oxygen and substrate storage capacity, it is particularly vulnerable in hypoxia and, therefore, at altitude. Testament to this vulnerability is that as little as a 5-s interruption of cerebral blood flow (CBF) can lead to unconsciousness [3]. Consequently, the brain is reliant on a consistently adequate cerebral oxygen delivery (CDO_2) to avoid

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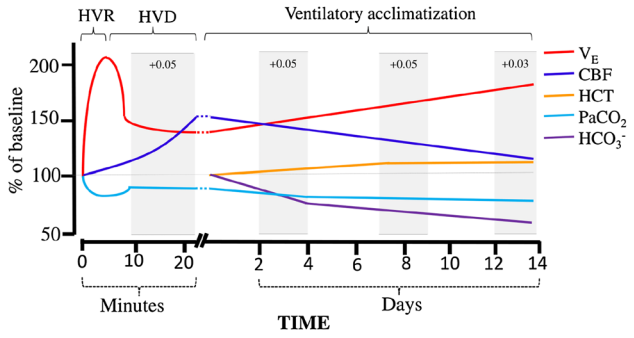

Fig. 1 Integrative physiological changes during acclimatization to very high altitude (~5000 m). Ascent to altitude stimulates a multitude of physiological adaptations. The immediate response to hypoxia involves a brisk increase in ventilation (V_E) (red line) and cerebral blood flow (CBF) (dark blue line), with a concurrent drop in $PaCO_2$ (light blue line). Hypoxic ventilatory decline ensues leading to a small attenuation of the drop in $PaCO_2$. Throughout acclimatization, V_E and CBF begin to progressively increase and decrease, respectively. Because of the respiratory alkalosis that follows the hypoxic ventilatory response, arterial and CSF pH (denoted by vertical grey bars) is increased; however, renal bicarbonate (HCO_3^-, purple line) excretion increases progressively leading to a stabilization of pH, and potential mitigation of respiratory alkalosis as acclimatization progresses. Finally, hematocrit (HCT) increases following ascent to altitude and throughout acclimatization. This figure represents general trends based on data from: [6, 51, 60, 65, 92, 93]

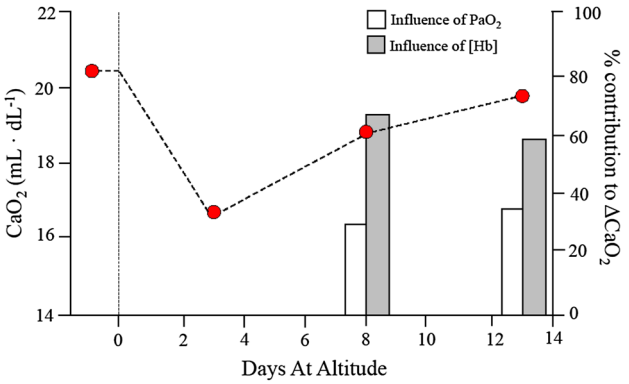

Fig. 2 Contribution of changes in PaO_2 and [Hb] in the increase in CaO_2 during acclimatization at altitude. Upon exposure to altitude, PaO_2 is reduced, thereby reducing SaO_2 and CaO_2. Hyperventilation mitigates, but does not alleviate this drop in PaO_2. Ventilatory acclimatization to high altitude contributes to progressive increases in V_E and leads to elevations in PaO_2, SaO_2, and CaO_2. Respiratory alkalosis-induced diuresis leads to the early increase in [Hb], with erythropoiesis contributing to later increases in [Hb], both aiding in the increase of CaO_2 across acclimatization. Determined using data from [6]

an energetic crisis and/or cell death. The maintenance of CDO_2 is dependent on adequate CBF and CaO_2 as demonstrated in Eq. 2:

$$CDO_2\left(mL \cdot min^{-1}\right) = \left[CBF\left(mL \cdot min^{-1}\right) \times CaO_2\left(mL \cdot dL^{-1}\right)\right] / 100. \quad (2)$$

Thus, cerebral homeostasis at high-altitude hinges upon an increase in CBF, primarily through hypoxic cerebral vasodilation, and a mitigation of hypoxemia, primarily through increased V_E and slower acting hematological changes (Fig. 2). However, an additional consequence of elevated V_E is that hypocapnia ensues resulting in cerebral vasoconstriction; therefore, depending on the degree of metabolic compensation for the respiratory alkalosis, this may act to constrain elevations in CDO_2. Although acclimatization to high altitude encompasses the integration of multiple physiological responses (Fig. 1), these physiological responses may differ slightly from those induced by normobaric hypoxia (even when matched for the same P_IO_2—reviewed in [4]). Nevertheless, with particular focus given to high altitude, we provide a brief overview of acid–base balance and then focus our discussion on the causes and consequences of ventilatory and CBF regulation and the potential inter-dependence of these two physiological pathways. The independent and combined influences of these two pathways on CDO_2 are further considered.

