Cerebral blood flow during exercise: mechanisms of regulation

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Abstract

Cerebral blood flow during exercise: mechanisms of regulation. J Appl Physiol 107: 1370–1380, 2009. First published September 3, 2009; doi:10.1152/japplphysiol.00573.2009.—The response of cerebral vasculature to exercise is different from other peripheral vasculature; it has a small vascular bed and is strongly regulated by cerebral autoregulation and the partial pressure of arterial carbon dioxide (PaCO2). In contrast to other organs, the traditional thinking is that total cerebral blood flow (CBF) remains relatively constant and is largely unaffected by a variety of conditions, including those imposed during exercise. Recent research, however, indicates that cerebral neuronal activity and metabolism drive an increase in CBF during exercise. Increases in exercise intensity up to ~60% of maximal oxygen uptake produce elevations in CBF, after which CBF decreases toward baseline values because of lower PaCO2 via hyperventilation-induced cerebral vasoconstriction. This finding indicates that, during heavy exercise, CBF decreases despite the cerebral metabolic demand. In contrast, this reduced CBF during heavy exercise lowers cerebral oxygenation and therefore may act as an independent influence on central fatigue. In this review, we highlight methodological considerations relevant for the assessment of CBF and then summarize the integrative mechanisms underlying the regulation of CBF at rest and during exercise. In addition, we examine how CBF regulation during exercise is altered by exercise training, hypoxia, and aging and suggest avenues for future research.

Keywords: cerebral autoregulation; autonomic nervous system; carbon dioxide tension; chemoreflex; baroreflex; hypoxia; aging

TO PREVENT ACUTE CHANGES in cerebral blood flow (CBF), arterial blood pressure is maintained within the range of 60–150 mmHg. (83). Furthermore, although the cardiovascular system is markedly modified during exercise, the effects of these exercise induced-changes on CBF regulation remain unclear. In contrast to other organ vasculature, traditional thinking is that global CBF remains relatively constant (50–60 ml per 100 g per min) (65) and is largely unaffected by a variety of conditions, including exercise. This belief is maintained despite the evidence of marked changes in the regional distribution of CBF associated with cerebral neuronal activity and metabolism (64); this concept is based on studies (33, 71, 104) that have shown global CBF to be unchanged during exercise. During one-side handgrip exercise, however, middle cerebral artery mean flow velocity (MCA Vmean) increases only on the contralateral side (54) (Fig. 1A). Consistent with this finding, during movement of one foot, cerebral mean flow velocity (Vmean) increases in the contralateral anterior cerebral artery (68) (Fig. 1B). In addition, during deep sleep, reductions in CBF of ~15% are also reflected in parallel ductions in cerebral metabolic rate (70). These findings suggest that Vmean in the basal cerebral arteries show regional rather than the global distribution of CBF that occurs during exercise (105) but not during sleep. This idea has been supported in recent reviews (98, 105) that further emphasize that an increase in global CBF during mild to moderate exercise intensities is reflected with a parallel increase in regional CBF, brain neuronal activity, and metabolism. Indeed, studies using a range of methods, including 133Xenon clearance (55, 56), internal carotid artery blood flow (41), and transcranial Doppler (TCD) (55, 56, 84, 85, 87–90), have shown exercise-induced elevations in CBF.

These inconsistencies (33, 71, 104) are likely due to methodological considerations pertaining to the measurement of CBF. For example, Scheinberg et al. (104) demonstrated that the effect of exercise on global CBF was minimal; however, they compared global CBF during upright exercise with supine rest. Because their results included the influence of the upright posture-induced decrease in CBF (36, 66), including a greater degree of hypocapnia, they underestimated the CBF response to exercise. In addition, the jugular vein is collapsed in the upright position (23), and CBF with the Kety-Schmidt method is complicated further by the asymmetry of the venous drainage from the brain (105).

