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Measurement and Changes in Cerebral Oxygenation and Blood Flow at Rest and During Exercise in Normotensive and Hypertensive Individuals

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Abstract

Purpose of Review Summarize the methods used for measurement of cerebral blood flow and oxygenation; describe the effects of hypertension on cerebral blood flow and oxygenation.

Recent Findings Information regarding the effects of hypertension on cerebrovascular circulation during exercise is very limited, despite a plethora of methods to help with its assessment. In normotensive individuals performing incremental exercise testing, total blood flow to the brain increases. In contrast, the few studies performed in hypertensive patients suggest a smaller increase in cerebral blood flow, despite higher blood pressure levels. Endothelial dysfunction and increased vasoconstrictor concentration, as well as large vessel atherosclerosis and decreased small vessel number, have been proposed as the underlying mechanisms.

Summary Hypertension may adversely impact oxygen and blood delivery to the brain, both at rest and during exercise. Future studies should utilize the newer, noninvasive techniques to better characterize the interplay between the brain and exercise in hypertension.

Keywords Brain oxygenation · Cerebral blood flow · Exercise · Hypertension · Microcirculation · Near-infrared spectroscopy

Introduction

Hypertension is one of the most prevalent diseases affecting more than 874 million people globally [1]. In 2015, it accounted for 143,000,000 disability-adjusted life years (DALYs) [1]. It increases stroke risk [2], inflicts dementia [3], and may accelerate its course [4–6]. Subclinical brain lesions, such as white matter hyperintensities, silent lacunar infarcts, and microbleeds, have all been reported in patients with hypertension [7••]. Recent data suggest that regular exercise training can assist with better blood pressure control [8] as well as with maintenance of cognitive function [9, 10]. Taking these into account, a better understanding of the adaptations of cerebral perfusion and oxygenation during exercise is of paramount importance, as it could identify molecular pathways activated or inhibited during exercise, which could constitute new therapeutic targets towards better cerebrovascular health in patients with hypertension.

In the first part of this review, we outline the methods used for the measurement of cerebral blood flow (CBF) and oxygenation. In the second part, we summarize the effect of hypertension on CBF and oxygenation at rest, as well as during exercise.

Methods for Measuring CBF and Oxygenation

The methods used to measure CBF and oxygenation (Table 1) have significantly evolved over time from invasive, using tissue or intravenous (IV) catheters, to noninvasive technologies

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Table 1 Summary of the most common methods used to measure cerebral blood flow and oxygenation

Method	Mechanism	Comments
Radioactive ^{133}Xe	IV infusion of isotope, radiation count probes placed over areas of interest, cerebral blood flow is proportional to radioactivity	First method used; of historical value at this point
PET scan	Radioactive $H_2{}^{15}O$ injection, blood flow estimated from the emitted radiation, and the time elapsed from the tracer injection	Gold standard method for measuring CBF. Involves radiation, not sensitive to rapid changes in blood flow, prone to motion artifacts. $H_2{}^{15}O$ tracer not readily available
SPECT scan	IV *^{99m}Tc-HMPAO* is injected, gets metabolized, and is ultimately distributed to the brain, the systemic circulation, and the venous compartment; cerebral blood flow is estimated by the radioactivity emitted from the 3 compartments	Involves radiation, not sensitive to rapid changes in blood flow, prone to motion artifacts
ASL-MRI	Cerebral perfusion is estimated by noninvasively labeling blood in neck arteries and measuring arrival of this label into the brain	Technically challenging, not well standardized, sensitive to motion artifacts, restricting its use mainly in stationary conditions
DCE-MRI	IV contrast creates signal change as it flows into the brain. CBF is calculated using the application of law of mass preservation for the different "phases" of the tracer i.e., plasma flow, plasma equilibration, tissue extraction, and tissue equilibration	Sensitive to motion artifacts, restricting its use mainly in stationary conditions
Neck vessel Doppler ultrasound	Blood flow is estimated by vessel diameter and blood velocity	Sensitive in detecting rapid changes in blood flow; ultrasound probe needs to be still over vessel which can be challenging during exercise
Transcranial Doppler ultrasound (TCD)	Ultrasound probe fixed on the skull, blood flow is estimated by vessel diameter and blood velocity	Fixation of ultrasound probe allows use in exercise, sensitive in detecting rapid changes in blood flow, concurrent measurement $PEtCO_2$ allows for correction of results for change in vessel diameter, provides only regional measurements, and does not assess small vessels
Near-infrared spectroscopy (NIRS)	Relative changes in oxygenated and deoxygenated hemoglobin concentrations measured by the modified Lambert-Beer law based on infrared light absorption	Able to detect rapid changes in oxygenation, not prone to motion artifacts enabling use during exercise; special software can correct results for regional skin blood flow; validated in many settings including carotid endarterectomy, orthostatic response, presyncopal episodes, systemic hypoxia, post-resuscitation, exercise; can provide information only in the region of the optodes; with the use of multiple channels, different brain areas can be assessed