Acid–base balance at altitude

Following hypoxic stimulation of the carotid bodies and consequent hyperventilation, the partial pressure of arterial carbon dioxide ($PaCO_2$) is reduced and both arterial and CSF pH are elevated. Laboratory investigations have demonstrated that within hours of the onset of respiratory alkalosis, excretion of HCO_3^- is upregulated and arterial pH begins to decrease back to normal values [5]. This excretion of HCO_3^- has been demonstrated to continue for > 2 weeks at a given altitude in concert with the progressive reductions in $PaCO_2$ that are characteristic of ventilatory acclimatization [6, 7]. Although measures of lumbar CSF may not directly reflect cisternal and/or extracellular medullary pH [8], lumbar CSF samples comprise the majority of data assessing central acid–base balance at altitude [7, 9–11]. Elimination of HCO_3^- from CSF follows that of the arterial blood [9, 11] indicating that passive exchange of CO_2 across the blood brain barrier and subsequent re-equilibration of the reaction between CO_2 and HCO_3^- leads to changes in CSF $[HCO_3^-]$ and pH (Eq. 3):

$$CO_2 + H_2O \overset{\text{Carbonic Anhydrase}}{\rightleftharpoons} H_2CO_3 \rightleftharpoons HCO_3^- + H^+ \quad (3)$$

How changes in PCO_2 and $[HCO_3^-]$ alter acid–base status of the CSF can be expressed mathematically by the

Henderson-Hasselbalch equation. Using the known pKa (i.e., reaction constant) at 37 °C of 6.1 for the above reaction (Eq. 3), the relationship between pH, CO_2 and HCO_3^- is as follows (Eq. 4):

$$\mathrm{pH} = 6.1 + \log \frac{\left[\mathrm{HCO_3^-}\right]}{\left(0.03 \cdot \mathrm{PCO_2}\right)} \quad (4)$$

Therefore, changes in pH (arterial or CSF) at altitude are contingent on the concurrent changes in PCO_2 and $[HCO_3^-]$. Following renal compensation for the respiratory alkalosis, any given change in PCO_2 will result in a larger change in pH (Fig. 3). Additional calculations derived from the modified Stewart Model [12] indicate that weakly dissociated protein anions (phosphate and albumin), which increase in concentration at altitude [13, 14], are also responsible for some correction of respiratory alkalosis and changes in $[HCO_3^-]$ [14]. The physiological implications of these changes in acid–base balance are discussed in the following sections.

Ventilatory acclimatization

During and following ascent to high altitude, ventilatory acclimatization is evidenced by a progressive increase in V_E (and alveolar ventilation) over the first days and/or weeks at altitude. This increase in V_E leads to a progressive reduction in $PaCO_2$ and a partial mitigation of the drop in PaO_2 [2]. Thus, acclimatized individuals will have a higher PaO_2 and lower $PaCO_2$ than unacclimatized individuals at any given altitude (Fig. 4). The time required to achieve ventilatory acclimatization varies with altitude ranging from approximately 4 days at ~ 3000 m [2], 8 days at 4000 m [15], ≥ 2 weeks at ~ 5000 m [6], and between 4 and 6 weeks at altitudes above 6000 m [16]. It is important to note that, although ventilatory acclimatization might occur, it will never be enough to return PaO_2 back to sea-level values. Rather, ventilatory acclimatization reflects the near maximal increase in PaO_2 for a given altitude as indicated via the alveolar gas equation—this is limited by P_IO_2.

Ventilatory acclimatization to altitude occurs in response to combined influences from central and peripheral chemoreception. Fifty years ago, it was postulated that CSF pH was the primary regulator of ventilatory acclimatization at altitude [10]; however, it was soon after realised that ventilatory acclimatization occurs irrespective of alkaline CSF and jugular venous blood [7, 9]. At present, the role of CSF pH has been more judiciously considered [18], and data indicate the peripheral chemoreceptors are essential for ventilatory acclimatization [18–21]. Acid–base changes should, however, not be fully ignored, as reduced HCO_3^- in the blood and CSF mitigates the rise in medullary pH and withdrawal of central chemoreceptor stimulation. Hence, the past 50 years have seen the adoption of carbonic anhydrase inhibitors (e.g., acetazolamide) as effective prophylactic drugs for acute mountain sickness by accelerating renal compensation, thus permitting central chemoreceptor stimulation (via low CSF pH) of ventilation to continue less inhibited [22].

Hypoxic ventilatory response at altitude

The maintenance of PaO_2 is paramount for sustaining normal CDO_2 at high altitude; therefore, the hypoxic ventilatory

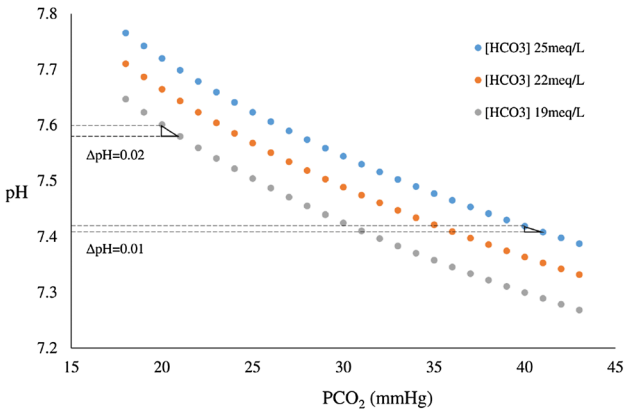

Fig. 3 Relationship between PCO_2 and pH with varying $[HCO_3^-]$. This figure highlights how, according to the Henderson-Hasselbalch equation, the magnitude of pH changes with varying PCO_2 are augmented at altitude following renal compensation for respiratory alkalosis. At sea level, where $[HCO_3^-]$ approximates 25 meq/L [43], an increase in resting $PaCO_2$ from 40 to 41 mmHg would lead to a reduction in pH of 0.01. Conversely, at altitude where $[HCO_3^-]$ may approximate 19 meq/L, an increase in resting $PaCO_2$ from 20 to 21 mmHg would lead to a reduction in pH of 0.02