In contrast to mild to moderate exercise, during heavy exercise to exhaustion, changes in global CBF are not matched with brain neuronal activity and metabolism. Increases in exercise intensity up to ~60% of maximal oxygen uptake produce elevations in CBF, after which CBF decreases toward baseline values despite further increases in exercise intensity and brain metabolism (41, 78). Increased brain neuronal activity and metabolism were maintained by increases in uptakes (a-v difference) of lactate, glucose, and oxygen (49) rather than changes in CBF. These findings indicate that, during exercise,
the regulation of CBF is influenced by other physiological factors rather than cerebral metabolic and neuronal activity, which require a preservation of adequate blood flow to the brain. In this review, we highlight methodological considerations relevant for the assessment of CBF and then summarize the integrative mechanisms underlying the regulation of CBF at rest and during exercise. In addition, we review how CBF regulation during exercise is altered by exercise training, aging, head position, predominantly in the supine position, these methods limit the measurement of CBF to conditions of rest and small muscle activation (120). Near-infrared spectroscopy (NIRS) is also used as an index of CBF because of the strikingly similar time course of changes in oxyhemoglobin and CBF (43). Also, Smielewsky et al. (108) demonstrated that the response of NIRS to changes in carbon dioxide (CO2) during hyperventilation and 5% CO2 inhalation was related to CBF velocity as determined by TCD. However, hemoglobin (Hb) is contained in arterioles, capillaries, and venules. Anatomically, the distribution of blood in the brain is located principally in the veins rather than in the capillaries (5%) and arterioles (20%), indicating that most of the Hb determined by NIRS is “postcellular” (50). In addition, tissue oxygenation is determined by arterial oxygen content, hematocrit, and blood flow. During exercise, both arterial oxygen content and hematocrit may be altered. Therefore, changes in cerebral oxygenated Hb and total Hb determined by NIRS may not reflect only changes in cerebral perfusion (50).

The TCD-determined blood flow velocity in the large basal cerebral arteries (i.e., MCA) is widely used as an index of CBF and can identify a transient change in CBF. An important consideration is that changes in the diameter of the insonated vessels could modulate CBF velocity independently of flow; however, the MCA diameter appears to remain relatively constant in humans during moderate variations in blood pressure and CO2 (32) and also during orthostatic stress or changes in end-tidal CO2 (106). In addition, the changes in MCA $V_{\text{mean}}$ during submaximal dynamic exercise appear to be similar to the changes in global CBF determined by other exercise-valid techniques, i.e., internal carotid artery blood flow (41) and $^{133}$Xe clearance technique (55, 56).

In contrast, Poulin et al. (97) demonstrated that there was a small (2.8%), but significant, reduction in the total power of the reflected Doppler signal (used as an index of cross-sectional area of MCA) during cycle exercise at 40% of maximal oxygen uptake (Fig. 2). Although this finding indicates that there is a decrease in vessel cross-sectional area, the authors also suggested that that flow reversal (or flow separation), occurred across some of the vessel during the increase in blood flow in systole, leading to a reduction in signal power (97). Importantly, however, the use of total power of the reflected Doppler signal has never been validated as an index of cross-sectional area of MCA and therefore should be treated with caution. Thus the effect of exercise on the diameter of the MCA remains controversial, and consequentially so does the validity of TCD measurement during exercise. The future development and validation of duplex ultrasound systems and the related capacity to monitor both diameter and velocity of intracranial arteries will have major implications for the development of CBF research, especially during exercise.
Another limitation of this technique is that the TCD signal can be compromised by head movement, especially during exercise. Although the use of a custom-made headband device can help to minimize artifact produced by small head movement, an important limitation of TCD measurement during exercise is that much of a response could arise as an artifact from the increased amplitude and frequency of the arterial pressure waveform and its consequent effect on the flow profile of the arterial flow in the MCA (97). Nevertheless, despite some limitations, compared with other CBF measurement techniques, TCD technique has many benefits in the measurement of CBF during exercise. In addition, TCD method allows noninvasive and beat-to-beat measurement of changes in MCA blood flow velocity; importantly, this measurement, when combined with beat-to-beat blood pressure, can be used to quantify static and/or dynamic cerebral autoregulation (CA).

Cerebral Autoregulation

CA strongly regulates CBF. Early work of Lassen (64) established that human CBF is maintained within a narrow range despite changes in mean arterial pressure (MAP) between 60 and 150 mmHg; this relationship is termed CA. They identified the range of CA by the relation between CBF and MAP resulting from 11 steady-state data points under several different conditions presented in previous publications. For example, the lower limit of CA was determined between different data points, MAP and CBF data in young normotensive human subjects who had a decreased CBF during acute hypotension (35 mmHg) (26) and in volunteers who had no change in CBF during a pharmaceutically induced mild hypotension (57 mmHg) (74). It is questionable whether the relation between steady-state CBF and blood pressure shows a pure CA because, under different conditions, steady-state CBF is likely to be influenced by other factors (e.g., extent and type of medication) as well as CA (83). Moreover, the traditional concept of static CA only provides the characteristic of static CA because there is no inclusion of transient response of CBF to changes in perfusion pressure (i.e., dynamic CA). Static measurements evaluate the overall effect (efficiency) of the autoregulatory action, i.e., the change in cerebrovascular resistance in response to the manipulation of arterial blood pressure, but they do not address the time in which this change in cerebrovascular resistance is achieved (i.e., its latency). Nevertheless, in humans with both intact and impaired autoregulatory capacity, a close relationship has been reported between both dynamic and static measurements of CA (113). In contrast, dynamic CA is preserved despite a reduction in CBF during orthostatic stress, which, when interpreted from a concept of static CA, would indicate an impairment of CA (17). More recently, however, an elegant study has identified that changes in cerebrovascular resistance attributable to steady-state (static) CA modulate the dynamic pressure-flow relationship of the cerebral circulation (125). It is unknown whether similar modulation occurs during exercise.