IV intravenous, *PET* positron emission tomography, *CBF* cerebral blood flow, *SPECT* single-photon emission computerized tomography, *^{99m}Tc-HMPAO* technetium-99m-d,l-hexamethylpropyleneamine oxime, *ASL-MRI* arterial spin-labeled magnetic resonance imaging, *DCE-MRI* dynamic contrast-enhanced magnetic resonance imaging, *$PEtCO_2$* partial pressure of end-tidal carbon dioxide

such as ultrasound (US), magnetic resonance imaging (MRI), and near-infrared spectroscopy (NIRS).

Radionuclide-Based Methods Traditional methods for assessing global cerebral blood flow used the Fick principle (Kety and Schmidt method, using nitrous oxide) [11] or radioactive ^{133}Xe [12]. Radioactive ^{133}Xe is infused intravenously and regional blood flow can be estimated by measuring the arterial ^{133}Xe concentration using radiation count probes placed over the areas of interest. The whole procedure takes approximately 11 min, but is not sensitive to rapid changes in blood flow, such as those observed with exercise, and is now rarely used [13]. Two other radioactive methods employed to measure blood flow to the brain are positron emission tomography (PET) and single-photon emission computerized tomography (SPECT). The PET scan tracer for that purpose is radioactive water, $H_2{}^{15}O$. Cerebral blood flow is a function of the emitted radiation and the time passed since the radioactive tracer injection. With $H_2{}^{15}O$ PET, regional and global estimates of cerebral perfusion can be obtained [14, 15]. $H_2{}^{15}O$ PET scan is considered the gold standard for measurement of CBF. Unfortunately, the short half-life of $H_2{}^{15}O$ (~2 min) creates the requirement for a cyclotron at the imaging site, making this method not readily available in clinical practice [16]. The SPECT scan uses IV technetium-99m-d,l-hexamethylpropyleneamine oxime (^{99m}Tc-HMPAO), a lipophilic radioactive tracer, which readily crosses the blood-brain barrier (BBB). Once in the brain, it gets metabolized to a large hydrophilic molecule and smaller hydrophilic moieties. Unlike the smaller moieties, the large molecule cannot cross BBB and return to the systemic circulation; thus, it stays in the brain. Cerebral blood flow is estimated as a function of the emitted radioactivity from the brain, the fraction of the tracer that returned to the systemic circulation, and the radioactivity

of the tracer in the venous compartment [17, 18]. Neither PET nor SPECT is very sensitive to rapid changes in blood flow. Moreover, head movement can cause artifacts, therefore limiting their use in supine exercise [13]. Finally, PET and SPECT methods expose research participants to ionizing radiation.

MRI-Based Methods MRI can be used to measure cerebral perfusion through the arterial spin-labeled MRI (ASL-MRI) sequence. Cerebral perfusion is estimated by noninvasively labeling the blood in neck arteries and measuring arrival of this label into the brain [19]. ASL-MRI is technically challenging, relying on assumed constants and imaging parameters set by the user, which can limit the accuracy of the measurements. Additionally, it is not well standardized, which can affect generalizability of the results across centers [16]. Another sequence used for cerebral blood flow measurement is the dynamic contrast-enhanced MRI (DCE-MRI). This entails the use of an intravascularly injected Gadolinium-based contrast agent, which causes a detectable signal change as it flows into the brain. Cerebral blood flow is calculated by applying the mass preservation law for the injected contrast. This takes into account the signal change during each phase of the tracer circulation (i.e., plasma flow phase, plasma equilibration phase, tissue extraction phase, tissue equilibration phase) while also factoring in the duration of the individual phase [20]. With MRI techniques, values for regional cerebral blood flow can be obtained. Unfortunately, these techniques are sensitive to motion artifacts. Hence, their use is restricted mainly in stationary/resting conditions.

