**Experimental Physiology – *Hot Topic Review***

# Regulation of cerebral blood flow in mammals during chronic hypoxia: a matter of balance

Philip N. Ainslie[1] and Shigehiko Ogoh[2]

[1] *Department of Human Kinetics, Faculty of Health and Social Development, University of British Columbia Okanagan, Kelowna, British Columbia, Canada*
[2] *Department of Biomedical Engineering, Faculty of Engineering, Toyo University, Saitama, Japan*

**Respiratory-induced changes in the partial pressures of arterial carbon dioxide ($P_{aCO_2}$) and oxygen ($P_{aO_2}$) play a major role in cerebral blood flow (CBF) regulation. Elevations in $P_{aCO_2}$ (hypercapnia) lead to vasodilatation and increases in CBF, whereas reductions in $P_{aCO_2}$ (hypocapnia) lead to vasoconstriction and decreases in CBF. A fall in $P_{aO_2}$ (hypoxia) below a certain threshold (<40–45 mmHg) also produces cerebral vasodilatation. Upon initial exposure to hypoxia, CBF is elevated via a greater relative degree of hypoxia compared with hypocapnia. At this point, hypoxia-induced elevations in blood pressure and loss of cerebral autoregulation, stimulation of neuronal pathways, angiogenesis, release of adenosine, endothelium-derived NO and a variety of autocoids and cytokines are additional factors acting to increase CBF. Following 2–3 days, however, the process of ventilatory acclimatization results in a progressive rise in ventilation, which increases $P_{aO_2}$ and reduces $P_{aCO_2}$, collectively acting to attenuate the initial rise in CBF. Other factors acting to lower CBF include elevations in haematocrit, sympathetic nerve activity and local and endothelium-derived vasoconstrictors. Hypoxia-induced alterations of cerebrovascular reactivity, autoregulation and pulmonary vascular tone may also affect CBF. Thus, the extent of change in CBF during exposure to hypoxia is dependent on the balance between the myriad of vasodilators and constrictors derived from the endothelium, neuronal innervations and perfusion pressure. This review examines the extent and mechanisms by which hypoxia regulates CBF. Particular focus will be given to the marked influence of hypoxia associated with exposure to high altitude and chronic lung disease. The associated implications of these hypoxia-induced integrative alterations for the regulation of CBF are discussed, and future avenues for research are proposed.**

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**Corresponding author** P. N. Ainslie: Department of Human Kinetics, Faculty of Health and Social Development, University of British Columbia Okanagan, Kelowna V1V 1V7, Canada. Email: philip.ainslie@ubc.ca

The partial pressures of arterial carbon dioxide ($P_{aCO_2}$) and oxygen ($P_{aO_2}$) play a major role in cerebral blood flow (CBF) regulation. Whilst the role of $P_{aCO_2}$ in the regulation of CBF has been well described (Ainslie & Duffin, 2009), the influence of hypoxia in the regulation of the cerebral circulation has received little focus, especially in humans. This is somewhat surprising given the development of arterial hypoxaemia in both 'normal' physiological endeavours, such as exercise and ascent to high altitude (HA), and during pathology (e.g. chronic lung disease and heart failure). It has been well reported that hypoxia, reflected in a fall in $P_{aO_2}$ below a certain threshold (<40–45 mmHg), produces cerebral vasodilatation. The mechanisms underling these responses of hypoxia upon CBF, appearing simple at first, are highly complex and involve interactions of many physiological, metabolic and biochemical processes. The major factors underlying the extent of change in CBF during exposure to reductions in $P_{aO_2}$ are depicted in Fig. 1. These factors, with particular focus on the integrative mechanisms linking reductions in $P_{aO_2}$ with cerebrovascular regulation, are discussed in detail in the first section of this brief review. Next, we provide a detailed update on the influence of hypoxia on cerebrovascular function in selected 'normal' physiological endeavours (e.g. ascent to high altitude) and during selected pathology (e.g. chronic lung disease).


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Finally, with emphasis on describing and clarifying the integrative mechanisms by which hypoxia regulates the cerebral function, we suggest avenues for future research. The majority of recent studies performed in this area have used transcranial Doppler ultrasound measurements to assess middle cerebral arterial (MCA) blood flow velocity, rather than absolute measurements of flow. Although for the purposes of this review, we will not make the distinction between changes in flow (CBF) and velocity (CBFv), we highlight the main ways in which CBF can be assessed at high altitude and consider the advantages and disadvantages of each method (see '*Measurement of cerebral blood flow at high altitude*').

## Control of CBF

Cerebral blood flow is regulated by vascular smooth muscle tone, which is under the influence of neural, chemical, metabolic and physical factors (Figs 1 and 2). Ultimately, it is the net effect of vasodilators and constrictors derived from the endothelium and neuronal innervations (and perfusion pressure) that determines CBF (Fig. 2). In the brain, vascular smooth muscle tone is closely controlled by endogenous substances, such as nitric oxide (NO; Bailey *et al.* 2009*b*) and prostanoids (Hortobágyi *et al.* 2007), as well as C-natriuretic peptide (Kobayashi *et al.* 1994) and endothelin-1 (Henze *et al.* 2007) produced by the neighbouring endothelial and neuronal cells (Fig. 2). Together, these endogenous mediators alter intracellular $[Ca^{2+}]$ in the smooth muscle cells via second messenger and $K^+$ channel activation/hyperpolarizing pathways, leading to smooth muscle contraction/relaxation. These endogenous mediators are activated in response to many stimuli, including the following: circulating substances, such as $P_{aCO_2}$, $P_{aO_2}$, pH, lactate, glucose and adenosine (for review see Edvinsson & Krause, 2002); postganglionic neurotransmitters, such as NO, acetylcholine, vasoactive intestinal peptide, calcitonin gene-related peptide and noradrenaline (for review see Gulbenkian *et al.* 2001); and mechanical factors, such as shear (Rebel *et al.* 2003) and stretch (Osol & Halpern, 1985). These factors are highlighted in Fig. 2. The physiological control of CBF has been described in detail, and readers are directed to the detailed literature (Edvinsson & Krause, 2002; Iadecola & Nedergaard, 2007; Kulik *et al.* 2008; Ainslie & Duffin,

