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Regulation of Cerebral Blood Flow During Exercise

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Abstract

Constant cerebral blood flow (CBF) is vital to human survival. Originally thought to receive steady blood flow, the brain has shown to experience increases in blood flow during exercise. Although increases have not consistently been documented, the overwhelming evidence supporting an increase may be a result of an increase in brain metabolism. While an increase in metabolism may be the underlying causative factor for the increase in CBF during exercise, there are many modulating variables. Arterial blood gas tensions, most specifically the partial pressure of carbon dioxide, strongly regulate CBF by affecting cerebral vessel diameter through changes in pH, while carbon dioxide reactivity increases from rest to exercise. Muscle mechanoreceptors may contribute to the initial increase in CBF at the onset of exercise, after which exercise-induced hyperventilation tends to decrease flow by pial vessel vasoconstriction. Although elite athletes may benefit from hyperoxia during intense exercise, cerebral tissue is well protected during exercise, and cerebral oxygenation does not appear to pose a limiting factor to exercise performance. The role of arterial blood pressure is important to the increase in CBF during exercise; however, during times of acute hypotension such as during diastole at high-intensity exercise or post-exercise hypotension, cerebral autoregulation may be impaired. The impairment of an increase in cardiac output during exercise with a large muscle mass similarly

impairs the increase in CBF velocity, suggesting that cardiac output may play a key role in the CBF response to exercise. Glucose uptake and CBF do not appear to be related; however, there is growing evidence to suggest that lactate is used as a substrate when glucose levels are low. Traditionally thought to have no influence, neural innervation appears to be a protective mechanism to large increases in cardiac output. Changes in middle cerebral arterial velocity are independent of changes in muscle sympathetic nerve activity, suggesting that sympathetic activity does not alter medium-sized arteries (middle cerebral artery).

CBF does not remain steady, as seen by apparent increases during exercise, which is accomplished by a multi-factorial system, operating in a way that does not pose any clear danger to cerebral tissue during exercise under normal circumstances.

The human brain receives approximately 750 mL/min of blood at rest, which represents close to 15% of total cardiac output.[1] It is primarily supplied by four arteries: two vertebral and two carotid arteries. Although the relative contribution of blood to cerebral tissue via the four arteries varies between species, the two systems are believed to be balanced in humans.[2] All of the major arteries converge to form the Circle of Willis, allowing flow to be maintained in the event of an occlusion in one of the major arteries; similarly, peripheral pial vessels also anastomose in order to sustain flow to cerebral tissue. Three pairs of arteries, the anterior, posterior and middle cerebral arteries begin at the Circle of Willis, with branches from the arteries perfusing different parts of the cortex. These large arteries differ from the smaller cerebral arteries with respect to their vasomotor actions and responses.[3]

Neurons are intolerant of ischaemia; therefore, in the resting condition, flow to the brain has originally been considered to be relatively constant.[4] Blood and nutrients are circulated to the brain primarily via the carotid and vertebral arteries. Although the two systems provide similar amounts of blood to cerebral circulation in humans, the relative contribution differs between species.[2] It has been proposed that the major role of the cardiovascular system is the maintenance of oxygen and glucose to cerebral tissue.[5]

Cerebral autoregulation is a mechanism by which the brain is able to maintain constant blood flow in the face of changes in arterial pressure. Humans experience changes in arterial pressure during times of physiological stress, such as exercise, which must be compensated by a change in cerebrovascular resistance via cerebral autoregulation. In addition to changes in arterial pressure during exercise, humans also experience alterations in arterial partial pressures of carbon dioxide (pCO_2), cardiac output and sympathetic activity. An alteration in arterial partial pressure of oxygen (pO_2) may also be experienced in elite athletes,[6] in diseased populations and at altitude. Modifications in fuel (glucose) and by-product (lactate) levels are also altered in response to exercise. These variables also play roles in the regulation of cerebral blood flow (CBF). Therefore, the changes experienced by these factors during exercise and their relative contribution to CBF warrant investigation.

Regardless of the response of CBF to exercise, investigation into the contributing factors regulating the changes in CBF during exercise could help to determine whether exercise poses any danger to cerebral health or whether the brain is a limiting factor to performance. This article presents the current knowledge on the factors that influence CBF during exercise. To search the available and relevant scientific literature, we conducted a PubMed search of the available and relevant scientific literature in addition to conducting manual journal searches. Bibliographies of articles selected were used to find additional pertinent references. The keywords included 'cerebral blood flow', 'exercise', 'carbon dioxide reactivity', 'cerebral autoregulation', 'cerebral blood flow blood pressure', 'cerebral blood flow cardiac output', 'cerebral blood flow catecholamines', 'cerebral blood flow sympathetic'. Although the article is mainly concerned with the

healthy, asymptomatic population, we included certain studies with diseased populations or studies at altitude if relevant.

Modulation of CBF is a coordinated effort, comprising many different systems. Of all the contributing factors, the chemical, cardiovascular, metabolic and neural influences encompass the most documented (figure 1), all of which are altered from rest to exercise. A brief review of commonly used measurement techniques is discussed, and possible flaws in methodology are presented. The CBF response to exercise and individual regulating factors are also discussed.

1. Measurement of Cerebral Blood Flow

The pioneering work by Kety and Schmidt[7] using inhalation of nitrous oxide (N_2O) is based on the principle that the rate at which N_2O in the venous circulation approaches the content in the arterial circulation is dependent upon the volume of blood flowing through the brain. Therefore, this assumes that the quantity of N_2O consumed by the brain from the perfusate (blood) in a given amount of time is equal to the amount of blood delivered (arteries) to the brain minus the amount of blood carried away (veins) from the brain.[8] The technique requires the subject to inhale a mixture of gas (≈15% N_2O, 21% O_2, 64% N_2) in order to saturate the brain. Arterial (femoral or brachial) and venous (internal jugular) blood samples are serially extracted, and with the application of the Fick principle, CBF can be quantified.[7] Measurement of CBF during exercise using the N_2O technique has failed to show significant increases (table I).[9,10] Zobl et al.[9] measured CBF during rest and during 14 minutes of steady-state cycling. They found a nonsignificant increase in CBF after exercise, suggesting that during exercise, the brain remains in a steady state with no increases in flow or metabolism.[9] However, difficulties with this method include the requirement of the measurements to be performed during steady-state blood flow. In order to obtain a representative index of CBF, it must be assumed that both jugular veins drain equal amounts of blood from the whole brain. Although there has been debate questioning whether this is indeed the case,[7,11] more recent work has suggested that there are differences in the quantity of blood drained between the internal jugular veins in humans.[12] Although arterial supply appears to be balanced between the vertebral and carotid systems, venous drainage via the two internal jugular veins is not equal.