Ultrasound-Based Methods These are sensitive to rapid changes in blood flow and are less prone to motion artifacts. However, they only assess the flow in the large- and medium-sized vessels [21, 22].

Cervical vessel (carotid artery (CA)-vertebral artery (VA)) Doppler can estimate blood flow to the brain by measuring blood velocity and vessel diameter. Through this method, global cerebral blood flow can be estimated, but regional blood flow information cannot be obtained. The US probe should be held still on the neck during the Doppler measurement, which can make its use during exercise challenging [22].

The most prevalent US-based method used for cerebral blood flow measurement during exercise is transcranial Doppler (TCD). This measures blood velocity in different cerebral vessels as a surrogate marker for cerebral blood flow. It provides an estimate of regional blood flow, based on the vessel examined. The US probe can be fixed on the subject's skull, enabling its use during exercise and motion. Results obtained with TCD have been validated by the ^{133}Xe method [21, 23–25].

Unfortunately, TCD is an indirect method of estimating cerebral blood flow. It directly measures blood velocity and operates under the assumption that vessel diameter remains unchanged in order to calculate blood flow. Whether or not this assumption is valid during exercise has been a topic of debate, with different studies providing mixed results [21]. One way to bypass this assumption is to measure the partial pressure of end-tidal carbon dioxide ($P_{Et}CO_2$), which is a potent cerebral artery vasodilator. Subsequently, an adjustment can be made to correct blood flow results for the change in vessel diameter [21, 25].

Near-Infrared Spectroscopy NIRS can measure brain oxygenation during rest or exercise. It is based on the Beer-Lambert's law, which states that the absorption of light through any medium is proportional to the distance the light has to travel, the concentration of chromophores, and a molar extinction coefficient (showing how strongly the chromophores absorb light at a given wavelength). Within the NIRS range, the main light-absorbing molecules in biological tissues are metal complex chromophores, i.e., hemoglobin, bilirubin, and cytochrome. The wavelengths of the NIR light used in commercial devices are sensitive between 700 and 850 nm, where the absorption spectra of deoxygenated hemoglobin (HHb) and oxygenated hemoglobin (O_2Hb) are maximally separated. Optodes are placed on the skin over the regions where tissue oxygenation will be measured.

NIRS detects relative changes in oxygenated and deoxygenated hemoglobin concentrations ($\mu M\ min^{-1}$), and provides information regarding tissue oxygen saturation and thus, brain activation in a specific region [26, 27]. NIRS has the ability to detect rapidly occurring changes in cerebral oxygenation and is relatively unaffected by motion. The results obtained with this technology can be confounded by blood flow to the skin of the area where the optodes are applied [28]. These results can be corrected with the use of special software algorithms [29•]. There is a penetration limit for NIRS. For the brain, the probing depth of NIRS is about 3 cm. In comparison with the MRI techniques, the NIRS collects information about more superficial parts of the brain. Moreover, NIRS collects information only in the areas of the optodes; however, multiple brain areas can be simultaneously assessed using a multichannel functional NIRS (fNIRS). The major advantage of NIRS is that with direct measurement of both oxygenated and deoxygenated hemoglobin, its signal provides a real-time evaluation of brain activation/function during different stimuli [30].