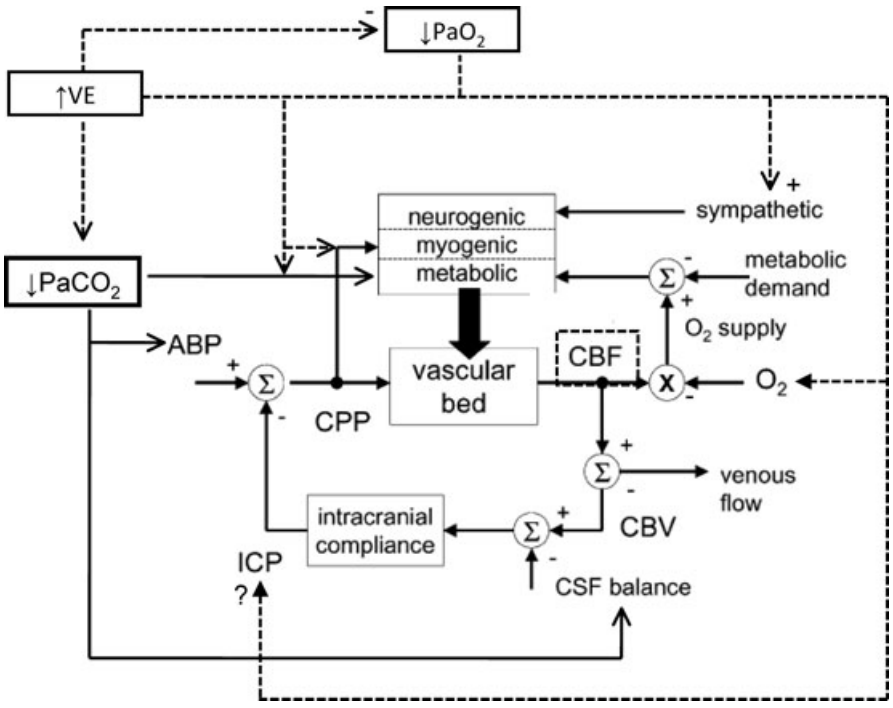


**Figure 1. Simplified block diagram of the main mechanisms responsible for the control of cerebral blood flow (CBF)**
The vascular bed corresponds to the passive properties of blood vessels, usually modelled as a combination of resistances and compliances. The dashed lines represent the potential areas—both direct and indirect—in which $P_{aO_2}$ may influence CBF. Modified from (Panerai, 2003; Ainslie & Duffin, 2009). Abbreviations: ABP, arterial blood pressure; ICP, intracranial pressure; CSF, cerebral spinal fluid; CPP, cerebral perfusion pressure; CBV, cerebral blood volume.

2009; Koehler *et al.* 2009; Toda *et al.* 2009). Rather than reproduce this information here, we focus the next section on summarizing the key factors that modulate CBF upon exposure to high altitude.

## Regulation of CBF – influence of high altitude

It has been known for some time that inhalation of hypoxic gas mixtures causes dilatation of pial vessels, a reduction in cerebral vascular resistance and increased CBF in humans (Kety & Schmidt, 1948; Cohen *et al.* 1967). However, whilst hypoxia *per se* is a cerebral vasodilator, reflected in a rise in CBF in proportion to the severity of isocapnic hypoxia (Cohen *et al.* 1967; Ainslie & Poulin, 2004), in normal conditions the hypoxia-induced activation of peripheral chemoreceptor activity leads to hyperventilatory-induced lowering of $P_{aCO_2}$ and subsequent cerebral vasoconstriction. It is important to note that the cerebrovascular response to hypoxia can be broadly grouped into two time domains, as follows: (1) acute hypoxic response (seconds to hours); and (2) short- to long-term hypoxia (days to years), i.e. during acclimatization. Since the majority of the adaptive changes in CBF occur within 3–4 weeks upon exposure to a constant level of hypoxia, we will focus on the latter time domain of this response.

Time-dependent changes in CBF are clearly evident during acclimatization to high altitude. Severinghaus *et al.* (1966) were the first to report that, compared with sea-level ($CBF = 42 \pm 2$ ml (100 g)$^{-1}$ min$^{-1}$) there was a 24% increase ($51 \pm 4$ ml (100 g)$^{-1}$ min$^{-1}$) in CBF on arrival (6–12 h) at high altitude (3810 m); after 3–5 further days, the increase in CBF was only 13%. Subsequent studies, in humans (Roy *et al.* 1968; Milledge & Sorensen, 1972; Moller *et al.* 2002; Thomas *et al.* 2008) and animals (Xu *et al.* 2004) have confirmed and added to these findings. In essence, these studies show that CBF reaches a peak approximately 2–3 days after arrival at high altitude and then returns to sea-level values within 1–3 weeks (see Fig. 3). The subsequent onset of ventilatory acclimatization coincides with the fall in CBF due to an increase in $P_{aO_2}$ and decrease in $P_{aCO_2}$ owing to reflex hyperventilation (Severinghaus *et al.* 1966; Milledge & Sorensen, 1972; Roy *et al.* 1968; Moller *et al.* 2002). Therefore, over this time period at