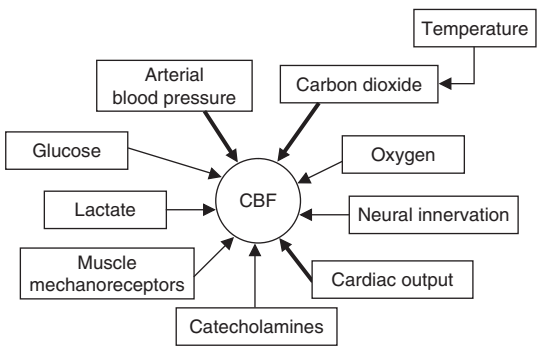

Fig. 1. Regulating factors of cerebral blood flow (CBF) during exercise. The bold arrows represent factors that are believed to be major contributors.

Measurement of CBF via radioisotope involves the administration (inhalation or injection) of an inert radioisotope (^{133}Xe), which is monitored extracranially by sensitive detectors.[36] With the application of the Fick principle, a measurement of CBF can be obtained. Examination of the change in CBF during exercise has not been consistent with the application of this technique. Globus et al.[13] measured the change in CBF from rest to exercise at 50% maximal oxygen uptake ($\dot{V}O_{2max}$) and found a nonsignificant decrease of 1.6%. In contrast, Thomas et al.[14] found an increase in CBF during steady-state cycling (56% $\dot{V}O_{2max}$). Major drawbacks of this technique include extracerebral contamination and recirculation. With inhalation, some of the isotope enters the circulation of scalp vessels, overestimating CBF.[36] Also, a large proportion of the isotope is taken up by other tissues, which causes an increase in the isotope returning for recirculation. These two factors affect the clearance rate, and this influences CBF values. In order to overcome the issue of recirculation, a correction must be applied to the isotope concentration in arterial blood and expired air.[37] Other drawbacks include subject (head) movement during exercise.[38] The time needed for measurement can also be challenging during exercise as data acquisition can last minutes[36,38] and transient changes can be missed.[39]

Table I. Cerebral blood flow (CBF), carbon dioxide and arterial blood pressure response to exercise in previous literature

Study[a]	Intervention	CBF		Carbon dioxide		Arterial blood pressure	
		technique	response	technique	response	technique	response
Scheinberg et al.[10]	7.2 km/h (4.5 mph), 4% grade, 40 min	N_2O washout	↔	pCO_2	↓	Ascultation	↓
Zobl et al.[9]	14 min cycling	N_2O inhalation	↔	pCO_2	↓	Catheter (brachial)	↑
Globus et al.[13]	50% $\dot{V}O_{2max}$ for 10 min on bike	^{133}Xe inhalation	↓	$PetCO_2$	↓	NR	NR
Thomas et al.[14]	Graded exercise test on bike	^{133}Xe washout	↑	$PetCO_2$	↔	Catheter (brachial), sphygmomanometer	↑
Friedman et al.[15]	Hand contraction	^{133}Xe inhalation	↑ in premotor and sensory motor areas			Catheter (brachial)	↑
Huang et al.[16]	5 min cycling at 0, 9, 68, 236W	ICA via TCD	↑	pCO_2	↔	Catheter (abdominal aorta)	↑
Jorgensen et al.[17]	Cycle at 30% and 60% $\dot{V}O_{2max}$	MCA via TCD; CBF via ^{133}Xe washout	MCA ↑; CBF ↑	pCO_2	↑	Catheter (brachial)	↑
Jorgensen et al.[18]	Submax cycling at 4 submax intensities	MCA and ACA via TCD; CBF via ^{133}Xe washout (injection)	↑ in MCA, ↔ in ACA, ↑ in CBF during loaded exercise	pCO_2	↔; ↑ at 60W	Catheter (brachial)	↑
Madsen et al.[19]	Graded exercise test on bike (60 rpm)	CBF via Kety Schmidt (^{133}Xe); MCA via TCD	CBF ↔, MCA ↑	pCO_2 (radial)	↓	Catheter (radial)	↑
Moraine et al.[20]	Graded exercise test on bike (50–70 rpm)	MCA via TCD	↑ up to 60% $\dot{V}O_{2max}$ then progressive ↓	$PetCO_2$	↑ up to 60% $\dot{V}O_{2max}$ then progressive ↓	Sphygmomanometer	↑ up to 90% $\dot{V}O_{2max}$ then slight ↓
Linkis et al.[21]	Cycling at 60 rpm	ACA or MCA via TCD	↑	pCO_2 (catheter)	↓	Catheter (brachial or radial)	↑

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Table I. Contd

Study[a]	Intervention	CBF		Carbon dioxide		Arterial blood pressure	
		technique	response	technique	response	technique	response
Hellstrom et al.[22]	Cycle at four different submax intensities (≈20–90% $\dot{V}O_{2max}$), each intensity for 6 min	Left CCA, left ICA (pulsed Doppler); MCA via TCD	MCAV ↑; ↓ (compared with baseline) during recovery; CCA ↑ at workloads 2, 3, 4, as well as recovery; ICA ↑ at workloads 3 and 4	$PetCO_2$	↑ at 2 lowest submax intensities, ↓ (compared with baseline) at highest workload and during recovery	Sphygmomanometer	↔
Pott et al.[23]	Graded exercise test; as well as five 5-min bouts at 50–90% $\dot{V}O_{2max}$	MCA via TCD	↑ from baseline at all submax workloads and max exercise	$PetCO_2$	↑ at all submax intensities; ↔ from rest at max	Sphygmomanometer	↑ during last four submax intensities; ↑ at max
Pott et al.[24]	Rowing at 75% $\dot{V}O_{2max}$ for 10 min	MCA via TCD	↑	pCO_2 (catheter) measured at rest and end of exercise	↓	Catheter (radial)	↑
Pott et al.[25]	3 min of rhythmic handgrip at 20% max contraction (1Hz)	MCA via TCD	↑	NR	NR	Catheter (brachial)	↑
Ide et al.[26]	Rhythmic handgrip (20% of maximal force, 1Hz, 5 min)	MCA via TCD	↑	Arterial pCO_2 (catheter)	↔	Catheter (brachial)	↑
Doering et al.[27]	Flexion and extension of upper and lower limbs, performed actively and passively	MCA via TCD	↑ in both active and passive	End tidal pCO_2	↔	Finger cuff photoplethysmography	↑ in SBP during active exercise, during passive exercise
Ide and Secher[12]	10 min of continuous cycling at 30% and 60% $\dot{V}O_{2max}$	MCA via TCD	↑ with exercise intensity	Arterial CO_2 (catheter)	↔	Catheter (brachial)	↑ with exercise intensity