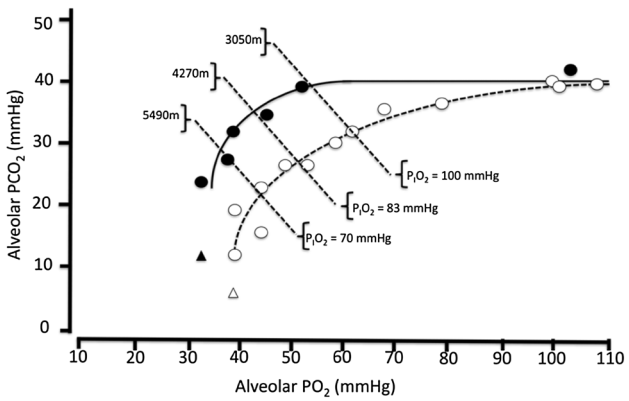

Fig. 4 Effect of altitude acclimatization on alveolar gas composition. Closed (black) symbols are unacclimatized. Open (white) symbols are acclimatized. Redrawn from original data of [2, 94, 95] and Wagner et al. [17]. Iso-altitude lines were calculated using the ideal alveolar gas equation and an assumed respiratory exchange ratio of 0.85. With permission from [93]

response (HVR) can be considered as one of the most important aspects that mediates ventilatory acclimatization to high altitude (VAH). Under normal conditions, the HVR occurs when PaO_2 falls below ~50 mmHg and the resulting hypoxemia is detected by the carotid bodies to stimulate hyperventilation, thereby slightly increasing PaO_2. The primary mechanism underlying VAH is a greater sensitivity of the HVR. Well-controlled laboratory data indicate that as little as 8 h (awake) [23] to 24 h (1 day/night) [24] of mild hypoxia (e.g., $P_IO_2 = 127$ mmHg) is adequate to increase isocapnic HVR [23, 24]; yet upon arrival to high altitude, HVR appears initially unaltered compared to sea level [25, 26]. However, it is well established that the slope of the V_E-SaO_2 response steepens following several days of acclimatization [23–28] with this response progressing in a graded manner over time (Fig. 5). Potentiation of the HVR can occur with very minor, but sustained, changes in PaO_2 (− 10 mmHg PaO_2) highlighting that the physiological mechanisms underlying this response are also important at sea level [24]. The HVR response is apparently similar between men and women [27, 29].

Laboratory studies have demonstrated that several hours following an 8 h period of isocapnic or poikilocapnic hypoxia V_E remains elevated during acute hyperoxic breathing, indicating that factors other than acid–base changes (i.e., increased carotid body activity) are responsible for the progressive rise in V_E [30]. In support of these findings, Barnard et al. observed that 2–3 h of hypoxia was insufficient to increase the carotid body activity of anaesthetized cats, but that it had increased following chronic exposure [31]. It is also noteworthy that, in line with acute laboratory studies [30], a potentiated HVR remains present 5 days after return to sea level from altitude [26] and that this aspect of acclimatization is partially retained on re-exposure to high altitude [32]. Hence, it appears that continuous exposure of the carotid bodies to hypoxemia might be required to elicit adjustments of HVR. Interestingly, whereas HVR is acutely increased in lowlanders after ascending to high altitude, the HVR is approximately halved in long-term (non-native) high altitude residents and is almost completely abolished in lifelong highlanders, suggesting chronic attenuation of the carotid body [33]. The subjects in the aforementioned study lived at high altitude in Colorado, USA (Rocky Mountains); therefore, "native" highlanders may have only populated this region for a couple of generations, indicating that chronic attenuation of HVR can occur independent of genetic adaptation [33]. The potential influences of genetic adaptation on ventilatory control at altitude are beyond the scope of this review and outlined elsewhere [34].

With respect to performance at altitude, a higher HVR measured at sea level has been demonstrated in some successful climbers [34–37]. However, HVR measurements conducted at sea-level and 5000 m indicate that a lower V_E and HVR—and thus greater ventilatory reserve (i.e., the difference between resting and maximal V_E)—coupled with optimal ventilatory efficiency are predictive of climbing success at extreme altitudes (i.e. summiting Mt. Everest or K2) in those not using supplemental oxygen [38]. These successful climbers are able to ascend to these extreme altitudes without prior maximization of their work of breathing [38]. These differing findings are dependent on the altitude at which success is considered and likely also a consequence of the altitude that HVR is measured at, and if hypoxic, the duration of hypoxia prior to measurement. Indeed, as highlighted above, HVR changes with exposure to altitude and thus comparing sea level to high altitude values is difficult, especially given alterations in afferent input [31], central integration [39] and efferent output [40] are all likely occurring. The underlying mechanisms influencing changes in HVR remain difficult to disentangle.

Hypercapnic ventilatory response at altitude

In addition to a direct influence on ventilation via central chemoreceptor stimulation, there are additional effects

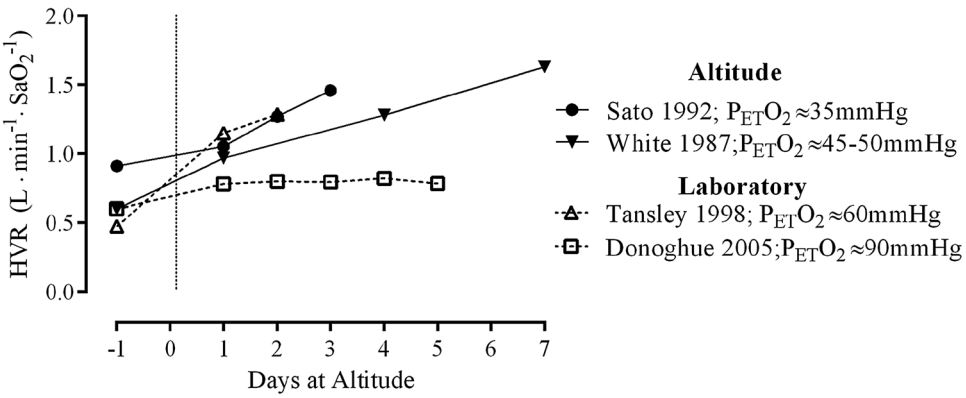

Fig. 5 Changes in HVR over time at high altitude and during laboratory hypoxia. Studies at altitude (filled symbols; solid lines) and in controlled laboratory settings (open symbols; dashed lines) have demonstrated a progressive increase in HVR over time. Further it can be seen the increase in HVR is related to the prevailing level of $P_{ET}O_2$ during hypoxia, as previously noted by Donoghue and colleagues [24]