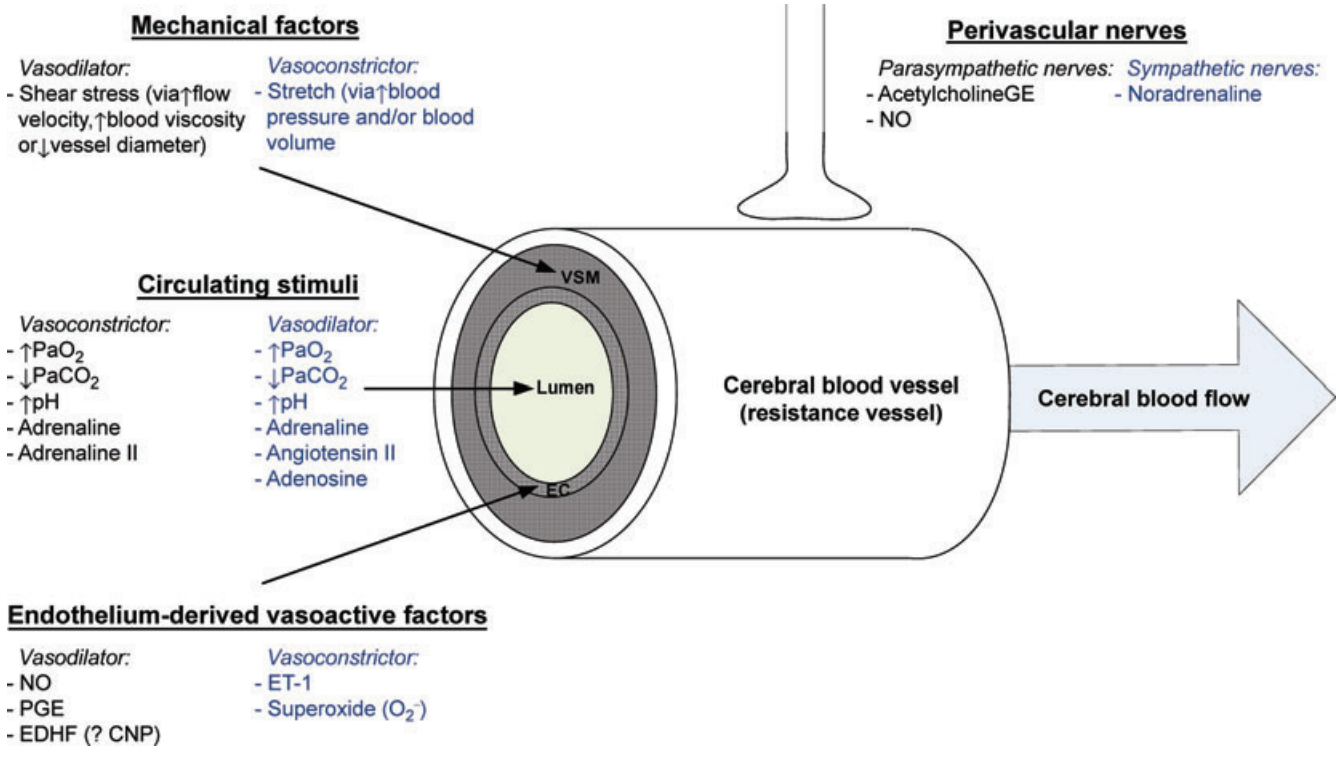


**Figure 2. The main factors influencing the diameter of cerebral resistance vessels**
Abbreviations: VSM, vascular smooth muscle; EC, endothelial cells; NO, nitric oxide; $P_{aO_2}$, arterial partial pressure of oxygen; $P_{aCO_2}$, arterial partial pressure of carbon dioxide; PGE, prostaglandins; ET-1, endothelin-1, EDHF, endothelium-derived hyperpolarizing factor; CNP, C–natriuretic peptide (modified from Morgan, 2007). Note that angiotensin and adrenaline can cause vasoconstriction or vasodilatation depending on which receptor they bind to (e.g. vasoconstriction is mediated by angiotensin I receptors and vasodilatation by angiotension II receptors; for adrenaline receptors, vasoconstriction is via the $\alpha$-receptors and vasodilatation is via the $\beta$-receptors].