Aaslid et al. (1) used TCD and rapidly deflating thigh cuffs to first identify dynamic CA both noninvasively and nonpharmacologically in resting humans by CBF response to a rapid and transient drop in arterial blood pressure. This technique, however, could not be used during exercise. Therefore, the characteristics of dynamic CA in humans during exercise were estimated by the relationship between the dynamic changes in arterial blood pressure with CBF. Reports of fluctuations in CBF during rhythmic resistance exercise (25) and rowing (96) indicate that fluctuations in arterial pressure with each muscle contraction can be too rapid to be countered by CA. Dynamic CA is a frequency-dependent phenomenon (126); therefore, recent reports used the TCD technique and the transfer function analysis to identify dynamic CA. Zhang et al. (126) demonstrated the quantification of this relationship using transfer analysis as >0.07 Hz, indicating a frequency dependence of dynamic CA. Some studies used this analyses technique to identify dynamic CA during exercise. Brys et al. (13) first examined the effect of dynamic exercise on dynamic CA and demonstrated that the variability of CBF is stable during progressive elevations in exercise workload despite an increased variability of arterial blood pressure. This indicates that exercise does not alter CA (Fig. 3A). Indeed, phase shift angle and absolute and normalized low frequency gains between arterial blood pressure and MCA $V_{mean}$, as an index of dynamic CA, remained stable during dynamic exercise despite increasing heart rate, arterial blood pressure, and the partial pressure of arterial CO$_2$ (PaCO$_2$). In contrast, Ogoh et al. (89) found the transfer function gain between diastolic blood pressure and diastolic MCA $V$ increased from rest to heavy exercise, indicating a loss of dynamic CBF control in the diastolic phase during exercise. In addition, Ogoh et al. (88) reported that dynamic CA was impaired during exhaustive exercise (Fig. 3B). This occurred despite arterial hypocapnia, which improves dynamic CA at rest. It is well established that cerebral vascular tone influences dynamic CA (1, 86, 127). Therefore, altered dynamic CA may be associated with intense exercise-induced change in cerebral vascular tone. Indeed, during moderate exercise in hypoxia, cerebral vascular resist-

![Fig. 2. Changes in total power of reflected Doppler signal (top) and 3 indexes of cerebral blood flow (CBF, bottom) in MCA at rest, during cycling exercise at 20% (WLI) and 40% of maximal oxygen uptake (WLII), and during recovery. CBF increased during cycle exercise at 40% of maximal oxygen uptake, whereas the reduction in the total power of the reflected Doppler signal as an index of cross-sectional area of the MCA was small (~2.8%), but significant. , maximal frequency of the Doppler shift; -- , entire velocity spectrum; m, product of total power and the entire velocity spectrum. [From Poulin et al. (97).]]
tance is higher, and dynamic CA is impaired compared with control exercise (2). In contrast, however, hyperglycemia (61) and aging (27) enhanced the increase in cerebral vascular tone associated with exercise, and, under these conditions, dynamic CA was well maintained. The mechanisms that might underlie impairment in dynamic CA during maximal exercise warrant further investigation.