of $PaCO_2$ on the peripheral chemoreceptors, and overall changes in ventilation occur much more readily with alterations in $PaCO_2$ versus that of PaO_2 only. At high altitude, hyperventilation (i.e., VAH) attenuates the reduction in PaO_2 and concomitantly respiratory alkalosis occurs (as described above). Accordingly, another important response implicated in VAH is a leftward shift of the V_E-$PaCO_2$ relationship to lower $PaCO_2$ values [25, 41, 42] following a reduction in the ventilatory recruitment threshold at altitude [14]. This resetting of the hypercapnic ventilatory response (HCVR) occurs due to peripheral chemoreceptor and acid–base adjustments secondary to hypoxia and respiratory alkalosis, respectively [42]. The slope of the V_E-$PaCO_2$ response also becomes greater at high altitude [25, 41, 43], which may facilitate hyperventilation in the face of hypocapnia and suppressed central chemoreceptor stimulation. Importantly, measurement of the effects of central chemoreceptor sensitivity on ventilation at high altitude may be obscured by the logarithmic relationship between $PaCO_2$ and $[H^+]$ [41] (see Fig. 3). For instance, a 1 mmHg change at a $PaCO_2$ of 20 mmHg following metabolic compensation (i.e., decreased $[HCO_3^-]$) will cause a much greater shift in pH compared to a 1 mmHg change in $PaCO_2$ at 40 mmHg without any metabolic compensation. Nevertheless, when V_E is indexed against $[H^+]$ the HCVR is still markedly augmented at altitude [43]. This latter observation indicates that intrinsic central chemoreceptor sensitivity is increased, and/or a peripheral-central chemoreceptor interaction is augmenting the V_E response to increased $[H^+]$ [44].

Alterations in peripheral chemoreceptor activity at altitude will also affect the HCVR, which is notionally supported by the observed blunting of the ventilatory response to CO_2 in individuals with unilateral and bilateral carotid body resections at sea level [45]. Furthermore, similar to HVR responses in lowlanders vs. highlanders, HCVR is greater in newcomers to high altitude whereas this response is inhibited in long term residents and high altitude natives [15]. The HCVR occurs in concert with changes in acid–base balance and cerebrospinal fluid pH and is therefore intimately linked to CBF (see next section "Cerebral blood flow acclimatization"). Collectively, the respiratory responses to reductions in both PaO_2 and $PaCO_2$ are extremely important factors underlying VAH. The integration of these responses further facilitates increased respiratory drive, which serves to improve PaO_2 values; however, as outlined earlier, full return of PaO_2 to sea level values can never occur at high altitude. This final point is highlighted by the fact that, despite long-term acclimatization and genetic adaptation, high altitude natives $\geq$ 3000 m above sea-level exhibit severe hypoxemia ($PaO_2 < 60$ mmHg) with reduced physical and cognitive function compared to sea level populations [46].

Cerebral blood flow acclimatization

During ascent and initial stay at high altitude, increases in CBF are elicited via reductions in CaO_2 and consequent hypoxic cerebral vasodilation (reviewed in [47]). The magnitude of this increase in CBF is altitude dependent and contingent on the countervailing influences of hypoxia ($\downarrow CaO_2$) and hypocapnia ($\downarrow PaCO_2$). The resulting cerebral vasodilation occurs throughout the cerebral vasculature from the large extra-cranial cerebral conduit arteries (i.e. ICA and VA) [48, 49], large intra-cranial arteries (e.g. MCA) [49–52], through to pial vessels and is adequate to maintain CDO_2 (Fig. 6). While hyperventilation mitigates the drop in CaO_2 at altitude, it leads to concomitant reductions in $PaCO_2$ resulting in an increased blood and CSF pH [53] (see "Acid–base balance at altitude"). As the cerebral vasculature is highly sensitive to alterations in pH [43, 54, 55], decreased $PaCO_2$ and increased pH produces a marked vasoconstrictor stimuli [56] that counteracts the hypoxic vasodilatory stimulus, although the hypoxic stimulus maintains a net vasodilatory outcome [43]. Given the interplay of CaO_2 and $PaCO_2$ on CBF regulation at altitude, overall regulation appears dependent on four primary factors: (1) the HVR, (2) the HCVR, (3) hypoxic cerebral vasodilation, and (4) hypocapnic cerebral vasoconstriction. The HVR and HCVR determine the prevailing arterial blood gas stimuli (see "Hypoxic ventilatory response at altitude" and "Hypercapnic ventilatory response at altitude"), while hypoxic cerebral vasodilation and hypocapnic vasoconstriction determine the magnitude by which the cerebral vasculature responds to the arterial blood gas stimuli.

Hypoxic cerebral vasodilation notably occurs via several pathways but appears to be primarily regulated by deoxyhemoglobin-mediated release of ATP and nitric oxide (Fig. 6). These signaling processes help to alleviate cerebral hypoxemia by facilitating increased CBF (reviewed in: [47]). Another important consideration in the regulation of CBF at altitude is sympathetic nervous activity [57]. However, laboratory study demonstrates no influence of α_1-adrenoceptor blockade on CBF during 6 h exposure to hypoxia ($F_IO_2 = 0.11$) [58]. Conversely, at altitude, combined α_1- and non-selective β-adrenoceptor blockade reduces CBF, yet this is due to a marked drop in mean arterial pressure (~25 mmHg) [59] and does not appear to have a direct influence on cerebrovascular tone.