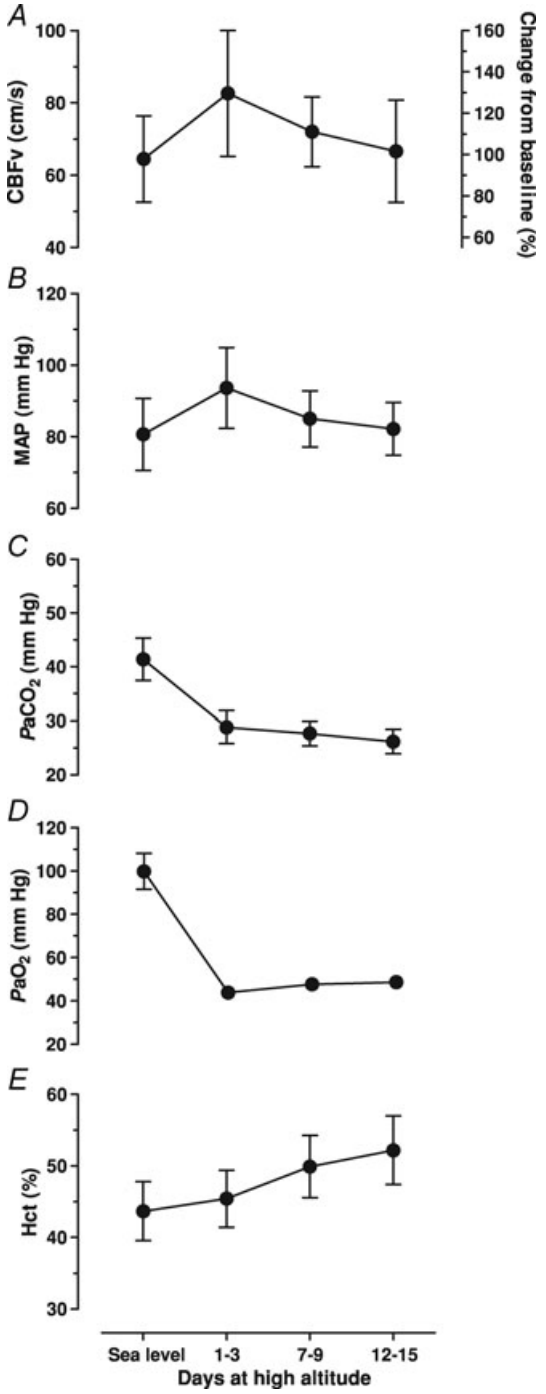


**Figure 3. Illustration of the time course of changes in cerebral blood flow velocity in the middle cerebral artery (CBFv), mean arterial blood pressure (MAP), partial pressure of arterial $O_2$ and $CO_2$ ($P_{aO_2}$ and $P_{aCO_2}$) and haematocrit (Hct) at sea level and at various time points throughout a 15 day stay at 5050 m**
Data are means ± S.D.; $n = 14$–18. (Modified from Thomas *et al.* 2008). Note: (1) ∼25% elevation in CBFv upon initial arrival at 5050 m, coinciding with elevations in MAP, the greatest fall in $P_{aO_2}$ and highest point of $P_{aCO_2}$ before ventilatory adjustments occur; and (2) progressive elevation in HCT during a 2 week stay at 5050 m. See text for details of these multifactorial influences that are likely to determine the extent of CBF change.

a constant altitude, the influence of the $P_{aO_2}$-induced threshold for cerebral vasodilatation (<40–45 mmHg) is removed and the degree of hypocapnia is accentuated; both of these factors, along with elevations in haematocrit, act to attenuate the initial rise in CBF. The time course of these ventilatory-induced changes in arterial blood gases, CBF velocity, blood pressure and haematocrit are illustrated in Fig. 3, and other factors acting to determine the CBF response to exposure to high altitude are further considered.

The initial factors that determine the magnitude of change in CBF depend upon the relative strengths of four reflex mechanisms: (1) hypoxic ventilatory response; (2) hypercapnic ventilatory response; (3) hypoxic cerebral vasodilatation; and (4) hypocapnic cerebral vasoconstriction. In addition to these reflex responses, which most probably are altered during the acclimatization process, CBF is also influenced by a myriad of other hypoxia-induced changes [e.g. capillary density (angiogenesis), adenosine, viscosity/haematocrit]; these factors are illustrated in Fig. 4, and the relative time courses of these events are depicted in Fig. 5. Following the first few days at high altitude, packed red cell volume begins to rise and, at least in animal studies, reaches ∼80% of maximum by 7 days (Xu *et al.* 2004). It should be noted, however, that in humans a similar degree of elevation in haematocrit does not occur until at least 2 weeks of exposure (Fig. 3). Differences in the experimental model (e.g. animal *versus* human) and degree of simulated hypoxia may explain this apprent difference. Initial elevations in hypoxia-inducible factor-1, indicative of tissue hypoxia, fall to about half after 4 days and return to baseline by 3 weeks (Chávez *et al.* 2000). Since brain oxygen delivery is preserved during the first 3–5 days of acclimatization, despite a reduction in CBF (Wolff *et al.* 2002; Moller *et al.* 2002), these results indicate that CBF is not a function of tissue oxygen tension to any great extent but that the process of angiogenesis does directly respond to tissue signals (Xu & LaManna, 2006). In the context of the influence of exposure to hypoxia on CBF regulation, the current knowledge of these conflicting factors is briefly reviewed below.

## Mechanisms acting to increase or decrease CBF at high altitude

**Respiratory factors.** During the first 1–3 days at high altitude, CBF is elevated via a greater relative degree of hypoxia compared with hypocapnia. This balance of arterial blood gases in the regulation of CBF is highlighted in Fig. 6, and shows that a low $P_{aO_2}$ to $P_{aCO_2}$ ratio results in a greater degree of hypoxic vasodilatation for a given hypocapnic vasoconstriction (Thomas *et al.* 2008); this balance, prior to ventilatory acclimatization, accounts

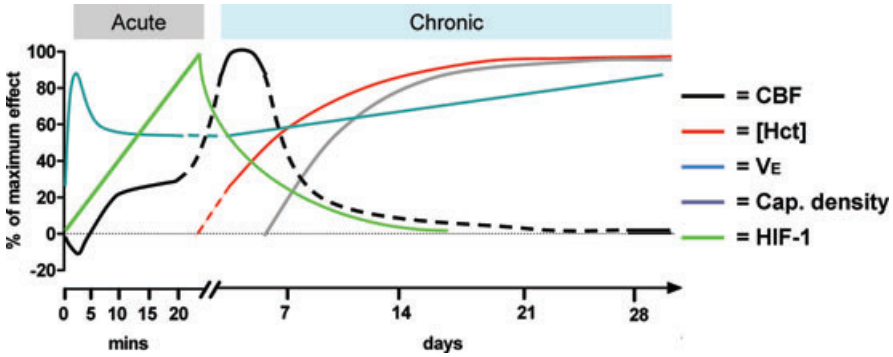


**Figure 4. Integrative changes in cerebral blood flow (CBF), haematocrit (Hct), ventilation (VE), cerebral capillary density and hypoxia-inducible factor-1 (HIF-1) during poikilocapnic hypoxic exposure**
During acute exposure to poikilocapnic hypoxia, the hypoxia-induced hyperventilation and subsequent hypocapnia causes cerebral vasoconstriction, thereby reducing CBF. Ventilatory decline associated with acute hypoxic exposure coincided with an increase in CBF. During chronic hypoxic exposure, the increase in CBF peaked after 1–2 days followed by a slow and progressive decline towards sea-level baseline. In addition, this decline coincided with a steady increase in basal ventilation and elevation in cerebral capillary density from ∼day 4. Furthermore, haematocrit concentration steadily increased with prolonged hypoxic exposure (Fig. 3). Modified from Xu & LaManna (2006).