Cerebral Perfusion and Blood Flow in Normotensive Versus Hypertensive Individuals at Rest

Cerebral blood flow at rest, assessed via ALS-MRI, has been shown to be similar in newly diagnosed hypertensive and normotensive individuals [31]. However, in the same study,

Lee et al. found that cerebral capillary blood flow time was prolonged in hypertensives, suggesting impaired microcirculation [31]. To evaluate the number and morphology of large and small brain vessels in humans with recently diagnosed, untreated hypertension, Kang et al. used ultrahigh-field 7 Tesla brain MRI [32]. Their study found no differences between the large vessels of hypertensives and normotensives, other than benign, expected anatomic variations. In terms of small vessels, hypertensives had 25% fewer lenticulostriate arteries. This difference could be either due to decreased number, decreased lumen size, or decreased flow in the brain vessels of hypertensive individuals, resulting in a lower signal intensity on the MRI scan [32, 33]. Pathology slides from macroscopically healthy brains of hypertensive individuals showed reduced number of capillary vessels (i.e., capillary rarefaction), as well as decreased lumen size compared with those of normotensives [34].

Established hypertension has been associated with decreased CBF [35, 36]. A sub-analysis of the SMART-MR (Second Manifestations of ARTerial disease-Magnetic Resonance) study in 575 individuals with hypertension and clinical atherosclerotic disease followed over 3–5 years showed that parenchymal cerebral blood flow (an indirect measure of brain tissue perfusion) and total cerebral blood flow were inversely associated with systolic blood pressure (BP) and diastolic BP levels [35]. Similar results were obtained from a follow-up of the CARDIA (Coronary Artery Risk Development in Young Adults) study in 517 individuals, in which BP levels were correlated with reduced gray matter blood flow. This was notable from systolic BP levels > 130 mmHg [36], highlighting the importance of treating patients with systolic BP > 130 mmHg, in congruence with the most recent guidelines for the treatment of hypertension by the American College of Cardiology/American Heart Association (ACC/AHA) [37••].

Interestingly, in the SMART-MR study, even well-controlled hypertension was associated with a non-statistically significant decrease in cerebral blood flow and perfusion. The groups with untreated and poorly controlled hypertension had a significant decline in parenchymal cerebral blood flow over 4 years of the study. Within the hypertensive population, treatment with angiotensin II receptor blockers (ARBs) was protective against the decrease in blood flow. This effect was not observed with other antihypertensive medication classes including angiotensin-converting enzyme inhibitors (ACEi) [35].

These data suggest that the reduction in blood flow observed in hypertension may stem from distinct underlying neurohormonal profiles in addition to the mere difference in blood pressure levels. More specifically, hypertension leads to increased vasoconstriction of the small vessels by inducing Acta 2 gene expression, and by reducing the expression of calcitonin gene-related peptide receptors [38]. Additionally, increased activation of the renin-angiotensin system promotes cerebral vessel remodeling [39, 40]. Angiotensin II increases matrix metalloproteinase 9 (MMP9) expression in the brain vessels through caveolin 1 expression [41]. Consequently, the elastin content of the vessel wall decreases, resulting in stiffer vessels [42]. The above changes combined with the decrease in total capillary cross-sectional area, and the impaired vasodilatory capacity, result in decreased cerebral blood flow. The above dysfunctions can play a central role in brain health, as cerebral blood vessels are responsible for the delivery of oxygen and nutrients. Thus, vascular damage and reduced blood to the brain can disrupt vital homeostatic mechanisms and contribute to structural brain lesions (such as white matter hyperintensities and cerebral infarcts), worsening of cognition, and development of dementia [35, 36].

Collectively, these findings suggest that in the early stages of hypertension, cerebral perfusion is limited by small vessel vasoconstriction and capillary rarefaction. Later in its course, vascular remodeling increases cerebral vascular resistance, resulting in decreased cerebral blood flow. Angiotensin II is one of the main molecules implicated in these alterations; blockage of this pathway could be protective.

Of note, other studies suggested that the hypertension–brain link can be bidirectional in the sense that hypertension is not the cause, but rather the result of brain dysfunction [43, 44]. In support of this concept, an MRI study in normotensive patients linked exaggerated BP reactivity with altered brain activation patterns in response to psychological stress [45]. More studies are needed to clarify this concept in hypertensive individuals, as a better understanding of hypertension-related brain functional reorganization could have important implications for the prevention of both cardiovascular disease and cognitive impairment.