**Sympathetic Nerve Activity**

The peripheral vasculature is regulated via the autonomic nervous system, which consequently influences arterial blood pressure. However, the control of cerebral vasculature is different from other peripheral vasculature during both rest and exercise; it has a small vascular bed and is strongly regulated by CA and PaCO₂. Although the cerebral circulation is richly innervated with sympathetic nerve fibers, it is traditionally held that increases in sympathetic activity have a limited effect on the cerebral vasculature of humans, particularly at rest (9, 38). In contrast, under a hypertensive condition, sympathoexcitation directly causes cerebral vasoconstriction (12, 40, 92, 102). Heistad et al. (40) demonstrated that sympathetic stimulation decreases CBF during severe hypertension in cats, dogs, and monkeys despite its minimal response under resting conditions (Fig. 4). Although Prazosin (an α-1 adrenergic receptor blocker) does not influence CBF under resting conditions in normotensive humans (92), in hypertensive patients, a significant increase in CBF along with reductions in blood pressure were observed (102). Together, these studies (12, 40, 92, 102) suggest that an increase in sympathetic nerve activity prevents forced dilatation of the cerebral arterioles with a resultant regional overperfusion and breakdown of the blood-brain barrier. Similarly, resistance exercise (10-repetition maximum leg press exercise) did not affect CBF despite an increased MAP (+17.3%, \( P < 0.05 \)) and no change in PaCO₂ (25), indicating that intense static exercise-induced increase in cerebral vascular resistance (vasoconstriction) results in the prevention of cerebral overperfusion. However, the effect of sympathetic nerve activity on the regulation of CBF remains controversial (116), and it is unclear whether exercise-induced cerebral vasoconstriction results from elevated sympathetic nerve activity. In addition to direct influence of the sympathetic nervous system, sympathetic activity indirectly influences CBF regulation, e.g., the reactivity of CBF to PaCO₂ (21, 53) and CA (86, 127), even at rest. Recently, Ogoh et al. (86) have found an impaired dynamic CA with an oral dose of the α-1 adrenergic receptor antagonist, Prazosin.

**Dynamic Systemic Vascular Regulation (Arterial Baroreflex)**

It is established that the arterial baroreflex does not directly control cerebral vasculature because this reflex works via sympathetic nervous system, which appears to have a limited effect on the cerebral vasculature of humans (9, 38). Thus the arterial baroreflex mainly regulates arterial
blood pressure such that it is maintained within the range of CA for cerebral circulation. However, anatomically, the autonomic nervous system via arterial baroreflex is directly linked to cerebral circulation (45, 51, 72, 79, 80). Several animal studies (45, 51, 72, 79, 80) have demonstrated close anatomical locations in the medulla acting as major control sites for both the cerebral and systemic circulation (i.e., the cardiovascular center). Unilateral electrical stimulation of the nucleus tractus solitarius increased CBF in rats with cervical cordotomy and vagotomy (79), whereas lesions within the nucleus tractus solitarius impaired CA (51). In addition, stimulation of baroreceptors influences cerebral vasomotion (34, 111, 112). Sinoaortic denervation eliminates cerebral vasodilatation during marked acute hypertension (112), and, during baroreflex deactivation, there are elevations in efferent sympathetic activity in the cervical sympathetic trunk (79), whereas lesions within the nucleus tractus solitarius impaired CA (51). In addition, stimulation of baroreceptors influences cerebral vasomotion (34, 111, 112). Sinoaortic denervation eliminates cerebral vasodilatation during marked acute hypertension (112), and, during baroreflex deactivation, there are elevations in efferent sympathetic activity in the cervical sympathetic trunk (111). Moreover, hemorrhage-induced baroreceptor deactivation causes mild cerebral vasoconstriction (34). In humans, Ogoh et al. (86) reported that cerebral vasodilatation during marked acute hypertension when arterial blood pressure increases via baroreflex, and this response is attenuated by $\alpha$-adrenoreceptor blockade. Ide et al. (46) have demonstrated that, during exercise, sympathetic blockade at the level of the neck eliminated the $\beta_1$- blockade-induced attenuation in CBF. These findings of human studies (46, 86) indicate that arterial baroreflex control of sympathetic nerve activity directly influences CBF during exercise as well as at rest. Cerebral vasomotion via baroreflex, however, is a paradoxical reaction with little physiological benefit (36). During orthostatic stress, for example, the arterial and cardiopulmonary baroreflexes, which are mediated by the autonomic nervous system, seem to be the major mechanisms for maintaining perfusion pressure homeostasis in the brain against hypotension. Thus the teleological relevance of cerebral vasoconstriction during orthostatic stress (36, 63, 66) is unclear.

Carbon Dioxide

Because CBF is highly sensitive to direct changes in $P_{aCO_2}$, $P_{aCO_2}$ serves as a mediator of CBF and therefore also influences the effectiveness of CA (50). Early work of Aaslid et al. (1) demonstrated that hypocapnia improves dynamic CA, whereas hypercapnia impairs it. Hypocapnia causes cerebral vasoconstriction which reduces CBF and therefore, because of a reduced “washout,” attenuates the fall of brain tissue $P_{CO_2}$. In contrast, hypercapnia increases CBF by cerebral vasodilation.