for ∼30% of the initial increase in CBF. Moreover, hypoxia-induced elevations in blood pressure (Fig. 3), coinciding with the greatest degree of hypoxia and loss of cerebral autoregulation (see below), may also be relevant factors that influence the initial increase in CBF. The process of ventilatory acclimatization results in a progressive rise of ventilation that increases $P_{aO_2}$ and reduces $P_{aCO_2}$ (reviewed by Dempsey & Forster, 1982). The balance of these changes in arterial blood gases, as mentioned, are time dependent (i.e. partly dependent on acid–base changes) and have a major influence on CBF. The key features underlying the early stages of ventilatory acclimatization to acclimatisation are reflected in increases in the acute ventilatory sensitivities to hypoxia and hypercapnia (Robbins, 2007). In terms of the relative contribution of the two, it seems that $P_{aCO_2}$ may be more important than $P_{aO_2}$ (Krasney *et al.* 1985). Nevertheless, at a given altitude, it is clear

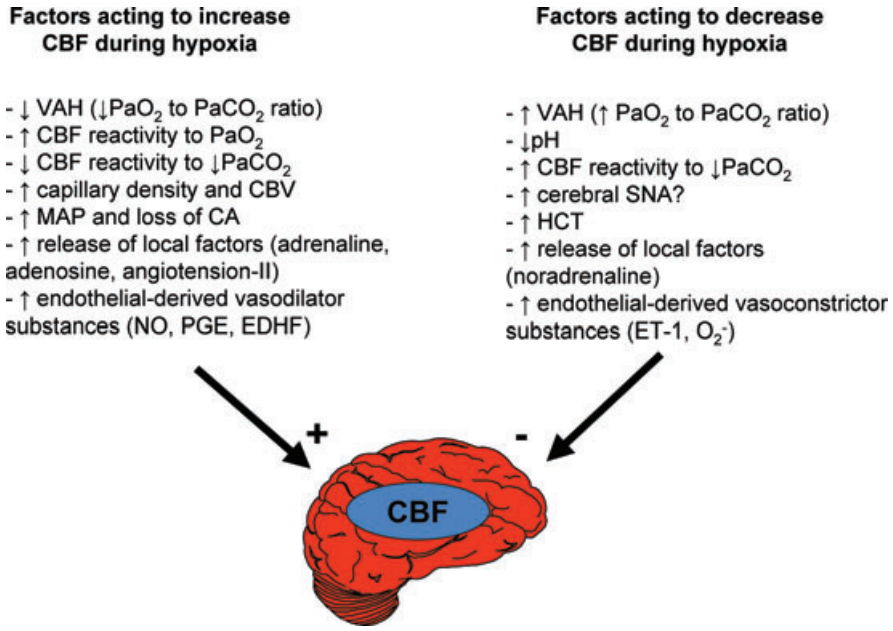


**Figure 5. Summary of the major factors acting to increase (+) and decrease (−) CBF during exposure to hypoxia**
Data are from sources cited in text. Abbreviation: VAH, ventilatory acclimatization to hypoxia; CBF, cerebral blood flow; CBV, cerebral blood volume; MAP, mean arterial blood pressure; CA, cerebral autoregulation; NO, nitric oxide, PGE, prostaglandins; EDHF, endothelium-derived hyperpolarizing factor; SNA, sympathetic nerve activity; HCT, haematocrit; ET-1, endothelin-1; $O_2$- , superoxide.

that those individuals who show a 'brisk' ventilatory response will have a higher $P_{aO_2}$ and lower $P_{aCO_2}$ than those individuals who have a 'blunted' response, and therefore are likely to have lower CBF (Fig. 6); a greater inhibitory response to the resultant hypocapnia may also accelerate this ventilatory drive to hypoxia. In addition, during ventilatory acclimatization, the associated change in cerebrospinal fluid (CSF) pH, and probably the resulting alkalosis, has been suggested as another factor responsible for the falling CBF (Severinghaus, 2001); however, it should be noted that experimental evidence to directly link changes in CSF with CBF regulation have not been reported.

**Neuronal, haematological and local factors.** A major factor acting to increase CBF is the hypoxia-induced stimulation of neuronal pathways that originate in or pass through the brainstem (Golanov & Reis 1996; Golanov *et al.* 2001); these are closely related to the blood oxygen content (Jones *et al.* 1981; Brown *et al.* 1985). In addition, during hypoxia, CBF is increased by hypoxia-induced release of adenosine (Meno *et al.* 1993), endothelium-derived NO (Faraci & Brian, 1994; Bailey *et al.* 2009*b*) and a variety of autocoids and cytokines. Conversely, factors acting to reduce CBF include the hypoxic upregulation of a range of other local and endothelium-derived vasoconstrictors in the brain (e.g. greater expression of endothelin-1, Kanazawa *et al.* 2005; superoxide and noradrenaline; Fig. 4). It is beyond the scope of the present review to provide details on the complexities of the cellular regulation of CBF; readers are therefore directed to elegant reviews on these topics (Edvinsson & Krause, 2002; Iadecola & Nedergaard, 2007; Kulik *et al.* 2008; Ainslie & Duffin, 2009; Koehler *et al.* 2009; Toda *et al.* 2009).

**Angiogenesis.** Another mechanism acting to elevate CBF during exposure to high altitude is angiogenesis. Indeed, the induction of angiogenesis in the mammalian brain is one of the more dramatic adaptations to hypoxia, causing a near doubling of the capillary density that occurs between 1 and 3 weeks of exposure (Miller & Hale, 1970; Xu & LaManna, 2006). The cellular mechanisms through which hypoxia stimulates angiogenesis are now beginning to be understood (for review see Dore-Duffy & La Manna, 2007). The fundamental importance of hypoxia-induced elevations in capillary density are related to an increase in cerebral blood volume (Shockley & LaManna, 1988; Julien-Dolbec *et al.* 2002) and, potentially, subsequent cerebral vasodilatation. Although experimental evidence in humans is lacking, hypoxia-induced elevations in cerebral blood volume have been directly related to capillary density (Dunn *et al.* 2004). It is clear that hypoxia causes a cascade of local mechanisms that underline the reported hypoxia-induced vasodilatation; however, the normalization of CBF over time at high altitude