Current recommendations for individuals with hypertension emphasize the benefit of regular exercise training as an efficient and complementary tool for BP management [46]. Recent studies also suggest that regular exercise training can be an important tool to prevent and reduce cognitive damage [47, 48•, 49]. Yet, only a few studies have specifically examined the potential positive effects of exercise on the cerebrovascular system and cognitive function in hypertensive individuals. In addition, exercise may be a sensitive method for the detection of early hemodynamic impairment in non-treated hypertensive individuals. However, information regarding the effects of hypertension on cerebrovascular control during exercise is very limited. The following sections aim to describe the adaptations in cerebrovascular circulation and oxygenation during exercise in healthy and in hypertensive individuals.

Cerebral Blood Flow and Oxygenation During Exercise in Normotensive Individuals

During exercise, as brain activity increases, oxygen consumption by the neurons also increases and cerebral blood flow

rises in order to meet the higher oxygen and substrate demands [50]. Cerebral perfusion increases in the brain areas orchestrating the motion to perform the particular exercise and in areas responsible for the adaptation of vital functions (e.g., blood pressure and respiration) [51, 52].

Interestingly, cerebral blood flow and oxygenation increase even in anticipation of exercise. Using NIRS, Matsukawa et al. [53] and Asahara et al. [54] found that oxygenation in the prefrontal cortex increases prior to the onset of voluntary exercise, possibly due to neuronal activation associated with exercise planning [55]. Using $H_2{}^{15}O$ PET, Thornton et al. [56] showed that even with the imagination of exercise, regional CBF increases in proportion to the imagined motor effort. More specifically, increased CBF was found in the supplementary motor area and the dorsolateral prefrontal cortex, which are brain areas associated with motor planning and executive function [57, 58].

During the actual exercise session, the acute responses/adaptations in brain blood flow and oxygenation can vary depending on the type/mode and intensity of the exercise bout (maximal exercise test or submaximal steady state exercise).

Adaptations in Cerebral Oxygenation and Blood Flow During Maximal Exercise Testing (Graded or Incremental Test to Exhaustion) The CBF response to an incremental exercise test to exhaustion (maximal test) has been described as biphasic (Fig. 1a), with a progressive increase in CBF up to approximately 60–70% of maximal oxygen uptake (VO_2max), followed by a plateau or a reduction in CBF [24, 59–68]. In more detail, during a maximal incremental exercise test, CBF has been shown to increase progressively by ~ 20–30% above resting levels [50, 69], and then to plateau at around 60–70% of peak work rate [68, 70]. During heavy/exhaustive exercise, CBF decreases towards baseline values despite further increases in exercise intensity and the high cerebral metabolic demand [50, 69]. Cerebral oxygenation, as assessed by the NIRS oxygenated hemoglobin, has also been reported to display a relatively similar response: It increases during low and moderate exercise intensities and then, at high-intensity exercise (above the anaerobic ventilatory threshold), a breakpoint occurs and a decline in oxygenated hemoglobin is initiated [71–73]. On the other hand, deoxygenated hemoglobin remains stable during low/moderate-intensity exercise, but then shows a rapid increase from high (> 60% VO_2max) to maximal-intensity exercise [50, 69, 73]. This adaptation suggests that when CBF reaches its upper limit, oxygen extraction from hemoglobin increases to meet the brain's metabolic demands [50, 69]. The disproportionate increase in deoxygenated hemoglobin at this point also likely reflects increased brain activation and metabolism at exhaustion [50]. Additionally, the increase in deoxygenated hemoglobin can be a compensation to overcome the reduced oxygen supply due to vasoconstriction induced by hyperventilation [13]. Cerebral cortex activation can be maintained up to the respiratory compensation point, after which it decreases [74]. The significant decline in cerebral oxygenation observed during heavy exercise may influence central fatigue and result in termination of exercise [13].