As time at high altitude progresses, CBF stabilizes and starts decreasing toward baseline values within 2–3 days after arrival (Fig. 7) [60]. This is a result of both systemic adaptations affecting CaO_2 and altered sensitivity of the cerebral vasculature [6]. Comprising the relevant systemic adaptations are: (1) altitude-induced diuresis whereby HCO_3^- is excreted at an elevated rate in an attempt to

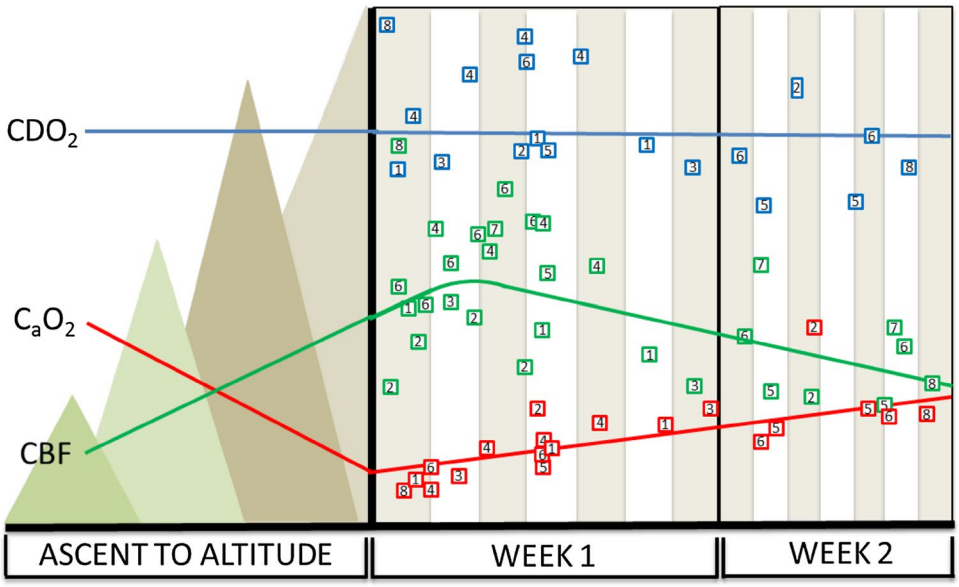

Fig. 6 Changes in cerebral blood flow and oxygen delivery following ascent to altitude. Following initial exposure to high altitude, arterial oxygen content (CaO_2) is reduced and cerebral blood flow (CBF) is commensurately increased. Increases and decreases in CaO_2 and CBF, respectively, then mirror each other throughout acclimatization and maintain cerebral oxygen delivery (CDO_2) constant. Alternating vertical bars represent individual days at altitude. Data are labelled based on their corresponding study. 1: [96], 2: [97], 3: [98], 4: [99], 5: [6], 6: [51], 7: [51], 8: [48]

compensate for respiratory alkalosis [61]; (2) a substantial loss of plasma volume, decreasing total blood volume, but eliciting a significant increase in hematocrit and hemoglobin concentration within days of exposure to altitude [62]. This particular physiological response is a key factor, in addition to ventilatory acclimatization, that drives the early increase in CaO_2 from initial hypoxic exposure (Fig. 2) and thus contributes to the progressive decrease in CBF. (3) Following ~ 1 week at altitude, erythropoiesis then increases hemoglobin mass leading to further increases in hematocrit [62–65]. Another necessary consideration is the influence of [Hb] on viscosity and the potential implications of viscosity in regulating CBF at altitude. To our knowledge no data have specifically examined the influence of viscosity on CBF at altitude; however, the existing data in humans at sea level indicates a likely negligible influence of viscosity on CBF in hypoxia (reviewed in [47]). It should be noted, of course, that excessive polycythemia is extremely detrimental to physiological function and health at high altitude in both lowlanders and those with chronic mountain sickness [66, 67].

Alterations in cerebral vascular reactivity to both O_2 and CO_2 may also be implicated in CBF regulation at high altitude [6]. Both increases [6, 68] and no change [28, 43] in hypocapnic cerebral vasoconstriction have been demonstrated upon ascent to and acclimatization at altitude. Therefore, given methodological (technical and logistical) differences between studies, physiological differences (e.g., acid–base balance) and the consequent inconsistency of results, it remains relatively unclear how altered hypocapnic vasoconstriction may contribute to the progressively reduced CBF throughout acclimatization. Relative to cerebral sensitivity to O_2, one study to date has conducted repeated measures indicating that hypoxic cerebral vasodilation is increased at altitude [69], which is corroborated by more well-controlled laboratory studies [70]. Yet, changes in hypoxic vasodilation with acclimatization have not been examined using volumetric measures of CBF, necessitating judicious interpretation of the currently available data. Nonetheless, the observed increase in hypoxic cerebral vasodilation may counteract the vasoconstrictor stimulus consequent to reduced $PaCO_2$ and underscore the net vasodilatory stimulus and maintained CDO_2 observed upon exposure to high altitude. Collectively, global CBF at altitude mirrors changes in CaO_2 and although $PaCO_2$ is a very potent regulator of tone, following initial exposure to altitude, arterial pH is minimally altered (Fig. 1). Therefore, it appears CaO_2 is the primary factor governing the pattern by which CBF changes following initial exposure to high altitude. Potential alterations in reactivity at altitude may further "fine tune" the observed changes in CBF.