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Table I. Contd

Study[a]	Intervention	CBF		Carbon dioxide		Arterial blood pressure	
		technique	response	technique	response	technique	response
Giller et al.[28]	5 min of maximal rhythmic handgrip	MCA via TCD	≈15% ↑	End tidal pCO_2	↔	Finger cuff plethysmography	≈20% ↑
Nybo and Nielsen[29]	Cycle ≈57% $\dot{V}O_{2max}$ for 60 min	MCA via TCD	↑ within the first 10 min, remained elevated until end	End tidal pCO_2	↔	Auscultation	↔
Nybo et al.[30]	Cycle ≈50% $\dot{V}O_{2max}$ for 65 min	^{133}Xe injection	↔ (measured at time 15 and 60 min of exercise)	pCO_2 (catheter)	↔ (measured at time 15 and 60 min of exercise)	Catheter (radial)	↔ from 15–60 min of exercise
Heckmann et al.[31]	Cycle ≈75–100W for 3 min	MCA via TCD	↑	Transcutaneous pCO_2	↔	Beat by beat tonometry	↑
Brys et al.[32]	3 min cycle at 50, 100, 150W	MCA via TCD	↑ at each intensity	$PetCO_2$ (nasal)	↑ at each intensity	Applanation tonometry (radial)	↑ at each intensity
Pott et al.[33]	15 sec static leg extension (max)	MCA via TCD	↑ at onset of exercise, progressive ↓ below baseline; overshoot during recovery	pCO_2 (catheter)	↓; returned to baseline during recovery	Beat by beat at finger (Finepress)	↑ at onset, remained elevated; ↓ below baseline during recovery
Ogoh et al.[34]	Cycle at 90, 120, and 150 bpm (all for 8 min)	MCA via TCD	↑ at 120 and 150 bpm	pCO_2 (catheter)	↔ at 90 and 120 bpm; ↓ at 150 bpm	Catheter (brachial)	↑ at 120 and 150 bpm
Imray et al.[35]	Graded exercise test; submax test at: 30%, 50% and 70% $\dot{V}O_{2max}$ (55 rpm, 15 min each)	MCA via TCD	↑ at 70% $\dot{V}O_{2max}$; ↓ below baseline at max exercise	$PetCO_2$	↓ at max exercise; ↔ throughout submax	Beat by beat (radial artery tonometry)	↔ throughout graded exercise test or submax

a Studies are in chronological order.

^{133}**Xe** = 133-xenon radioisotope; **ACA** = anterior carotid artery; **bpm** = beats per minute; **CCA** = common carotid artery; **ICA** = internal carotid artery; **max** = maximal; **MCA** = middle cerebral artery; **MCAV** = MCA velocity; **N_2O** = nitrous oxide; **NR** = not reported; **pCO_2** = arterial pressure of carbon dioxide; **$PetCO_2$** = end tidal pressure of carbon dioxide; **rpm** = revolutions per minute; **SBP** = systolic blood pressure; **submax** = submaximal; **TCD** = transcranial Doppler; **$\dot{V}O_{2max}$** = maximal oxygen uptake; ↑ indicates increase; ↓ indicates decrease; ↔ indicates no change.

Measurement of blood flow velocity via transcranial Doppler ultrasound (TCD) in a major cerebral artery allows non-invasive, beat-by-beat measurement of changes in the vessel's blood velocity, which can be taken as an indication of cerebral autoregulation. CBF velocity (CBFV) is calculated from the maximal frequency of the Doppler shift, which is assumed to represent the mean flow in the centre of the vessel. Interpretation of an increase in CBFV as a reflection of an increase in flow is also dependent upon the assumption of a constant diameter of the insonated vessel. Different indexes of flow have been developed and have been shown to change CBFV results depending on the index used.[40] Poulin et al.[40] had subjects cycle at two different submaximal intensities (20% and 40% $\dot{V}O_{2max}$) for 6 minutes at each intensity. Middle cerebral arterial velocity (MCAV) was measured throughout the session, while the following indexes of flow were compared: the maximal frequency of the Doppler shift (Vp), the intensity-weighted mean frequency of the Doppler spectrum (V_{IWM}; a measure based on the entire Doppler spectrum), and the product of the power (P, a measure of the amount of red blood cells) and V_{IWM}; this index provides a measure of flow, which accounts for changes in cross-sectional area. The results showed that each index of flow provided a different increase in CBFV from rest to exercise; where V_{IWM} provided a more accurate estimate than Vp.[40] TCD is often implemented for investigations into beat-to-beat changes to cerebral perfusion, especially during exercise. It should be noted that changes in flow can also be modified depending on the vessel insonated. Hellstrom et al.[22] measured the changes in the internal carotid artery (ICA), common carotid artery (CCA), and middle cerebral artery (MCA) during increasing workloads. The ICA and MCA both experienced increased blood flow at the onset of exercise, which decreased at the highest workload. In contrast, the CCA increased at every workload; it did not experience the decrease at the higher work rates as the ICA and MCA did. This suggests that conclusions drawn with use of this technique may be limited.[28,40] Contrary to information suggesting that flow is distributed evenly between major arteries, this study by Hellstrom et al.[22] suggests that flow to the brain is not evenly distributed during exercise. Similar to previous methods, TCD requires a high-quality signal, which can be compromised by head movement, especially during exercise; although the use of a custom-made headband device can help to minimise artifacts produced by small head movements.[40]

Other methods for the measurement of CBF include magnetic resonance imaging, positron emission tomography and dynamic perfusion CT; however, this article will focus on the most widely used techniques with exercise. For additional information on CBF measurement techniques, the reader is directed to Wintermark et al.[38]

2. Cerebral Blood Flow and Exercise

Various studies have shown an increase,[15,18,29,40,41] no change[9,10] or a decrease[13,42] in CBF during exercise. However, upon review of the literature, there is consistent support for an increase in CBF during exercise.[14-18,20-29,31,32,34,43] Table I summarises the overwhelming evidence over the last 50 years showing an increase in CBF, as well as the change in pCO_2 and mean arterial blood pressure (MAP), which are commonly measured and are thought to be important in the regulation of CBF during exercise. Some of the earlier work investigating the effects of exercise on CBF failed to show a resulting increase.[10,42] More recent work with the use of TCD has shown sudden increases in CBFV in response to exercise.[17,21,23-25,29,31,32,34,35,43] The increase is intensity dependent,[18,20] with the magnitude of the change contingent on the vessel insonated.[22] Increases in exercise intensity cause an increase in CBFV up to a certain exercise intensity (≈60% $\dot{V}O_{2max}$), after which CBFV decreases towards baseline values (sometimes decreasing below baseline values) with increasing exercise intensity.[20,22] This is most likely attributed to a hyperventilation-induced decrease in pCO_2 (discussed in section 3.1.1).[20,21] Although CBF may be modulated by pCO_2, it has been proposed that the initial trigger for the increase in CBF is an increase in brain metabolism. Herholz et al.[44] showed that cycling at 100W produces a greater increase in CBF (^{133}Xe washout) than cycling at 25W; the greater increase in CBF was attributed to an increase in brain neuronal activity and metabolism. Linkis et al.[21] measured increases in MCA and anterior carotid artery (ACA) blood flow velocity during right-hand contractions,

right-foot movements and cycling. The greatest increase in flow was seen in the left MCA, and the left ACA during the right-hand contraction and right-foot movements, respectively. Also, the mean flow velocity in the left and right MCA and ACA increased to the same extent during cycling. This suggests that the increase in flow is regional to the arteries that supply the cortical representation of the exercising extremity.[21]

Timing of the measurement of exercise CBF is crucial, as cerebral autoregulation has been shown to be attenuated during the post-exercise period;[45] also sudden drastic decreases in CBFV have been shown to occur within the first 5 seconds after cessation of dynamic leg-press exercise.[46] Moreover, the mode of exercise may modify the CBF response.[17,26] Extra attention should be given to interpretation of the response, as the intensity of the exercise and method used to quantify CBF are of critical importance.