Cardiac Output

In addition to arterial blood pressure control, cardiac output is another factor that can directly influence CBF. When cardiac output was reduced by $\beta_1$-blockade (46) or in patients with heart failure (42) and atrial fibrillation (47), the increase in CBF during dynamic exercise is reduced. In addition, in healthy human volunteers, Ogoh et al. (85) reported a linear relationship between cardiac output and CBF, both at rest and during exercise (Fig. 5). In addition, this relationship is independent of $P_{aCO_2}$, and CA (85). These findings indicate that cardiac output is an important factor in the establishment of the CBF, and any regulation of cardiac output via the cardiac baroreflex would directly influence dynamic CBF regulation at rest and during exercise. Interestingly, the changes in CBF that occurred in response to the central blood volume-induced changes in cardiac output were decreased from rest to exercise. Moreover, Ogoh et al. (87) demonstrated that, with increasing exercise intensity, the reductions in cardiac-arterial baroreflex function that occur at its operating point do not influence the dynamic control of CBF, even when the exercise-induced increase in cardiac output is reduced by cardiac $\beta_1$-adrenergic blockade. This finding also indicates that the arterial baroreflex regulation of blood pressure via reflex regulation of the systemic vasculature becomes more involved in maintaining CBF during exercise.

![Graph showing the linear relationship between cardiac output (Q) and femoral blood flow (FBF, A) or MCA $\nu_{mean}$ (B) at rest (•) and during exercise (∙).](http://jap.physiology.org/)[Reproduced from Ogoh et al. (85) with permission from Wiley-Blackwell.]
which limits elevations in brain tissue PCO₂. However, there is a difference in CBF response between conditions of hypo- and hypercapnia. Hypercapnic cerebral CO₂ reactivity is greater than hypocapnic reactivity because an increase in CO₂ exponentially elevates CBF when a wider range of CO₂ challenge was applied (90, 100). Animal studies indicate that the mechanisms underlying the greater reactivity to hypercapnia compared with hypocapnia may be related to a greater influence of vasodilator mediators on intracranial vascular tone compared with vasoconstrictive mediators (114). In humans, Peebles et al. (94) recently reported that, during hypercapnia, there is a large release of nitric oxide from the brain, whereas this response was absent during hypocapnia.

During exercise, however, cerebral CO₂ reactivity at the operating point (a steady-state value before stimulation) is enhanced (90, 100). During such exercise, cerebral CO₂ reactivity to hypercapnia was increased, whereas it was unchanged during hypocapnia (90). Meadows et al. (75) reported that sleep decreased cerebral CO₂ reactivity (Fig. 6A), suggesting that the level of cerebral activation influences the cerebral CO₂ reactivity. In contrast, our recent work (84) demonstrated that the onset response of CBF was not enhanced during exercise (Fig. 6B). This finding suggests that exercise-induced enhancement of cerebral CO₂ reactivity (steady state) does not correlate with the onset response of CBF (dynamic) to hypercapnia. However, the effect of classic cerebral CO₂ reactivity (steady state) on dynamic cerebral CO₂ reactivity remains unclear even at rest.

Because the blood-brain barrier is permeable to CO₂ and relatively impermeable to [H⁺] and [HCO₃⁻] ions, CO₂ is also a powerful respiratory stimulant at the level of the central chemoreceptors. The periodic nature of inspiration and expiration is finely controlled by changes in PaCO₂ via the respiratory chemoreflex to maintain pH nearly constant. Therefore, changes in CBF have an important role in stabilizing the breathing pattern during fluctuating levels of chemical stimuli, especially Pco₂ at the level of the central chemoreceptors (122). For example, [H⁺] decreases at the level of the central chemoreceptors when CBF increases. Indeed, many studies (8, 19, 24, 121, 122) suggest that cerebrovascular CO₂ reactivity seems to be tightly linked to ventilatory response to CO₂. Severe brain ischemia blunts the ventilatory responses to CO₂ in goats (19). Peebles et al. (93) reported that hypercapnic cerebral CO₂ reactivity was inversely related to the increase in minute ventilation (Vₑ). In other words, a reduced cerebral CO₂ reactivity results in less central CO₂ washout and a greater Vₑ stimulus. Ogoh et al. (90) reported that, under conditions of hypercapnia and exercise, the total respiratory loop gain (i.e., the sensitivity of total respiratory system including central chemoreflex and lung system to changes in CO₂) was markedly reduced, whereas cerebrovascular CO₂ reactivity was increased. These findings indicate that, despite an attenuated chemoreflex system controlling Vₑ, elevations in cerebrovascular reactivity might help maintain CO₂ homeostasis in the brain during exercise. At rest, we have shown (84) that the onset response of MCA Vmean to hypercapnia was faster than