Although global changes in CBF have been shown to maintain CDO_2 in hypobaric hypoxia throughout ascent and stay at high altitude, regional differences in the flow response to altitude have been demonstrated [48, 49]. These altitude studies, and those conducted in well-controlled laboratory settings [48, 49, 71, 72] display preferential blood flow distribution to the posterior circulation, which perfuses brain regions such as the brainstem, hypothalamus, thalamus and cerebellum [71]. Despite no relationship between global CBF and AMS [60] and failure of globally maintained CDO_2 to explain cognitive deficits in hypoxia, the aforementioned regionalization of CBF is suggested to be responsible for AMS [73], as well as cognitive impairment [72] at altitude. However, given the number of inconsistent studies [52, 60], sufficient data are still lacking with regard to the intricacies

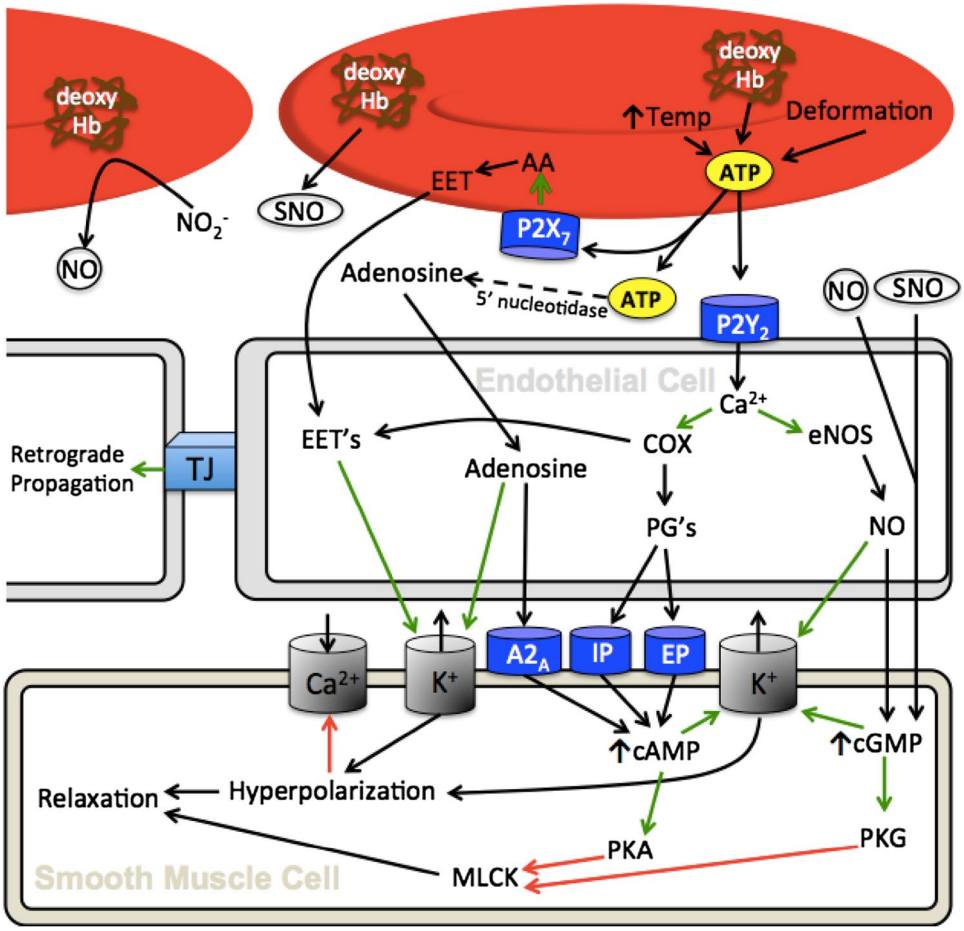

Fig. 7 Putative pathways regulating cerebral blood flow during hypoxia. Increased temperature, erythrocyte deformation, and the conformational change concomitant to transition of oxy- to deoxy-hemoglobin all signal erythrocyte mediated release of ATP [97–103]. Released ATP can then bind to the erythrocyte $P2X_7$ receptor in an autocrine fashion to induce erythrocyte mediated EET release [104], which will increase vascular smooth muscle cell K+ channel conductance [105]. The released ATP also binds endothelial P_2Y_2 receptors to initiate a signal cascade involving NO and potentially PGs [106]. Moreover, ATP will breakdown into AMP and subsequently adenosine [107] that will also exert a vasodilatory effect on vascular smooth muscle through binding adenosine A_{2A} receptors [108, 109], increasing cAMP levels [110, 111] and also through increasing inward rectify potassium channel conductance [108]. Prostaglandins, if implicated, bind IP and EP receptors [112] which increases intracellular cAMP [113]. NO, derived from the endothelium, through the nitrite reductase activity of erythrocytes [114], and s-nitrosohemoglobin [115, 116] will lead to increased guanylate cyclase activity and cGMP [117] as well as directly increase K+ channel conductance [118]. Cyclic nucleotides will upregulate cAMP dependent protein kinase (PKA) and cGMP dependent protein kinase (PKG) activity, which act to inhibit myosin light chain kinase (MLCK; [119]), and therefore, reduce smooth muscle tone [120]. Cyclic nucleotides will also increase potassium channel conductance [121], with increased potassium efflux hyperpolarizing cells and reducing activity of voltage gated Ca2+ channels [122]. Overall, ATP leads to vasodilation that can be conducted through gap junctions [123, 124]. Green arrows represent activation of a downstream factor, and red arrows represent inhibition of downstream factors. Permission not required. Copyright © 2016, The American Physiological Society

of regionalized CBF regulation and its consequent impact(s). Nevertheless, regionally differential distribution of blood flow likely occurs as a survival mechanism to prioritize delivery to the posterior areas of the brain responsible for controlling functional and homeostatic processes while consequently reducing delivery to areas responsible for higher cognitive function. Although we have intentionally focused on CBF (i.e., inflow), it should be noted that a mismatch between cerebral inflow and venous outflow is critical in the pathophysiological of AMS [74] and potentially cerebral edema [75]. In the latter landmark study, it was reported that CDO_2 was maintained via increased arterial inflow (i.e., CBF) and this preceded the development of cerebral edema thus implicating venous outflow restriction as a key mechanism [75].