3. Contributing Factors to Cerebral Blood Flow During Exercise

3.1 Chemical Factors

Of all the factors contributing to CBF regulation, pCO_2 appears to be the most important.[3,47] Hypercapnia, and to a lesser extent hypoxia, produce an increase in flow by vasodilation, whereas hypocapnia, and possibly hyperoxia,[48] cause a decrease in flow via vasoconstriction. pCO_2 may be of greater importance than pO_2, whereby hypocapnia-induced vasoconstriction caused by hyperventilation can override any vasodilation produced by a fall in pO_2.[49] Ainslie and Poulin[50] tested the hypoxic CBF response at rest during conditions of hypocapnia, isocapnia and poikilicapnia. It was found that during the poikilocapnic condition, the increase in ventilation caused a decrease in the hypoxic CBF response compared with the isocapnic condition. This effect was attributed to hypocapnic-induced cerebral vasoconstriction at rest.[50] Therefore, the constricting effects of hypocapnia appear to attenuate or abolish the dilating effects of hypoxia.[51]

3.1.1 Carbon Dioxide

Although it has been suggested that the main regulating factor of CBF is extracellular pH, this is most likely not the only factor controlling cerebral vascular resistance.[3] Carbon dioxide readily diffuses across the blood-brain barrier where it dissociates to form H^+ and HCO^{3-}; it has been suggested that H^+ cause changes in vessel diameter and vascular resistance. Therefore, it would not be CO_2 *per se* that causes dilation. However, an increase in blood H^+ does not necessarily cause cerebral vessel dilation since H^+ crosses the blood-brain barrier very slowly.[4,49] Furthermore, taking blood pH as an indication of CSF pH is problematic, since respiratory acidosis causes the pH of the CSF to change much less than blood pH.[52]

The mechanism responsible for the change in diameter of the vessel may be attributed to the effect of pH on transmembrane potential of smooth muscle cells.[53] On the other hand, it has been suggested that CO_2 is the major dependent variable modulating CBF, and that changes in pH are secondary.[1] Cerebral vessels react similarly to arterioles of skeletal muscles; where H^+ has a direct local relaxant effect on the vessels with the magnitude of change similar between the two vascular beds.[1] The time-course of the response of the cerebral pial (resistance) vessels to a low pH is relatively rapid, with changes in diameter occurring within 10 seconds, independent of the resting vessel diameter.[54] In humans, the relationship has also been suggested to be dependent on an individual's level of activity and core temperature, with the relationship at rest being linear.[55] Rasmussen et al.[55] tested subjects' CO_2 reactivity during rest, exercise, and exercise combined with hyperthermia. The relationship between CBFV and pCO_2 was linear at rest, curvilinear at submaximal exercise and exercise combined with hyperthermia. The CO_2 reactivity increased from 30.5% • kPa^{-1} at rest to 40.6% • kPa^{-1} and 61.4% • kPa^{-1} at exercise and hyperthermic exercise, respectively.[55]

CO_2 levels also regulate the CBF response after instantaneous decreases in arterial blood pressure. In hypocapnia, the autoregulatory response to a drastic decrease in arterial pressure is quicker and accompanied by a transient overshoot in MCAV, compared with a slower response with minimal overshoot in hypercapnia.[39] This demonstrates a negative relationship between pCO_2 and the rate of cerebral regulation.

As with the ample support for pCO_2 as the major regulator of resting CBF, there is also an abundance of evidence to suggest that it is pCO_2 that plays the major role modulating the changes in CBF during exercise.[20,22,29,30,47,55] Most evidence stems from the association between exercise-induced increases in ventilation and CBFV.[56] Many of these studies are correlative in nature, where a decrease in CBFV is seen during intense exercise, which occurs during exercise-induced hyperventilation.[22] Nybo and Nielsen[29] found that 56% of the decrease in MCAV during hyperthermic exercise can be attributed to changes in CO_2;[29,30] further investigation has also shown an 18% decrease in global CBF during hyperthermic exercise to be accompanied with an 18% decrease in pCO_2.[30] Rasmussen et al.[55] measured the mean MCAV during exercise at 67% $\dot{V}O_{2max}$ in both a thermoneutral and hyperthermic environment.[55] pCO_2 decreased in the hyperthermic condition as the exercise trial progressed, and there was a concurrent progressive decrease in mean MCAV. The authors of the study attributed the drop in mean MCAV to a hyperventilation-induced drop in pCO_2.[55]

Although there is a strong association between CO_2 and CBF, there is also some evidence to suggest that the importance of CO_2 in modulating CBF during exercise has been over-emphasised.[27,41,57] Heckmann et al.[41] had subjects cycle in the supine position for 3 minutes at a submaximal work rate from 75 to 100W. Mean MCAV increased after the first minute of cycling, and remained elevated for 1 minute into recovery. In contrast, the measured transcutaneous pCO_2 did not increase beyond baseline values until the last minute of exercise; attributing the increase in mean MCAV, at least in the early part of the exercise session, to some other factor than CO_2.[41]

3.1.2 Oxygen

The relationship between pO_2 and CBF is curvilinear or semi-logarithmic.[2,49,58] Low pO_2 causes vessel dilation (perhaps via hypoxia-related release of adenosine, and possibly K^+, H^+ and prostaglandins),[2,49,59] whereas hyperoxia may cause cerebral vasoconstriction.[48,60] Extreme hypoxia (pO_2 <30mm Hg) can cause a vessel dilation similar in magnitude to that observed in hypercapnia.[2] Maximal dilation does not occur at the onset of inspiring hypoxic gas, but rather, when breathing 10% oxygen (≈40mm Hg), occurs 6 minutes after the onset of hypoxia.[51] Significant increases in CBF have been shown to occur in rats at a pO_2 of 50mm Hg.[58] Furthermore, cerebral autoregulation is abolished once arterial oxygen saturation decreases below 60%,[61] and the CBF response to hypoxia is similar regardless if the hypoxic insult is in an ascending or descending pattern.[50] In contrast, hyperoxia has been shown to cause a slight decrease in CBF.[59]