Acute Adaptations of Brain Oxygenation and Flow During Constant Load, Low/Moderate-Intensity Exercise At the onset of steady state exercise, middle cerebral artery blood flow velocity increases exponentially (to ~ 15% above resting values) [75]; total cerebral blood flow also increases (to ~ 20–28% above resting values) [51]. Thereafter, the magnitude of the increase and the CBF and oxygenation responses to constant load exercise depend on the type (dynamic/aerobic, resistance, isometric) and intensity of exercise [76, 77]. More specifically, Tsubaki et al. [77] reported that during low-intensity dynamic exercise (20 min at 30% VO_2max), oxygenated hemoglobin (as assessed by NIRS) was not constant, despite participants (healthy volunteers) performing constant load exercise. That is, oxygenated hemoglobin increased over the first 6 min of exercise, then plateaued for 10 min, and then slowly declined (during the last 4 min of exercise). However, Takehara et al. [78] reported that during a cycle-ergometer exercise bout at 30% and 50% of VO_2peak, oxygenated hemoglobin showed a transient decrease at exercise onset, after which it was significantly increased from the mid- to final exercise phase (in both intensities examined) compared with resting values. The authors reported that the duration of the initial transient decrease in oxygenated hemoglobin in the beginning of exercise varied according to the brain region examined [78]. This idea was further examined by Ishii et al. [76] using multichannel NIRS. The authors assessed the oxygenation responses in different brain areas during exercise (one-armed cranking), at 30% and 60% of the maximal effort. At the beginning of both voluntary cranking tasks, the oxygenation increased only in some parts of the prefrontal and sensorimotor cortices. Then, during the higher intensity exercise (cranking at 60% of maximal effort), the oxygenation increased gradually in all cortical areas examined, whereas, during the lower intensity (at 30% of maximal effort), oxygenation increased only in the frontoparietal area and some of the frontal areas. Interestingly, passive (motor-driven) exercise of one or two limbs caused a reduction in the oxygenation of most cortical areas [76, 79]. During resistance exercise (submaximal continuous or intermittent handgrip) in normotensive individuals, oxygenated hemoglobin (measured by NIRS) in the prefrontal cortex progressively increased and plateaued towards the termination of exercise, despite the constant load of exercise [80, 81]. Therefore, differences in the intensity and duration of exercise used [82], the type of exercise (higher responses during high-intensity sprint versus steady state) [83], and the body position [84, 85] during exercise and the area of interest examined [78] possibly explain the

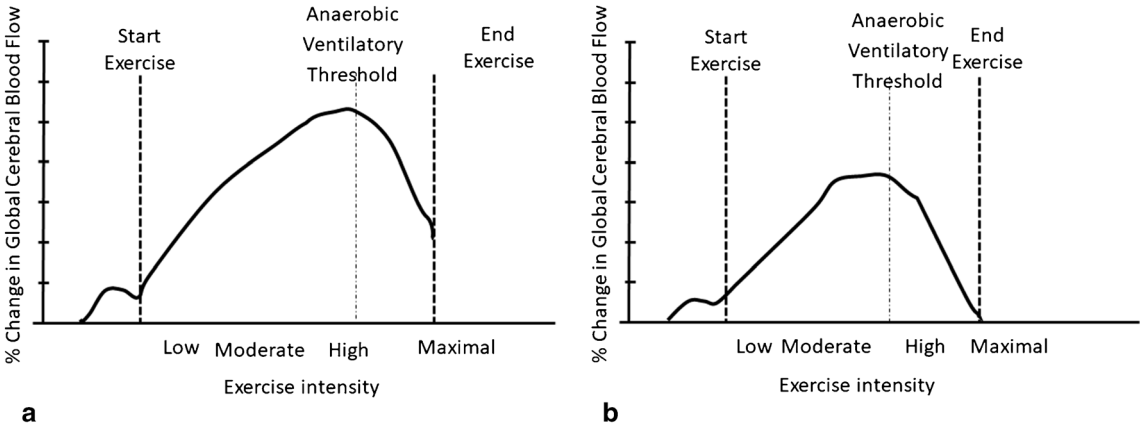

Fig. 1 Typical response of cerebral blood flow (CBF) during a maximal test (incremental test to exhaustion) in a normotensive individual (**a**) and in an individual with low cardiorespiratory fitness (**b**). **a** A typical response in cerebral blood flow (CBF) in a healthy normotensive individual. CBF increases even in anticipation of exercise. During an incremental exercise test to exhaustion, cerebral blood flow (as well as oxygenation) increases, up to approximately 60–70% of peak work load; but then at higher intensities, beyond the anaerobic threshold, CBF plateaus and during maximal exercise, it may even decline. **b** In individuals with low cardiorespiratory fitness levels, the appearance of the anaerobic threshold occurs at a lower percentage of VO_2max (< 65%). In addition, in individuals with cardiovascular disease, there is a blunted response in cerebral blood flow and oxygenation during exercise versus healthy controls

differences in reported results regarding brain oxygenation/flow during exercise.