Technological advancements in imaging modalities have greatly improved the quantification of CBF (e.g., MRI), yet difficulties persist with regards to the portability and feasibility of such equipment during high altitude studies. As such, transcranial Doppler and portable duplex ultrasound

devices remain standard tools for assessment of CBF during high altitude expeditions. Although the latter approach can be quite accurate and effective [51, 76, 77], the former fails to provide a complete assessment of CBF [75, 78]. Thus, changes in flow as reported through changes in blood velocity using transcranial Doppler ultrasound measurements should be interpreted cautiously in hypoxic environments. This discrepancy between imaging techniques largely underlies the methodological differences that make comparing high-altitude studies difficult.

Systems integration

Throughout this review we have described the regulation of CBF and V_E at high-altitude in a relatively isolated manner. However, we do not disregard the likely inter-dependence between these two physiological systems at altitude. Although the magnitude of cerebrovascular and ventilatory changes at high altitude may directly impact upon the other it is not as clear which system may lead in a cause/effect relationship, spurring a "chicken or the egg" conundrum. At the simplest level, a brisk HVR will lead to improved CaO_2 and theoretically CDO_2; however, this will come at the expense of augmented hypocapnia, which will have a countervailing influence on CDO_2 by reducing CBF through hypocapnic vasoconstriction that is dependent on the degree of metabolic acidosis (i.e. HCO_3^- excretion; see Fig. 3). Conversely, large increases in CBF will increase CDO_2 , but may also increase central CO_2/H^+ washout and reduce central chemoreceptor mediated drive to breathe [79]—a response that would lead to transient reductions in CaO_2 and hence potentially lower CDO_2 subsequent to a reduced V_E. Herein, we discuss the animal and human data explicating the interdependence of V_E and CBF, and discuss how this may pertain to regulation at high altitude.

Ultimately, CBF and its reactivity to changes in arterial blood gases and acid/base changes influences V_E by altering the central chemoreceptor stimulation (not sensitivity). This stimulation in the setting of alterations in $PaCO_2$ or PaO_2 is contingent upon manipulation of the $PaCO_2$ to brain tissue PCO_2 ($PbCO_2$) gradient. Irrespective of the type or magnitude of blood gas changes, $PbCO_2$ will be greater than $PaCO_2$ due to metabolic CO_2 production, resulting in a positive $PbCO_2$–$PaCO_2$ gradient (e.g., [80, 81]). At a constant $PaCO_2$, increases in CBF raise central pH by reducing the $PbCO_2$–$PaCO_2$ gradient, as greater flow through the arterial system will draw $PbCO_2$ closer to equilibrium with $PaCO_2$ (Fig. 8). While it is the $PbCO_2$ to $PaCO_2$ gradient manipulation governing CBF mediated alterations in V_E, experimental models have primarily indexed $PbCO_2$ with measures of jugular venous CO_2. Previous animal work has demonstrated that increases in CBF [82], and presumably decreases in CBF, will increase and decrease ventral medullary pH, respectively. The impact of such changes is reflected in the elevated V_E sensitivity to hypercapnia and hypoxia during moderate reductions in CBF [83]. However, these increases in V_E sensitivity were dependent upon the indexing of V_E against $PaCO_2$, as V_E sensitivity to jugular venous CO_2 was unaltered demonstrating the importance of the $PbCO_2$–$PaCO_2$ gradient in ventilatory control [84, 85]. Manipulation of cerebrovascular reactivity and

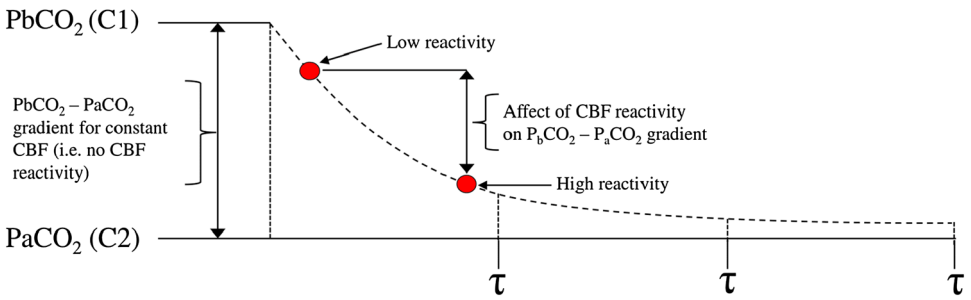

Fig. 8 A theoretical schematic representing the relationship between two fluid compartments separated by a semi permeable membrane. When two fluid compartments separated by a semipermeable membrane are adjacent to one another, a square wave change in the concentration of a substance in one fluid compartment (c1) will be 95% equilibrated with the opposite compartment (c2) over three time constants. A time constant (τ) represents the time required for a volume of fluid equal to that of c1 to flow through c2 (e.g., if c1 is 500 mL, 1.5 L would have to flow through c2 to reach 95% equilibration). This model can be applied to the cerebral vasculature and brain tissue compartment to understand the effect of cerebrovascular reactivity in producing varying stimuli to breathe despite the same value for $PaCO_2$ (or $P_{ET}CO_2$). The major limitation of this model is that if we use c2 to represent arterial blood vessels proximal to the central chemoreceptors, and c1 to represent the tissue compartment where the central chemoreceptors reside, c1 is in contrast to a steady-state, constantly producing CO_2 via metabolism. Therefore, a simple square wave change cannot be assumed between blood and tissue CO_2, but for simplicity we can assume that the relationship between arterial and tissue CO_2 resides somewhere on the dotted line, based upon the magnitude of flow and metabolic production of CO_2 at any given time. Assuming constant CO_2 production, higher flow would result in a rightward shift down the line, and an overall reduced blood to tissue gradient. This would then ultimately lead to a reduction in central chemoreceptor stimulation and reduced V_E. Modified with permission from [90]

arterial-jugular venous gradients in humans have corroborated this role of $PbCO_2$–$PaCO_2$ gradient changes in ventilatory control [85, 86].