The effects of hypoxia are additive with concurrent hypercapnia.[2] Although suggestions have been made that CBF increases once a certain hypoxic threshold is met,[62] the accompanying hypocapnia may override the dilatory effects of hypoxia giving the false interpretation of a threshold.[2,50,51]

During exercise, although a greater proportion of total blood is diverted to working muscles, CBF must not be compromised. Nonetheless, there is evidence showing decreased cognitive function[63] and hypoxaemia in some elite athletes during high-intensity exercise.[6,64] Furthermore, the drop in pH during high-intensity exercise can compromise oxyhaemoglobin binding. This would lead to the impression that CBF may only be compromised during exercise when arterial saturation is decreased, thereby limiting exercise performance. In addition, increases in CBF occur only at an intensity of around 50–60% $\dot{V}O_{2max}$, and further increases in intensity are not accompanied by a further increase in CBF.[14,20,22] Taken together, one might assume that during maximal exercise, CBF may provide a severe dilemma to cerebral neurons. Although there is a negative relationship between maximal handgrip strength and cerebral oxygenation,[65] pO_2 is usually unchanged during exercise in the general population;[66] therefore, most likely not a contributing factor to CBF changes during exercise. Also, Gonzalez-Alonso et al.[67] demonstrated that although the cerebral cardiac output measured with transcranial Doppler progressively decreased at maximal exercise, the cerebral tissue oxygen extraction increased.[67] Additionally, with the simultaneous measurement of MCAV via transcranial Doppler and cerebral tissue oxygenation via near-infrared spectroscopy, the increase in flow appears to surpass

the needed oxygen demand of the brain;[43] implying that the brain is well protected during exercise.[67] These data suggest that it is not cerebral oxygen extraction that limits exercise, but rather systemic delivery that limits exercise performance. In contrast, there is evidence that it is a decrease in CBF, which is the result of a decrease in arterial pressure during high-intensity exercise at altitude, which is the limiting factor to exercise performance, rather than systemic muscle fatigue.[35] There is also evidence for cerebral tissue desaturation during high-intensity exercise and the decrease is attenuated by oxygen supplementation by elite athletes. Nielsen et al.[68] had highly trained rowers perform two, 6-minute 'all-out' rowing sessions under normoxia and hyperoxia (FiO_2 = 30%). Cerebral tissue oxygenation measured during the exercise session showed desaturation during the normoxic trial, whereas the decrease in cerebral tissue oxygenation was abolished in the hyperoxic trial. Furthermore, rowers reported that it was easier to maintain rhythm in the hyperoxic trial; they reportedly 'felt better', with some subjects demonstrating slight increases in performance.[68] It must be noted that elite-level rowers who experienced a decrease in cerebral oxygenation and pO_2 during intense exercise in normoxia were recruited for this study. Therefore, it is intuitive that cerebral oxygenation would increase with the addition of hyperoxia in these subjects; whereas oxygen supplementation by an individual with an average aerobic capacity may not prove useful since exercise-induced arterial hypoxaemia does not tend to occur in such individuals.[69] Extending these results to the general population may not be appropriate.

3.2 Cardiovascular

CBF is dependent upon arterial pressure, cerebral venous pressure and intracranial pressure. Stable CBF is maintained over the wide range of MAP from 50–60 to 150–175mm Hg, which is accomplished by myogenic properties of the vessels and the vessels' ability to respond to metabolic products produced by surrounding tissue.[1,49] CBF is retained in face of changes in arterial pressure by active constriction during higher pressures and dilation when pressure decreases.[70] There have also been significant correlations between MAP and MCAV during acute hypoxia.[50]

3.2.1 Arterial Pressure

In order to increase the needed flow to working muscles during exercise, MAP increases; systolic blood pressure (SBP) increases with exercise intensity, while diastolic blood pressure (DBP) changes little with increases in exercise intensity.[71] The magnitude of this vessel response takes 3–7 seconds depending on the baseline diameter of the vessel.[70]

Even though CBF remains stable within the autoregulatory range, there also appears to be changes of 6% per 10mm Hg change in MAP.[72] Therefore, while cerebral autoregulation maintains CBF within the autoregulatory zone, it is also modified under sudden drastic changes in arterial pressure.[3] Furthermore, cerebral autoregulation in individuals with hypertension is preserved, although the lower and upper limits are shifted up.[4] Cerebral autoregulation is also attenuated in normotensive elderly subjects[31] and healthy subjects during hypoxia and hypercapnia.[50]

There is sufficient evidence demonstrating that MAP plays a major role in the regulation of CBF during exercise.[24,30,43,73] During steady-state cycle exercise at 30% and 60% $\dot{V}O_{2max}$, the increase in MCAV is shown to occur with a concomitant increase in MAP, while pCO_2 is unchanged from rest.[43] The increase in cerebral perfusion has been suggested to be dominated by increases in MAP, which has been demonstrated in rowing, an exercise type that causes rapid fluctuations in MAP. Pott et al.[24] measured MAP and MCAV in rowers within each rowing stroke. The MAP and MCAV both responded to the stroke in a cyclic manner, where the peak values were shown to occur at the beginning of the catch phase of the rowing stroke; however, the MCAV then showed a nadir at the beginning of the recovery phase of the stroke, which was lower than baseline, while arterial pressure was stable.[24] This suggests that increased MAP and intra-thoracic pressure may affect cerebral perfusion.

Perfusion pressure has also been suggested to be the reason for a maintained CBF during exercise at altitude; however, a drop in MAP during high-intensity exercise at altitude may also be the limiting factor to performance.[35] Exercise in hot environ-

ments causes a decrease in MAP, which is accompanied by a decrease in global CBF (gCBF).[30] The treatment of hypertension with anti-hypertensive drugs shows a decrease in baseline MCAV after 3 years of treatment when compared with a non-compliant group; this suggests a beneficial effect of anti-hypertensive drugs on cerebral vessel walls. However, changes in MCAV are indistinguishable between a compliant and non-compliant group during exercise.[73]

A strong correlation between MAP and MCAV during and post-exercise is not a universal observation.[17,20,21,25,27,33,43,45] In response to a sudden change in MAP, there is no change in MCA diameter,[39] meaning that the change in CBF is due to vascular responses of the smaller resistance vessels.[70] There have also been suggestions that there is no correlation between MAP and MCAV during high-intensity exercise.[20] Pott et al.[33] measured MAP and MCAV during static leg extension exercise both with Valsalva breathing manoeuvres and without. Although there was a good correlation at the onset of exercise between MAP and MCAV in the trials with and without a Valsalva manoeuvre (r^2 = 0.95 ± 0.02 and 0.93 ± 0.02, respectively), the increase in MCAV during the continued breathing trial was lowered, as was the post-exercise overshoot, which was seen in greater magnitude in the Valsalva condition.[33] The same group found a similar decrease in MCAV without a concurrent decrease in MAP during post exercise muscle ischaemia.[25]