Cardiorespiratory fitness levels, aging, and disease can also alter resting and exercise CBF and oxygenation [86, 87]. In sedentary older men, aerobic exercise training increased CBF in the frontal lobes (by 27%, as assessed by ASL-MRI) [88]. The acute increases in cerebral blood flow and oxygenation during an exercise bout have been suggested to augment the release of various markers of brain plasticity and possibly promote improvements in cognitive domains (i.e., executive function and processing speed) and brain structures [89–91]. In fact, in older adults with higher cardiorespiratory fitness levels, greater cerebral oxygenation was related to better executive functioning [87]. Furthermore, among older adults, changes in fitness were associated with changes in hippocampal microstructure and hippocampal volume [91, 92]. Besides the changes in cerebral perfusion, mechanisms that have been reported to underlie the exercise training-induced beneficial effects on executive function include favorable changes in brain volume and connectivity, synaptic plasticity, and neurogenesis. The latter occurs via release of neurotrophins, such as vascular endothelial growth factor (VEGF) and brain-derived neurotrophic factor (BDNF) [90]. In addition, improvements in glucose metabolism as a result of exercise training can assist in better CBF and improved executive function [88]. In contrast, in older individuals [67] and patients suffering from diseases such as type 2 diabetes [93] or heart failure [94], lower cerebral perfusion and oxygenation (versus healthy controls) in response to acute dynamic exercise have been described (Fig. 1b), which might induce brain-regulated limitations to exercise tolerance.

In summary, blood flow, oxygenation, and cortical activation in specific brain regions are influenced by the characteristics (intensity, type, and mode) of the exercise bout. During incremental exercise testing (maximal test), CBF progressively increases to a plateau at high exercise intensity, and then declines towards exhaustion. Cerebral oxygenation also increases (up to approximately 60–70% of peak work load), but then at higher intensities (beyond the anaerobic ventilatory threshold), it decreases. At maximal exercise intensity, concurrently with the decrease in CBF, oxygen extraction by the brain increases in an effort to maintain homeostasis. Higher cardiorespiratory fitness can enhance CBF at rest and during exercise, and might therefore contribute to brain health and decelerate cerebral decrease.

Alterations in Cerebral Blood Flow During Exercise in Hypertensive Individuals

Alterations in the macro- and microcirculation are observed with hypertension, which can result in changes in tissue perfusion and oxygenation during exercise. For example, decreased oxygen supply and utilization by skeletal muscle were correlated with higher central-aortic systolic BP and indices of arterial stiffness [95]. Additionally, BP of individuals with untreated hypertension rises to significantly higher levels during exercise than those of normotensive individuals [96••].

To study the effect of hypertension on cerebral blood flow, Magyar et al. [96••] compared TCD measured changes in blood velocity in middle cerebral artery (MCAv) and BP during an incremental test (up to 85% HRmax) on a cycle ergometer in non-treated, neurologically symptom-free hypertensive and normotensive individuals. Most individuals continued the test for more than 6 min, and data are reported up to the 6-min mark. At rest, MCAv did not differ significantly between groups. However, during exercise, MCAv continuously

increased in normotensives until the end of the incremental test, whereas it plateaued after 2 min in hypertensives. Overall, CBF increased by 20% in the hypertensive group. This is a smaller increase to that observed in normotensives of the study (34%) [96••]. Interestingly, end-tidal CO_2 levels did not differ significantly between the two groups despite the difference in MCAv. This could imply that MCA of patients with untreated hypertension has a blunted response to the vasodilating CO_2, and thus a lower decrease in cerebrovascular resistance during exercise. Alternatively, the augmented sympathetic tone owing to hypersensitivity to the exercise pressor reflex in hypertensive patients results in increased cerebral vessel tone, and hence a smaller vessel diameter. Therefore, even if the vessel responsiveness to CO_2 is the same between hypertensive and normotensive individuals, that difference in their diameter could explain the decreased cerebral blood flow during exercise despite similar CO_2 levels [96••].