CBF and ventilation in hypoxia

At sea level in the laboratory setting of isocapnic hypoxia, jugular venous CO_2 is reduced following hypoxic cerebral vasodilation [87, 88] concomitant to increased jugular venous pH [87]. In our previous study, progressively reduced SaO_2 from 98% at rest to 70% led to an increase in jugular venous pH of 0.02 despite the maintenance of $PaCO_2$ [87]. This magnitude of change holds relevance for the control of breathing given that small changes in pH possess a profound influence on ventilation—a 0.01 change in tissue pH may result in up to a 5 L min^{-1} change in alveolar ventilation [89]. Further, our lab has demonstrated that posterior cerebrovascular reactivity to hypoxia is directly correlated to the magnitude of hypoxic ventilatory decline in humans, further supporting the notion that elevated CBF may attenuate V_E [90]. While these data are in the setting of isocapnic hypoxia, the greater influence of changes in $PaCO_2$ on pH (Fig. 3) [43] coupled with the markedly increased ventilatory sensitivity to arterial and jugular venous PCO_2/H^+ [43], should collectively increase the influence of CBF mediated central CO_2 washout on V_E throughout acclimatization. Consistent with this notion, it has been suggested that lower posterior CBF reactivity to poikilocapnic hypoxia contributes to the high HVR measured at sea level [91] that is generally characteristic of successful mountaineers [35, 36]. However, as previously noted, a reduced HVR when measured at altitude is related to improved performance at extreme altitude (~ 8000 m) [38]. At high-altitude, the physiological responses between V_E and CBF occur rapidly with the responses reaching a steady state balance governed by the bidirectional influences of V_E on CBF and vice versa (Fig. 9).

Conclusion

Upon ascent to altitude CBF and V_E increase and are responsible for maintained CDO_2. As medullary pH is dependent on arterial pH, medullary metabolism, and medullary blood flow, CBF changes at altitude are poised to directly influence central chemoreceptor stimulation. On the other hand, the ventilatory response to high-altitude determines the overall arterial blood gas and acid/base stimulus regulating CBF. Thus, these two responses are intimately intertwined in the determination of cerebral homeostasis at altitude.

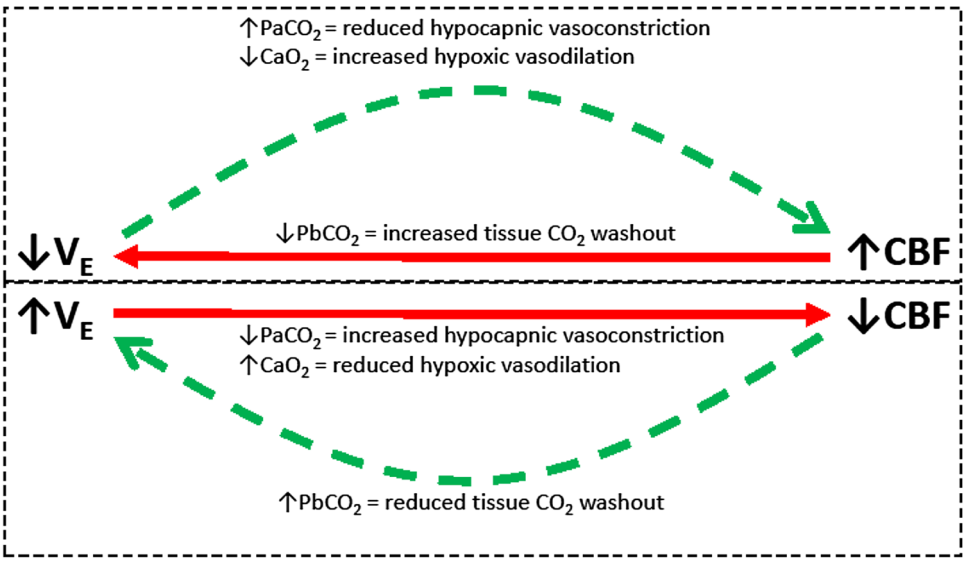

Fig. 9 Proposed model of the opposing influences of ventilation and cerebral blood flow at altitude. Red arrows indicate a consequent reduction, while green arrows indicate consequent increases in V_E and/or CBF for the noted physiological changes at altitude. Top box: increased CBF will cause a reduction in $PbCO_2$, due to an increased washout from the brain tissue, and thus reduce central chemoreceptor stimulation. This will lead to a reduction in ventilatory drive. The consequences of reduced V_E are an increased $PaCO_2$ and reduced CaO_2 (relative to normal values at a given altitude), which both act to increase CBF. Bottom box: Increased V_E reduces $PaCO_2$ and increases CaO_2 (relative to normal values at a given altitude), which both lead to reduced CBF. Consequently, central washout for CO_2 is reduced and $PbCO_2$ increased, which augments central chemoreceptor stimulation and ventilatory drive. The top box represents a scenario whereby increased CBF and reduced VE occur, while the bottom box portrays the opposite scenario—ultimately these pathways reach a set point, likely governed by ventilatory and cerebrovascular sensitivities

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