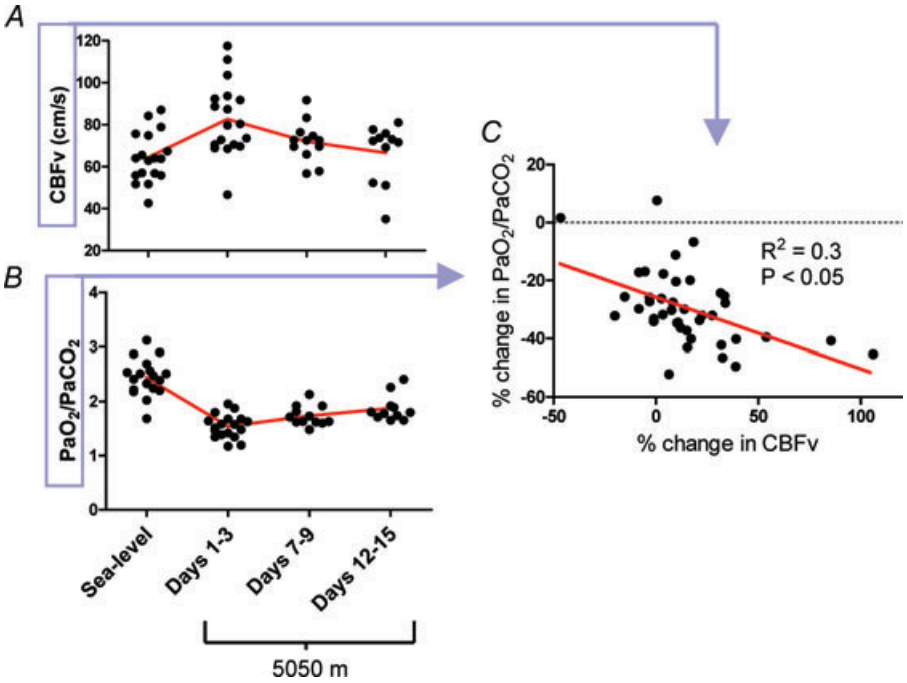


**Figure 6. Relationships between changes in the arterial $P_{O2}$ and $P_{CO_2}$ ratio with changes in cerebral blood flow velocity (CBFv) during 14 days at 5050 m**
Individual changes in cerebral blood flow velocity (CBFv, *A*) and $P_{aO_2}$ to $P_{aCO_2}$ ratio (*B*). A low $P_{aO_2}$ to $P_{aCO_2}$ ratio indicates (*C*) more hypoxic vasodilatation for a given hypocapnic vasoconstriction. Each point represents an individual response (Modified from Thomas *et al.* 2008).

indicates that the vasodilatory factors are balanced out by the various factors acting to attenuate CBF. The relative contributions of these aforementioned factors, especially in humans, are unknown.

**Haematocrit.** Cerebral blood flow varies inversely with haematocrit in many species in both acute (i.e. acute anaemia) and chronic experimental conditions (i.e. erythropoiesis). While the mechanism(s) behind this relationship remains unclear, two possible explanations have been proposed, as follows: (1) alterations in plasma viscosity elicit shear stress-mediated compensatory changes in the cerebral vascular resistance in order to maintain CBF constant (Brown & Marshall, 1985); and (2) reductions in arterial $O_2$ content elicit vasodilatory responses in order to maintain bulk $O_2$ transport (e.g. CBF $\times$ cerebral arterial $O_2$ content) to the brain (Brown *et al.* 1985).

**Cerebral autoregulation.** Cerebral autoregulation adjusts cerebral arteriolar caliber to ensure that CBF levels are matched to metabolic needs relatively independent of changes in blood pressure. Although the mechanism(s) for cerebral autoregulation have not been clarified, they are most likely to involve a complex interplay of myogenic, metabolic and neurogenic mechanisms (Paulson *et al.* 1990). As indicated in this review (Figs 1–6), many of these mechanisms are influenced by hypoxia. There have been a number of studies that have examined the influence of high altitude on CA. Studies indicate an impairment in cerebral autoregulation (Levine *et al.* 1999; Jansen *et al.* 2000; Ainslie *et al.* 2007) in both newcomers to high altitude and in permanent high altitude residents living above 4000 m (Jansen *et al.* 2007), especially in the presence of acute mountain sickness (Van Osta *et al.* 2005; Bailey *et al.* 2009*a*). Impairment in cerebral autoregulation, leading to overperfusion and vasogenic odema subsequent to mechanical disruption of the blood–brain barrier, has been implicated (Roach & Hackett, 2001) in the selective accumulation of intracellular cytotoxic and extracellular vasogenic odema observed in acute mountain sickness (Kallenberg *et al.* 2007). The implications of such of loss of cerebral autoregulation seem to be apparent in both a susceptibility to acute mountain sickness and, potentially, breathing instability during sleep (Ainslie *et al.* 2007). Moreover, in the presence of impaired cerebral autoregulation, any elevation in blood pressure is likely to result in a pressure-passive increase in CBF.