Data from a study in mice with angiotensin II-induced hypertension support this theory [97]. MCA of hypertensive mice reacted to acutely increased intraluminal pressure (mimicking exercise conditions) with increased vasoconstriction compared with the normotensive control group. This was mediated by increased 20-hydroxy-5,8,11,14-eicosatetraenoic acid (20-HETE) concentration. 20-HETE is produced by the action of cytochrome P450 4A omega-hydroxylases, and through activation of the transient receptor potential cation channel subfamily C (TRPC), it causes an increase in intracellular Ca^{2+} resulting in vasoconstriction. The end result was a 20% decrease in CBF at systolic BP levels > 160 mmHg [97].

Regarding the decreased vascular reactivity seen in hypertensive patients, results of human studies showed that it is improved after L-arginine infusion. L-arginine is the substrate for endothelial NO synthase, activation of which increases NO production [98]. Therefore, the reduced NO concentration seen in hypertensive individuals [99] could explain the blunted cerebral vasoreactivity of that patient population. Additionally, higher levels of soluble vascular adhesion molecule (sVCAM) seen in uncontrolled hypertension were associated with reduced MCAv at rest, as well as with diminished cerebral vasodilation in response to CO_2 [100•]. The postulated mechanism is that adhesion molecules attract lymphocytes, which impair endothelial function either by reducing endothelial-dependent vasodilation, or by increasing protein and fluid leak from the capillary vessels [101]. Moving forward, further studies should evaluate whether MCAv measurement during exercise could be a marker of the functional integrity of cerebral circulation in hypertension, and whether it could yield any prognostic data on the risk of those individuals for stroke. Finally, it is likely that the decreased number of small cerebral vessels [32] and the intracranial atherosclerosis and narrowing of large vessels [102] provide a smaller reserve for blood flow increase.

In summary, data from the small number of studies that examined this topic suggest that cerebral blood flow during exercise increases to a lesser extent in hypertensive patients. This possibly happens due to both anatomic and functional changes (Table 2). However, further studies are required to fully elucidate alterations in cerebral oxygenation and circulation during exercise in hypertensive individuals. In addition, the optimal doses or mode of exercise to improve brain oxygenation and maximize cognitive benefits in individuals with hypertension are not clear; thus, interventional training studies in individuals with hypertension are needed.

Conclusions and Recommendations for Further Research

Recent technological advances have enabled the assessment of cerebral perfusion both at rest and during exercise. Cerebral oxygenation and blood flow change with exercise. The exact adaptations depend on the intensity and duration of exercise, among other factors. During dynamic exercise in healthy individuals, brain blood flow increases to a peak observed at 60–70% of maximal intensity. There it plateaus or even declines at maximal intensity. Hypertension alters the response of cerebral blood flow to exercise. The increased concentration of circulating vasoconstrictor molecules, a hypersensitivity of the exercise pressor reflex, as well as the stenosis and reduced number of vessels supplying the brain, limit the body's capacity to increase cerebral blood flow, despite a marked increase in BP levels. Future studies should assess if impairments of cerebral blood flow are associated with other target organ damage in the hypertensive population. More importantly, their role as heralds of adverse neurologic outcomes, such as dementia and stroke, should be explored. The need for biomarkers and diagnostic testing for the earlier identification of those at high risk for stroke cannot be

Table 2 Hypertension-induced changes that could limit cerebral blood flow increase during exercise

Decreased serum concentration of nitric oxide
Increased 20-hydroxy-5,8,11,14-eicosatetraenoic acid concentration
Reduced endothelial-dependent vasodilatation
Loss of capillary integrity
Decreased number of small vessels
Atherosclerosis of large brain vessels
Increased sympathetic tone
Decreased vessel response to the vasodilatory carbon dioxide (decreased cerebrovascular reactivity to hypercapnia)

overemphasized, as timely blood pressure control could lead to significant reductions in stroke and dementia-related morbidity and mortality.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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