Dynamic cerebral autoregulation describes the ability for CBF to return to original values in the face of acute changes in arterial blood pressure. Under a hypocapnic background, dynamic cerebral autoregulation is enhanced.[39] This would suggest that dynamic cerebral autoregulation is enhanced during high-intensity exercise, when pCO_2 is lowered. In fact, this is not the case. Ogoh and colleagues[74] investigated whether dynamic cerebral autoregulation is affected during high-intensity cycle exercise. Interestingly, they found that the effectiveness of dynamic cerebral autoregulation was in fact reduced during exhaustive exercise, although there was a decrease in pCO_2.[74] Further, dynamic cerebral autoregulation is disturbed following maximal exercise (leg curls).[45] A drastic increase in MCAV was observed in the early recovery phase with a concomitant decrease in MAP. The authors suggest that absolute changes in MAP are not of major importance for dynamic cerebral autoregulation, but rather it is the relative change in MAP, which is of prime importance.[45] It is thought that the significance of this mechanism is an 'emergency reaction' in order to maintain consciousness in the face of drastic decreases in MAP.[45]

It is postulated that cerebral autoregulation during exercise is sustainable; however, a relative decrease in pressure, as experienced in every cardiac cycle during diastole, may pose a stress to cerebral autoregulation. High-intensity exercise results in an increase in mean MCAV ($MCAV_{mean}$) and MAP with the $MCAV_{mean}$/MAP being unchanged.[34] However, examining MCAV during systole ($MCAV_{systole}$) and SBP, as well as MCAV during diastole ($MCAV_{diastole}$) and DBP, reveals that with increasing intensity the $MCAV_{systole}$/SBP also remains unchanged. The DBP varies slightly with increasing exercise, reaching a small increase from rest to high-intensity exercise; simultaneously, the $MCAV_{diastole}$ continuously decreases with increasing intensity.[34] Therefore, the $MCAV_{diastole}$/DBP reaches a nadir during high-intensity exercise. Consequently, a decrease in MCAV without a concurrent decrease in MAP may be due to a greater decrease in $MCAV_{diastole}$ than a decrease in DBP.

3.2.2 Cardiac Output

Given that perfusion pressure plays a major role in CBF, cardiac output must be considered for its importance in cerebral autoregulation during exercise.[26,29,57,75] Decreases and increases in cardiac output by lower-body negative pressure and infusion of albumin, respectively, show a significant linear relationship between MCAV and cardiac output at rest and during exercise.[57] This relationship changes from rest to exercise, as shown by the greater change in MCAV to cardiac output when at rest compared with during exercise.[57] Ide et al.[26] tested the hypothesis that pharmacologically inhibiting the increase in cardiac output during exercise with a large muscle mass would attenuate the increase in MCAV.[26] Participants performed hand contractions and cycle ergometry both with and without β_1-adrenergic blockade. The increase in

MCAV was not affected by blockade during hand contractions; however, there was a decrease in cardiac output and MCAV during cycling. The authors attributed the mechanism to the active larger muscle mass and the concurrent compromise of cardiac output for cerebral perfusion.[26] The regulation of CBF by cardiac output is also seen in cardiac patients (clinically stable valvular disease), where the increase in cardiac output is greatly attenuated during exercise; a decreased cerebral oxygenation during exercise was noted in cardiac patients and was attributed to a decreased perfusion as a result of a compromised cardiac output.[75]

The contribution of heart rate to cardiac output in the regulation of CBF does not appear to have a significant effect on MCAV.[76] Bogert et al.[76] manipulated pacemaker settings in human ventricular paced untrained patients in order to control the heart rate response to graded exercise on a cycle ergometer. An induced decrease in heart rate was compensated by an increase in stroke volume, making cardiac output similar between controlled and uncontrolled heart rate. The response of the MCAV, as well as the time to exhaustion, was not different between the two trials, concluding that the HR response is unlikely to have an effect on CBF during exercise.

The importance of cardiac output in the regulation of CBF during exercise may be overemphasised due to evidence showing no increases in CBF with a simultaneous increase in cardiac output,[13] and may be more likely due to other contributing factors. During maximal exercise, MCAV quickly peaks, and then rapidly declines, indifferently to resting levels. Cardiac output peaks similar to MCAV, but remains elevated while MCAV experiences a decline.[67] In another study, it was shown that exercise in the heat produced similar cardiac output values when compared with exercise in normothermic environments; even though decreases in gCBF are observed in hyperthermia.[30] The decrease in gCBF was greatly attributed to a hyperventilation-induced decrease in pCO_2. This suggests that there are other factors aside from cardiac output that contribute to CBF regulation during maximal exercise.[67]

3.2.3 Muscle Mechanoreceptors

The simple act of movement also produces increases in CBF, which may point to a key role of muscle mechanoreceptors in regulating CBF.[15,17] During static handgrip exercise, regional CBF in the premotor and motor cortex increases; however, after axillary blockade, this increase is eliminated, despite no change in $PetCO_2$ and similar changes in HR and MAP between trials.[15] This suggests the importance of afferent feedback from the active muscles. It must be noted that the study used a small muscle mass, and low exercise intensity, of which could possibly mask other contributing factors. Jorgensen et al.[17] found a nonsignificant increase in MCAV during static exercise of a large (leg) muscle mass and a significant increase during dynamic exercise that occurred even though the increase in blood pressure was similar between trials.[17] Similarly, increases in MCAV have been shown to occur during both active and passive movements. Doering et al.[27] tested the response of the MCAV and MAP during four different exercise protocols: movement (flexion, extension, abduction and adduction of shoulder) of the upper limb, movement (flexion and extension of hip and knee) of the lower limb, both performed actively and passively. They found an increase in MCAV during all trials; however, there was only an increase in MAP during the active trials.[27]

3.3 Metabolic

Oxidative metabolism and blood flow increase during exercise. As with skeletal muscle, exercise is thought to increase the brain's oxygen demand[1] with a concurrent increase in CBF.[4] It is generally assumed that an increase in cerebral activation is accompanied with an increased metabolic rate manifested through an increase in blood flow.[77] However, the assumption that an increase in metabolism will lead to an increase in CBF is an assumption that is not consistent. The increase in flow may be regional with the global CBF being minimal.[2] Even still, the oxygen demand of the brain during exercise is exceeded by delivery. In contrast, cerebral oxygenation has been shown to decrease during exercise, which is reversed in elite athletes with the supplementation of hyperoxia.[68] It is important to note that the decrease in cerebral tissue oxygenation

occurred at maximal exercise; therefore, comparisons between the two studies are difficult.