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**Fig. 6.** A: changes in CVR in each individual from wake to sleep. Open symbols, individual values; solid symbols, group mean values (± SE). [From Meadows et al. (75).] B, left: continuous recordings of the MCA Vmean during hypercapnia at rest (solid regression line) and during exercise (dashed regression line) in 1 representative subject. Hypercapnia was started at time 0. Right: group-averaged time constant (τ) of MCA Vmean and minute ventilation (Vₑ) exponential fitting curves at rest and during exercise. Values are means ± SE. *Different from MCA Vmean (P < 0.05); †different from rest (P < 0.05). [From Ogoh et al. (84).]
that of the respiratory chemoreflex. However, dynamic exercise did not enhance the onset response of MCA $V_{\text{mean}}$ to hypercapnia despite the greater elevation of $P_{\text{ACO}_2}$ and subsequent elevation in the ventilatory onset response (Fig. 6B). These findings indicate that the onset response of CBF influences respiratory control via a central chemoreflex and that exercise modifies the interaction between CBF and ventilatory onset responses. These findings raise the possibility that abnormal chemoreflex control of breathing evident in a range of pathological events (e.g., chronic lung disease, heart failure, and sleep apnea) may alter dynamic CBF regulation.

**Cerebral Metabolism**

Alterations in cerebral metabolism in response to activation by exercise have been elegantly reviewed (105). However, a brief mention of cerebral metabolism is provided because CBF regulation during exercise is critical for maintaining cerebral metabolism. During exercise, increases in cerebral metabolism require increased CBF to deliver the oxygen required for aerobic metabolism of the brain (105). Indeed, mild to moderate exercise increases CBF; thus it is likely that cerebral metabolism markedly controls CBF during exercise. Dynamic movement is associated with cortical activation and results in elevations in blood flow to the supplementary motor area and the primary sensorimotor area (91). Such regional flow changes are accompanied by a much smaller increase in regional metabolism (50). Gross et al. (35) demonstrated that, in exercising dogs, blood flow increased in regions of the brain associated with motor control. In contrast, following doxapram (a known respiratory stimulant, which in low doses increases ventilation by stimulating the peripheral chemoreceptors) at rest, CBF was reduced despite a similar degree of hypocapnia, hypertension, and sympathetic nerve activation to that observed during exercise. This indicates that the vasodilatory effects of the exercise-induced increase in brain metabolism overrode the vasoconstrictor effects of hypocapnia, hypertension, and sympathetic nerves on the cerebral vasculature. Linkis et al. (68) demonstrated that right-handed contractions elevated MCA $V_{\text{mean}}$ in the left MCA (+19%), whereas the increase in MCA $V_{\text{mean}}$ in the right MCA was slight (+4%) (Fig. 1A). These findings suggest that the vasodilatation effects of the exercise-induced increase in brain metabolism overrode the vasoconstrictor effects of hypocapnia, hypertension, and sympathetic nerves on the cerebral vasculature.

However, it is unlikely that exercise-induced elevations in metabolism lead to proportional increases in global CBF because increases in exercise intensity cause an increase in CBF to around 60% of maximal oxygen uptake. At higher exercise intensities, CBF returns toward baseline values because of hyperventilation-induced hypocapnia despite further elevations in cerebral metabolism (41, 78). Thus, during heavy exercise, the hyperventilation-induced hypocapnia seems to be a stronger regulator of CBF compared with that of elevations in cerebral metabolism (88). Nevertheless, brain oxygen ($O_2$) uptake is important for cerebral neuronal activity. For example, unconsciousness occurs within a few seconds after the brain is deprived from its $O_2$ supply following a cardiac arrest (105). In addition, hyperoxia can enhance exercise performance and is associated with increases in cerebral rather than muscle oxygenation (81). During dynamic exercise at mild to moderate intensities, brain $O_2$ uptake remains unchanged (49, 71), whereas, at maximal exercise intensities, brain $O_2$ uptake increases despite a reduction in CBF (49). This increase in brain $O_2$ uptake likely compensates for the hyperventilation-induced decreases in CBF to maintain high cerebral metabolism during heavy to exhaustive exercise.