**Cerebrovascular reactivity.** The magnitude of change in CBF also depends upon the relative strengths of hypoxic vasodilatation and hypocapnic vasoconstriction. The significance of alterations in cerebrovascular reactivity to hypoxia and hypocapnia is related to whether or not the intrinsic ability of the cerebrovascular bed to dilate or constrict at high altitude is altered from that at sea level. Experimental studies that have examined the influence of exposure to high altitude on cerebral reactivity are limited and have produced variable results. For example, Jensen *et al.* (1996) reported a 34% increase in CBF response (estimated by transcranial Doppler) to acute isocapnic hypoxia following 5 days at high altitude (3810 m). They also observed increases in estimated CBF reactivity to $CO_2$, and suggested that this increase in reactivity could be fully accounted for by the proportional and gradual changes in $P_{CO_2}$ and cerebrospinal fluid [$HCO_3^-$] with acclimatization, which resulted in larger cerebrospinal fluid pH changes per millimetre of mercury $P_{CO_2}$ change. It should be noted that experimental data to support this possibility are not available and that in order to clarify the mechanisms involved, knowledge of arteriovenous $P_{CO_2}$ gradients and $CO_2$ flux across the brain would be needed. In contrast, other studies have reported that, when compared with sea level, CBF reactivity to hypercapnia is reduced (Ainslie *et al.* 2007; Fan *et al.* 2009; Lucas *et al.* 2009) or unchanged (Ainslie & Burgess, 2008) at high altitude, and CBF reactivity to hypocapnia is either enhanced (Blaber *et al.* 2003; Fan *et al.* 2009; Lucas *et al.* 2009) or unchanged (Ainslie *et al.* 2007; Ainslie & Burgess, 2008). In reconciling these divergent findings, it has been reported that subjects with acute mountain sickness have greater cerebral haemodynamic responses to hypocapnia and a greater reduction in hypercapnic reactivity (compared with no-acute mountain sickness subjects; Jansen *et al.* 1999). Thus it seems that maladaption to altitude (e.g. Jansen *et al.* 1999; Blaber *et al.* 2003) might lead to a differential change in CBF reactivity to hypocapnia compared with well-acclimatized subjects (e.g. Ainslie *et al.* 2007; Ainslie & Burgess, 2008; Lucas *et al.* 2009) and high altitude natives (Jansen *et al.* 1999; Fan *et al.* 2009). However, it is important to point out that differences in experimental protocol (length of hypoxic exposure), method of assessing CBF reactivity (steady-state *versus* rebreathing; Ainslie & Duffin, 2009), degree and type of hypoxic exposure (simulated *versus* high altitude) and limited sample size may explain the differences in the observed CBF reactivity following exposure to high altitude.

**Role of pulmonary vascular vasoconstriction in the regulation of CBF.** Alterations in pulmonary vascular tone may also play a critical role in regulating cerebrovascular function at high altitude. It is well known that, because of hypoxia-induced pulmonary vasoconstriction, pulmonary systemic pressure increases during hypoxic exposure (Bärtsch & Gibbs, 2007). Pulmonary oedema is a commonly observed effect of

such pulmonary hypertension, especially in patients with chronic mountain sickness at high altitude. Elevations in pulmonary vascular resistance can also impair cardiac function, e.g. increase right ventricular end-diastolic and atrial pressure, and reduce left atrial filling (Bärtsch & Gibbs, 2007). Accordingly, elevated right atrial pressure can lead to venous drainage obstruction in certain organs, such as the brain, resulting in increased cerebral venous pressure, cerebral blood volume and subsequent cerebral oedema at high altitude (Wilson *et al.* 2009). This venous drainage obstruction may impede CBF, potentially accounting for some of the reported alterations in cerebrovascular reactivity at high altitude. Likewise, pulmonary vasoconstriction may impair left ventricular filling, potentially impairing left ventricular function and reducing cardiac output. Since a number of studies have found a positive relationship between cardiac output and CBF (Ide *et al.* 2000; Ogoh *et al.* 2005), it is reasonable to assume that an impaired cardiac function at high altitude may further alter cerebrovascular function.

**Autonomic control of CBF at high altitude.** A number of studies have reported general elevations in sympathetic activity (Saito *et al.* 1988; Hansen & Sander, 2003) following ascent to high altitude. Although the cerebral circulation is richly innervated with sympathetic nerve fibres, the effect of sympathetic nerve activity on the regulation of CBF remains controversial. At least during conditions of rest, increases in sympathetic activity appear to have a limited effect on the cerebral vasculature of humans (Ogoh, 2008; Ainslie, 2009). It seems likely that any potential influence of sympathetic nerve activity on regulating CBF is masked by the other more powerful regulatory influences on CBF (e.g. autoregulation, cerebrovascular $CO_2$ reactivity and cardiac output; Ogoh, 2008; Ainslie, 2009; Ainslie & Duffin, 2009). Work in experimental animals (Mayhan *et al.* 1987) and humans indicates that the importance of sympathetically mediated vasoconstriction in the cerebral circulation may be to protect the blood–brain barrier when limits of cerebral autoregulation are exceeded (Ainslie *et al.* 2005; Ogoh *et al.* 2005; Bailey *et al.* 2009*a*). Thus, hypoxia-induced elevations in sympathetic nerve activity have the potential to affect CBF by both direct and indirect mechanisms (Figs 1 and 2). Based on studies of sheep at simulated high altitude, it has been reported that increased sympathetic tone might increase cerebrovascular resistance, acting to attenuate CBF over time (Curran-Everett *et al.* 1992). Although it would seem plausible that elevations in sympathetic nerve activity at high altitude would act to constrain elevations in CBF, experimental data are lacking to support or refute this possibility.

## Measurement of cerebral blood flow at high altitude

Cerebral blood flow can be measured using a number of different techniques, each having certain advantages and also potential methodological flaws (for recent reviews see Querido & Sheel, 2007; Secher *et al.* 2008; Ogoh & Ainslie, 2009). A critical question is whether different methods might, in part, explain some of the divergent findings reported in alterations in CBF at high altitude. Our insights into cerebral perfusion are determined by where, how and when during the ascent to altitude the measurements have been made. Advanced imaging techniques, such as magnetic resonance imaging, are restricted to use in a hospital or research institute and are not currently available at high altitude. There are four main options for the estimation of CBF in the field, as follows: (1) direct brain arteriovenous differences; (2) pulsed Doppler assessment of blood flow in the internal carotid and vertebral artery; (3) transcranial Doppler ultrasound; and (4) near-infrared spectroscopy.