3.3.1 Glucose

Under resting conditions, the brain is nearly entirely dependent on glucose for oxidative metabolism. Similar to other tissues, as the activation and oxidative metabolism of the brain increases, there is an increase in glucose uptake.[67,78] The reliance on brain glucose during exercise may occur as the brain experiences an increased metabolism during exercise.[43,79] Ide et al.[43] measured the arteriovenous glucose difference (a-$vD_{glucose}$) at 30% and 60% $\dot{V}O_{2max}$. The a-$vD_{glucose}$ at 30% $\dot{V}O_{2max}$ decreased, whereas it increased to values higher than baseline at 60% $\dot{V}O_{2max}$, suggesting that brain glucose utilisation increases with moderate exercise intensity. MCAV significantly increased at both exercise intensities. This suggests that brain blood flow velocity and glucose utilisation are not related. On the other hand, decreases in brain glucose have also been shown to occur at exercise intensities of 55–75% $\dot{V}O_{2max}$.[79] Kemppainen et al.[79] measured brain glucose uptake via positron emission tomography while subjects cycled at 30%, 50% and 75% $\dot{V}O_{2max}$. They found a decrease in brain glucose uptake at 55% and 75% $\dot{V}O_{2max}$. Also, plasma lactate levels increased at the two higher exercise intensities (55% and 75% $\dot{V}O_{2max}$), and there was a negative relationship between plasma lactate and brain glucose uptake.[79] With the decrease in glucose utilisation, the suggestion of an increased reliance on circulating plasma lactate has been proposed.[79] Prolonged exercise also initiates decreases in muscle and liver glycogen;[80] however, supplementation of glucose may attenuate the role of central fatigue by lowering the increase in cerebral serotonin levels (possible mediator of CNS fatigue). Nybo et al.[81] measured CBF (^{133}Xe) throughout 3 hours of cycling (≈210W) with glucose supplementation or without. There was no difference in the CBF response between the two groups. However, in the hypoglycaemic group, the cerebral metabolic rate decreased, and uptake of substrates was not large enough to compensate for the reduced brain glucose uptake (a-$vD_{glucose}$). The authors suggested that prolonged exercise with concomitant hypoglycaemia restricts cerebral glucose uptake, which results in a greater rating of perceived exertion.[81] Therefore, although no changes in actual CBF was observed between a euglycaemic and hypoglycaemic exercise, this demonstrates the importance of cerebral metabolic activity, and possibly displays the limited information that CBF gives in terms of actual exercise performance.

3.3.2 Lactate

Blood lactate increases linearly with exercise intensity to a threshold beyond which lactate ion concentration increases more rapidly. Brain lactacidosis has habitually been considered as a dangerous disorder;[4] however, the evidence for lactate as fuel for cerebral metabolism is growing.[67,78,79] Nybo et al.[78] suggested that lactate only becomes important in fueling the brain when lactate levels are high.[78] Furthermore, brain glucose uptake has been shown to decrease 17% when sodium lactate is infused during rest.[82] This would help support previous results by Kemppainen et al.[79] where the brain glucose uptake at 55% and 75% $\dot{V}O_{2max}$ was lowest,[43] an intensity most likely above the lactate threshold (55% $\dot{V}O_{2max}$).[80] It is important to note that lactate may not directly affect CBF. Rather, the lactate/pyruvate ratio has recently become of increased interest due to the positive relationship between CBF and the lactate/pyruvate ratio.[83] Also, the lactate/pyruvate ratio appears to only modulate CBF during cerebral activation. Mintun et al.[84] investigated the effect of lactate injection on CBF at rest and during visual stimulation. During the visual stimulation task, there was a strong relationship ($r \approx 0.93$) between CBF and the plasma lactate/pyruvate ratio, a less strong relationship between CBF and plasma lactate, and no relationship between CBF and plasma pyruvate.[84] This has been supported with data showing a correlation between MCAV and the lactate/pyruvate ratio during rhythmic handgrip.[85] During physiological activation, there is an increase in glycolysis. This leads to a greater need for regenerating nicotinamide adenine dinucleotide (NAD^+), which is accomplished by the transfer of electrons from the reduced form of NAD^+ (NADH). Regeneration of NAD^+ can also occur by the reduction of pyruvate to lactate. Injection of lactate increases the lactate/pyruvate ratio, thereby increasing the NADH/NAD^+ ratio. The rise in NADH will increase CBF, [84] since cytosolic free NADH senses the need for blood flow.[83] As expected, a bolus

injection of pyruvate attenuates the CBF during visual stimulation.[86] Therefore, the opposing effects of lactate and pyruvate, as well as the correlation between CBF and the lactate/pyruvate ratio (which is in near-equilibrium with the NADH/NAD+ ratio) suggests that modulation of CBF during stimulation can occur in response to changes in the NADH/NAD+ ratio. [83-86] However, this mechanism is only pertinent once lactate is elevated, suggesting that the initial increase in CBF is modulated by other factors.

3.3.3 Catecholamines

The influence of circulating hormones on CBF may be relatively minimal since the blood-brain barrier protects against the passing of water-soluble molecules.[49] Vasoactive influences during exercise on CBF could pose a stress not only to CBF, but could also lead to false conclusions if using a technique that assumes a constant vessels diameter (i.e. TCD). However, plasma catecholamines may play a role in the increase in MCAV during high-intensity exercise. Pott et al.[23] measured MCAV and venous catecholamine levels (adrenaline, noradrenaline) during rhythmic handgrip, submaximal and maximal cycle exercise. Plasma catecholamine and MCAV during rhythmic handgrip and submaximal cycling were similar; whereas increases in plasma catecholamines (14-fold) and MCAV (≈50%) were observed during dynamic exercise >80% $\dot{V}O_{2max}$, even though $PetCO_2$ was similar between rhythmic handgrip and maximal exercise.[23] This suggests that plasma catecholamines may be influential in the CBF response to exercise at high levels of intensity.