The brain possesses a capacity for anaerobic metabolism (30), providing an important means to enhance energy turnover to sustain cerebral activation during high-intensity exercise (95). Ide et al. (48) reported that the arterial-venous glucose difference decreased during exercise at 30% of maximal oxygen uptake ($V_{\text{O}_2\text{max}}$), whereas it increased to a higher value than rest at 60% $V_{\text{O}_2\text{max}}$. In addition, the increase in glucose uptake is extreme in the first minute after the cessation of exercise (49). However, changes in CBF and glucose uptake are not related during exercise (105). In addition to the uptake of glucose, the brain also takes up lactate. At rest, the arterial lactate level is $<$1 mM and of little or no importance for the cerebral metabolism. However, as blood lactate increases during exercise with workload, lactate is taken up by the brain in proportion to its arterial concentration (49, 105). Cerebral metabolic ratio (CMR) is useful to express changes in cerebral metabolism independently of those in CBF (105). CMR is calculated by oxygen uptake/(glucose uptake + lactate uptake). Decreases in CMR are associated with cerebral activation (105). CMR decreases gradually during increasing exercise workload, and this ratio remains low even after the cessation of exercise. Low CMR may be a limitation to ongoing exercise performance and may be associated with central fatigue (105). Dalsgaard et al. (22) measured CMR during exercise to exhaustion, with and without β-blockade. β-Blockade reduced time to exhaustion (16 min) compared with control (25 min), whereas the CMR decreased to a similar level. During exercise, $O_2$, glucose, and lactate uptake are not related with CBF; however, during strenuous exercise, hyperventilation lowers the $P_{\text{ACO}_2}$ and blunts the increase in CBF, which can lead to an inadequate oxygen, glucose, and lactate delivery to the brain and contribute to the development of central fatigue. In addition, there appears to be a correlation between CBF and CMR during visual stimulation (76) and rhythmic handgrip exercise (99). Therefore, it seems reasonable to suggest that a large reduction of CBF could limit the capability to sustain high-intensity exercise.

**Oxygen**

Partial pressure of oxygen ($P_{\text{A}_2}$) is also a mediator of CBF. Although we focus below on the influence of hypoxia on CBF, it should be noted that hyperoxia can also have a marked influence on CBF. For example, at least at sea level, hyperoxia (>60 s) is a respiratory stimulant in adults (11), which results in subsequent reduction in end-tidal $P_{\text{CO}_2}$ and accompanying vasodilatation in the arterioles reducing CBF (28, 118). In addition to the hyperoxic-induced reduction in $P_{\text{A}_2}$ and accompanying vasodilatation in the arterioles reducing CBF (28, 118), increases in $P_{\text{A}_2}$ have a direct vasoconstrictive effect independently of the $P_{\text{ACO}_2}$ response (28, 62). Interestingly, a recent study (15) has demonstrated that reductions in regional CBF can occur at relatively low levels of acute hyperoxia ($F_{\text{O}_2}$ = 0.4) and that more marked hyperoxia ($F_{\text{O}_2}$ = 1.0) only reduced CBF by a further ~3%; thus the influence of

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hyperoxia is nonlinear. Despite the critical dependency of the brain on oxygen, the means by which altered levels of CO₂ and O₂ in the blood, plasma, and tissues effect CBF are not fully known (15).

Hypoxia, reflected in a fall in PaO₂ below a certain threshold (<40 mmHg), produces cerebral vasodilation (37). In addition, hypoxia induces activation of peripheral chemoreceptor activity, which influences CBF regulation indirectly. Although hypoxia per se is a cerebral vasodilator, reflected in a rise in CBF in proportion to the severity of isocapnic hypoxia (20, 124), under normal conditions the hyperventilatory-induced lowering of PaCO₂ via peripheral chemoreflex leads to a reverse response, namely cerebral vasoconstriction and subsequent cerebral hypoperfusion (3). Therefore, the balance between the ventilatory response of the peripheral chemoreflex to hypoxia and cerebral CO₂ reactivity seems to be more important for CBF regulation under conditions of hypoxia than oxygen itself. In contrast, at extreme high altitude, the vasodilator influence of the hypoxia seems to override the hypocapnic-induced vasoconstriction (4, 5). At any rate, these physiological responses to hypoxia maintain O₂ homeostasis in the brain because there is no evidence for hypoxic-induced alterations in cerebral metabolic rate for oxygen (77), even during severe hypoxia that induces unconsciousness (107).