Whilst some previous studies (e.g. Roy *et al.* 1968; Milledge & Sorensen, 1972; Moller *et al.* 2002) have used direct measurement of global CBF, based on the Fick principle, the invasiveness of arterial and internal jugular vein cannulation limits its use in repeat testing, and also for the assessment of cerebrovascular reactivity and autoregulation. Non-invasive Doppler ultrasound assessment of blood flow velocity in the internal carotid and vertebral arteries has also been used (e.g. Huang *et al.* 1987); however, because the probe cannot be fixed, and is therefore subject to movement artifact, this measurement is limited to short periods of time. For more than 20 years, transcranial Doppler ultrasound has been used extensively to study CBF regulation and cerebrovascular $CO_2$ reactivity in otherwise healthy subjects as well as in patients with various forms of cerebrovascular disease. It has been extensively used in the field at high altitude (e.g. Otis *et al.* 1989; Baumgartner *et al.* 1994; Imray *et al.* 2005; Ainslie *et al.* 2007; Ainslie & Burgess, 2008; Thomas *et al.* 2008). Since transcranial Doppler measures flow velocity rather than CBF *per se*, only assessment of changes in flow rather than absolute values can be made. Nevertheless, research indicates that CBFv is a reliable and valid index of CBF (reviewed by Secher *et al.* 2008; Ainslie & Duffin, 2009) and mirrors the reported increases in CBF upon initial exposure to HA as determined by the direct Fick method (e.g. Otis *et al.* 1989; Baumgartner *et al.* 1994; Thomas *et al.* 2008). Moreover, since determinations of cerebrovascular reactivity and autoregulation are based on stimulus–response principles, absolute CBF values are not as important as reliable and repeatable recordings with short (beat-to-beat) time resolution. Continuous transcranial Doppler measurements of CBFv can also be used for extended periods of time, including during

exercise (Imray *et al.* 2005) and during sleep (Ainslie *et al.* 2007). For these reasons, therefore, transcranial Doppler is a well-suited technique both in experimental research and in the field setting.

Near-infrared spectroscopy for the monitoring of local cerebral oxygenation has also been used in the assessment in cerebral perfusion at high altitude (e.g. Imray *et al.* 2005). The use of near-infrared spectroscopy attractive, since it is non-invasive, does not require frequent calibration, is robust and, contrary to transcranial Doppler, the problem of a constant and precise location of the probes is not an issue. It should be noted, however, that cerebral oxygenation or estimated changes in perfusion via changes in haemoglobin metrics measured by near-infrared spectroscopy may be influenced by changes in CBF, cerebral metabolism, arterial saturation and haematocrit (Kurth & Uher, 1997). As outlined in this article, since many of these factors are altered during ascent to high altitude, caution needs to be used in the interpretation of near-infrared spectroscopy parameters alone without complimentary information, such as CBF, arterial saturation and haematocrit.

## Regulation of CBF – influence of chronic lung disease

Arterial hypoxaemia is a common consequence of many chronic lung diseases. While many studies have been conducted to investigate the mechanisms that regulate CBF upon ascent to high altitude, relatively few have considered the effect of pathological changes that occur as a consequence of chronic lung disease. In patients with chronic obstructive lung disease, the majority of reports indicate that CBF is unchanged (Cannizzaro *et al.* 1997; Van de Ven *et al.* 2001, 2002; Jensen *et al.* 2002) from control groups, although this is not a universal finding (Albayrak *et al.* 2006). The unchanged CBF in these patient groups is remarkable in face of the marked hypoxaemia and absence of hypocapnia (or in the presence of acidosis), since these factors act to augment the CBF response to hypoxia (Ainslie & Poulin, 2004). Thus, it seems reasonable to suggest that the powerful vasodilatory influence of hypoxaemia and relative hypercapnia is counteracted by various factors acting to reduce CBF (Figs 2 and 5). In three studies, cerebral reactivity to $CO_2$ was maintained (Cannizzaro *et al.* 1997; Van de Ven *et al.* 2001, 2002), whereas it was impaired in another study (Clivati *et al.* 1992). At high altitude, cerebral metabolic rate of oxygen appears maintained (Moller *et al.* 2002), yet this important variable was found to be reduced markedly in patients with COPD on mechanical ventilation (Sari *et al.* 1992). The disparities between studies are probably explained by the following factors: (1) different tools to assess CBF; (2) experimental considerations that may influence CBF and cerebral metabolism (e.g. medications, mechanical ventilation, sleep and wakefulness); (3) the degree of hypoxaemia in the presence or absence of acidosis; and (4) the extent of hypoxia-induced secondary polycythaemia (York *et al.* 1980). Comparative studies over time in patients with chronic lung disease are lacking. Furthermore, the related mechanisms of CBF regulation (e.g. autoregulation, reactivity and sympathetic nerve activity) and the balance between vasoactive factors acting to dilate or constrict the cerebral vessels (Fig. 5) in this patient group are currently unknown.

## Conclusions and future directions

We have attempted to examine the key mechanisms, and their interactions, involved in the regulation of CBF during exposure to the hypoxia of high altitude. Although the scarce literature is also reviewed in the context of CBF regulation in the hypoxaemic conditions of chronic lung disease, it would seem reasonable to suggest that many of the described operant factors that regulate CBF at high altitude will also play a critical role in normalizing CBF in patients with chronic lung disease. Many aspects of CBF regulation at high altitude clearly warrant further investigation, with particular focus on integrative systems physiology. How does hypoxia alter cerebral autoregulation, reactivity and sympathetic nerve activity regulation of CBF over the period of ventilatory acclimatization (weeks to months)? What mechanisms underlie these changes? Do alterations in CBF regulation cause or contribute to acute mountain sickness, high altitude cerebral oedema and central sleep apnoea? What are the interactions between hypoxia-induced elevations in pulmonary vascular resistance and CBF regulation? Addressing some of these intriguing questions will not only provide new information on how CBF is regulated at high altitude, but will also provide insight into the understanding of cerebral hypoxia in the clinical setting of chronic lung disease and altitude illness.

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