3.3.4 Temperature

With the concomitant competition for blood flow between the active muscles and thermoregulation (cutaneous vessels), an enhanced cutaneous blood flow that occurs during exercise in the heat, may present a dilemma to CBF. Cardiac output increases with exercise; however, there is a greatly attenuated response in cardiac output when exercise is performed in a hyperthermic environment.[87] Hyperthermic exercise results in a decrease in MCAV and performance when compared with exercise in a normothermic environment.[29] The decrease in MCAV in hyperthermia may be partly explained by an exercise-induced hyperventilation, which could cause cerebral vessel vasoconstriction, thereby increasing the risk to cerebral tissue.[80] Despite these findings, after CO_2 correction, the MCAV is still lower in the hyperthermic trial, conferring part of the reduced increase in MCAV during exercise to a decreased cardiac output.[29] Temperature also affects cerebral glucose uptake. An increased $a\text{-}vD_{glucose}$ is seen during recovery after exercise in hyperthermia. The increase in glucose uptake transpires with a decrease in glucose delivery.[67]

Nybo and Nielsen[29] measured the MCAV response during 1 hour of exercise in a thermoneutral environment, as well as exercise in a hyperthermic environment until volitional fatigue. In the control (thermoneutral) trial, the MCAV increased within the first 10 minutes of exercise, then remained stable throughout the rest of the trial. In the hyperthermic trial, MCAV increased within the first 10 minutes, then progressively decreased until reaching a nadir at exhaustion that was significantly different from the control trial. The hyperthermic trial was accompanied with a progressive increase in ventilation; however, after CO_2 correction, the MCAV was still significantly lower at exhaustion during the hyperthermic trial when compared with the control trial.[29] Attributing the decrease in MCAV to heat may be erroneous based on the suggestion by Nybo and Nielsen[29] that the decrease may be due to factors that are secondary to hyperthermia, such as cardiac output and arterial pressure. However, a study by the same group found a decrease in gCBF with exercise in hyperthermia, and no change in normothermia, even as cardiac output was similar between the two conditions.[30] Furthermore, exercise in the heat increases the cerebral metabolism for oxygen and glucose,[30] which may relate central fatigue to glycogen depletion, requiring the use of lactate for fuel.[78]

3.4 Neural Innervation

There is general consensus that cerebral vessels are highly innervated by both myelinated and unmyelinated nerve fibres.[3] There has been speculation over whether or not the role of neural innervation on CBF is important.[1,88] There have been suggestions that it is the larger vessels that respond to neural input.[1] Furthermore, the more peripheral pial arteries are innervated by sympathetic nerves, which

respond to sympathetic activity with constriction causing a decrease in flow; although the constricting response of pial vessels to neurogenic control has been suggested to be minimal.[3,89] Stimulation of sympathetic nerves innervating cerebral vessels produces only minor and transient tonic contractions of vessels, which tend to be only a fraction of neurogenic contractions in skeletal muscle.[49] Furthermore, any increase in flow during exercise tends to be regional to cortical areas that are responsible for the moving limb,[21] and could be compensated by a decrease to flow elsewhere in the brain.[49] It is therefore believed that neurogenic control of CBF is constrained to small pial vessels; despite that, if neural innervation does exert constriction on vessels, it appears to be small, similar to a pCO_2 change of 1–2mm Hg.[4]

The importance of neural innervation in the regulation of CBF has recently received more attention.[32,41,57] Neural mechanisms have been suggested to be responsible for the initial rise in MCAV during low-intensity exercise.[41] It has further been suggested that cerebral autoregulation during exercise remains intact, which is mainly a function of autonomic neural influence.[32] Changes in cardiac output from rest to exercise cause an increase in the brain cerebrovascular resistance, which was greater than the calculated resistance in the forearm.[57] This suggests cerebral sympathetically mediated vasoconstriction, which may act as a protective mechanism by increasing cerebrovascular resistance during large increases in cardiac output or by redistributing blood to systemic circulation.[57] Despite this, cerebral autoregulation may be perturbed during early recovery from exercise with an activation of sympathetic vasomotor activity.[45]

Neither sympathetic activation by head-up tilt nor ganglionic blockade with trimethaphan causes increases in MCAV.[56] Reliance on muscle sympathetic nerve activity is most often taken as an index of whole-body sympathetic activity.[90] Pott et al.[25] measured MCAV, muscle sympathetic nerve activity (peroneal nerve) and luminal diameter of the dorsalis pedis artery during rhythmic handgrip, post-exercise muscle ischaemia and recovery. MCAV increased during exercise and returned to baseline during post-exercise muscle ischaemia and recovery; luminal diameter remained stable at baseline until increasing during recovery; whereas muscle sympathetic nerve activity increased only during post-exercise muscle ischaemia. This suggests that periphery sympathetics to the muscle are not directed to moderate-sized arteries.[25]

4. Conclusion

The maintenance of a constant CBF during exercise and the ability to dampen any sharp changes experienced in arterial pressure is crucial for the survival of cerebral tissue. Attempting to isolate the sole contributing factor in this tightly regulated system is likely not possible as regulatory mechanisms are multi-factorial. As shown, the relative contributions can only be considered after reviewing the coordinated fashion in which they work. For example, the relationship between an increased sympathetic activation and cerebral hypoperfusion may be partly explained by a sympathetically mediated increase in ventilation.[56] Similarly, the possible dilation of vessels in response to carbon dioxide can also be dependent on present dilation from changes in MAP.[2] Moreover, the possible substrate for fuel is dependent on the baseline levels of the prospect substrates and their relative concentration.[78,79] Caution must be used when generalising CBF responses from rest to exercise, as the relationship between CBF and modulating variables have been shown to change.[55,57,84]

Although pCO_2 changes during exercise have been shown to cause great changes in CBF, actual changes in exercise performance do not seem to be accompanied by the hyperventilation-induced decrease in CBF at higher exercise intensity. Cerebral tissue does not appear to be in any danger of ischaemia, as CBF exceeds metabolic demand.[43] The brain's reliance on carbohydrate for fuel appears to be well maintained by glucose, and more so by lactate when glucose levels are low.[79] Cerebral glucose metabolism may pose a threat to exercise performance under prolonged (3 hours) hypoglycaemic exercise.[81] Although MAP does seem to contribute to the increase in CBF during exercise, and may play a role in central fatigue during exercise at altitude, during sea-level exercise, this does not seem to pose any threat.

Trials increasing MCAV during exercise show gCBF may not actually increase, questioning the

practical relevance on certain techniques; whereas other techniques might have crucial assumptions, or poor resolution, which may limit its practicality, especially during exercise.[19] Considerable variation in the distribution of major cerebral arteries makes interpretation troublesome.[91] Animal models are vital to our development and knowledge of CBF; but interpretation of these results in generalising the conclusions to humans must be done cautiously, as species differences have been reported.[92,93] Although CBF increases with exercise intensity up to a point (≈60% $\dot{V}O_{2max}$),[20,22] the practical relevance of this information is less clear. However, the relative contributions of modulating factors to CBF during exercise appear to maintain cerebral tissue health and do not appear to pose any limitations to exercise performance under normal exercise conditions.

Notably, the focus of this article concerns the regulating factors to CBF during exercise, and contemplates whether cerebral tissue is compromised during exercise. We acknowledge that this article does not encompass all facets of exercise. Research shows the value of a regular exercise programme to improve many disease states such as depression and anxiety,[94] and is integral in the maintenance of brain health in the elderly.[95] Physical activity is also suggested as a means to increase quality of life, increase glycaemic control in patients with diabetes mellitus,[96] improve body composition[97,98] and reduce the risk of cardiovascular disease.[99]

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