An important question, therefore, is whether exposure to hypoxia might influence these sensitivities and thereby affect the intrinsic ability of the brain to vasodilate or constrict. Exposure to either continuous hypoxia (e.g., high altitude; Refs. 29 and 101) or intermittent hypoxia (e.g., as used for training purposes by athletes or as a consequence of sleep apnea; Refs. 31, 58, 73, 115) results in elevations in ventilatory sensitivity to hypoxia following subsequent hypcapnia. In contrast, there is a reduction in cerebrovascular reactivity to hypcapnia (4) and hypercapnia (5) at high altitude. The mechanism(s) by which prolonged exposure to hypoxia may compromise cerebrovascular reactivity to CO₂ is yet to be established although hypoxic-induced vascular remodeling, or elevated sympathetic nerve activity, or both, may be potential influencing factors. Although speculative, a reduction in the cerebrovascular reactivity to hypcapnia may be one reason why hypoxic-induced vasodilatation might dominate, at least at extreme altitudes over 5500 m (4, 5). Though potentially to a lesser extent, hypoxic-induced impaired dynamic CA (4, 52, 67, 117), elevations in sympathetic nerve activity (3), and hematocrit (39, 109) may act to further influence the CBF response to hypoxia.

During normoxic exercise, ventilatory chemosensitivity is only one of multiple signals that integrate to increase ventilation (119). However, following exposure to intermittent hypoxia (and presumably high altitude), an enhanced chemosensitivity activation has been observed during hypoxic exercise (59). CBF is well maintained (3, 7) during hypoxic exercise despite a greater degree of hypoxemia and an enhanced cerebral CO₂ reactivity (90, 100). This finding indicates that exercise modifies the interaction between Pao₂ and PaCO₂ in the regulation of CBF, potentially because of hypoxia-induced changes in CA, sympathetic nerve activity, and/or changes in the sensitivity of the cerebrovascular bed to hypoxia and hypocapnia (3). The extent to which CBF is altered in hypoxic environments at rest or during exercise is multifactorial and highly influenced by the balance between the vasodilatory effects of hypoxia and the reflex hyperventilatory-induced hypocapnia and cerebral vasoconstriction. During acute hypoxic exercise, CBF is generally maintained until chemoreflex activation lowers PaCO₂ enough to result in cerebral vasoconstriction, a response that is enhanced at high altitude or following acclimatization to intermittent hypoxia.

**Aging and Physical Activity**

With healthy human aging, there is a progressive decline in CBF in the order of 28–50% from the age of 30 to 70 yr; this finding has been confirmed by a variety of imaging techniques (6, 10, 14, 57, 103, 110). These studies collectively indicate that, because aging is associated with global cerebral atrophy, the decreases in CBF reflect a global decrease in cerebral perfusion, without any disturbance of regional perfusion or oxygen consumption. Our findings (6) indicate that habitual physical activity may offset the normal age-related declines in MCA V̇mean. The influence of physical fitness may therefore explain some of the variation in the degree of decline in CBF with aging. However, from an experimental perspective, it should be noted that, at least using Doppler ultrasound, relatively large sample sizes (>n = 45) are required to show an influence of physical fitness on resting MCA V̇mean. It is not known to what extent, if any, the cerebrovascular response to exercise might differ between those with higher levels of physical fitness.

Despite marked reductions in CBF observed with aging, CA is well maintained (16, 18, 69, 123) although this is not a universal finding, as two studies have observed impairments in cerebral vascular function at rest in older compared with younger patients (44). Moreover, Hoffman et al. (44) suggested that cerebral autoregulatory mechanisms demonstrated a delayed responsiveness in older participants during exercise. Despite greater increases in MAP, the regulation of MCA V̇mean is well maintained via dynamic cerebral autoregulation during dynamic mild- to moderate-intensity exercise in healthy middle-aged (57 ± 7 yr) participants (27). It is not known whether this response is altered with progressive aging (i.e., >65 years) or with increasing elevations in exercise intensity.

**Conclusions**

From an integrative systems approach, in addition to the traditional mechanisms describing CBF regulation (e.g., CA and PaCO₂), a variety of other factors, such as cardiac output, the arterial baroreflex, and chemoreflex control, independently, synergistically, and sometimes antagonistically participate in the regulation of CBF. Integrative physiological research exploring these complex interactions during exercise as well as during hypoxia and aging is currently lacking.

**REFERENCES**


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