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A framework of transient hypercapnia to achieve an increased cerebral blood flow induced by nasal breathing during aerobic exercise

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ABSTRACT

During exercise, cerebral blood flow (CBF) is expected to only increase to a maximal volume up to a moderate intensity aerobic effort, suggesting that CBF is expected to decline past 70 % of a maximal aerobic effort. Increasing CBF during exercise permits an increased cerebral metabolic activity that stimulates neuroplasticity and other key processes of cerebral adaptations that ultimately improve cognitive health. Recent work has focused on utilizing gas-induced exposure to intermittent hypoxia during aerobic exercise to maximize the improvements in cognitive function compared to those seen under normoxic conditions. However, it is postulated that exercising by isolating breathing only to the nasal route may provide a similar effect by stimulating a transient hypercapnic condition that is non-gas dependent. Because nasal breathing prevents hyperventilation during exercise, it promotes an increase in the partial arterial pressure of CO_2. The rise in systemic CO_2 stimulates hypercapnia and permits the upregulation of hypoxia-related genes. In addition, the rise in systemic CO_2 stimulates cerebral vasodilation, promoting a greater increase in CBF than seen during normoxic conditions. While more research is warranted, nasal breathing might also promote benefits related to improved sleep, greater immunity, and body fat loss. Altogether, this narrative review presents a theoretical framework by which exercise-induced hypercapnia by utilizing nasal breathing during moderate-intensity aerobic exercise may promote greater health adaptations and cognitive improvements than utilizing oronasal breathing.

Introduction: components of cerebral blood flow

The human brain is a highly vascularized organ that is dependent on a continuous blood supply. The delivery of blood to the brain, known as cerebral blood flow (CBF), is defined as the total volume of blood per brain tissue over time (mL_{blood}/100 g tissue · min) and is critical to deliver nutrients and meet cerebral energetic demands [1]. If the CBF of a given brain region is dramatically reduced, localized brain cells become hypoxic and die, leading to permanent brain damage and neurological disorders [2]. To maintain a sufficient CBF, the cerebral perfusion pressure (CPP) is tightly regulated to ensure a constant blood supply to the cerebral tissue [3]. CBF can be maintained constant because CPP can be adjusted acutely by regulating its two primary determining variables. Specifically, CPP is the difference between mean arterial pressure (MAP) and intracranial pressure (ICP), where CPP = MAP – ICP [3]. MAP is a representation of whole-body blood delivery per every cardiac cycle and can be calculated by accounting for systolic and diastolic blood pressure [diastolic pressure + 1/3 (systolic – diastolic pressure)], along with pulse pressure [diastolic pressure + 1/3 (pulse pressure)] [4]. Evidence suggests that a MAP of ≥ 65 mmHg is needed to maintain a constant CBF [5]. On the other hand, ICP represents brain stress, where a high ICP (> 20 mmHg) denotes a negative brain environment that is not adequately regulated [6]. Currently, the primary method to assess ICP is invasive and involves the transcranial application of a catheter that monitors ICP within the parenchymal brain ventricles [7], while non-invasive applications to monitor ICP are currently being investigated.

Considering that CBF is critical for brain health, the overall ability of the brain to maintain a constant CBF is referred to as cerebral autoregulation (CA). Specifically, CA is calculated by accounting for CPP and cerebrovascular resistance (CVR), ultimately determining the overall cerebral perfusion [8]. To put this into perspective, CA is represented as follows:

High Cerebral Autoregulation = Homeostatic Cerebral Blood Flow

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$$\text{Cerebral Blood Flow} = \text{Cerebral Perfusion Pressure} \div \text{Cerebral Vascular Resistance}$$

$$\text{Cerebral Perfusion Pressure} = \text{Mean Arterial Pressure} - \text{Intracranial Pressure}$$

$$\text{Cerebral Vascular Resistance} = \text{Regulated by Vasodilation/Vasoconstriction}$$

Evidence examining the adaptations following aerobic exercise supports that the metabolic activity permitted by an increased CBF can expose the brain to hyperemia and therefore bolster improvements in CA [1,9,10]. However, the adaptations to aerobic exercise may differ depending on the breathing pattern and the exercise intensity utilized [10,11]. Under this scope, this review manuscript aims to describe how CBF increases during exercise in relation to different exercise intensities and how the breathing pattern can affect how much CBF can increase. Moreover, an introductory overview regarding adaptations following hyperemic exposure is presented, along with a description of the strengths and weaknesses of different methods employed to assess CBF during exercise.

Change in cerebral blood flow during aerobic exercise

Exercise intensity and hypoxia

During exercise, CPP increases as believed to be, in part, related to an increase in MAP, sympathetic-related vasoconstriction, or dehydration-induced increments in CVR [12–16]. A consequence of the increased CPP is that CBF can only continue to increase up to a moderate-intensity aerobic effort during exercise. This means that past 70 % of a maximal aerobic effort, CBF is expected to decline because of an increased CPP and/or the need to buffer the excess pressure building within the brain that could otherwise be harmful [17,18]. This is important to highlight because, among the benefits of aerobic exercise in relation to cognitive health, it has been demonstrated that the increments in CBF provided by aerobic exercise are linked to cognitive improvements. Such as, increasing CBF during exercise permits an increased cerebral metabolic activity that stimulates neuroplasticity and other key processes of cerebral adaptations that ultimately improve the ability to CA [18–20]. Thereof, it is worthwhile to contrast that there is a probable link between interventions that employ a moderate intensity (65–70 % of maximal effort) aerobic exercise protocol and the subsequent improvements in cognitive function with the fact that the participants are also benefiting from an increased CBF throughout the intervention. Moreover, evidence in older men has shown that their CBF increased by more than 20 % compared to their baseline, alongside an improvement in cognitive function after 12 weeks of aerobic exercise using a cycle ergometer at 70 % of their maximal effort [21]. Similar benefits of exercising on CBF have also been reported acutely and not just after long-term interventions. For example, an acute bout of maximal aerobic effort revealed that the trained men and women had a higher degree of CA than the sedentary participants [22]. Noteworthy, the trained individuals had over 10 years of prior aerobic training experience exercising at a moderate intensity, unlike the sedentary individuals with no prior history [22].

Furthermore, a remarkable adaptation following aerobic exercise training revolves around the ability to provide dependable benefits so long the frequency of exercise is maintained. Such as individuals exercising over a period of 1 year demonstrated continuous improvements in CA throughout the entire intervention period [19], denoting that the brain is continuously adapting and improving its ability to CA so long it continues to be metabolically challenged via exercise [19,22,23]. In the context of cognitive health, a major reason why increasing CBF during exercise is beneficial to sustain a healthy cognitive function is that the associated increased metabolic demand driving the increment in CBF also stimulates the entire brain to work and adapt. For example, moderate-intensity aerobic exercise has been demonstrated to be critical in older individuals with poor cerebrovascular health and at risk of dementia. That is because aerobic bouts can significantly increase hippocampal CBF [24], which counteracts the decline in CBF attributed to a sedentary lifestyle. Increasing hippocampal CBF is beneficial for geriatric populations because the hippocampus is a critical region for memory formation and the maintenance of cognitive function [25], which is a relationship that is critical to improving the prognosis of individuals with a history of suffering a stroke [26].

It is well documented that frequent moderate-intensity aerobic exercise provides beneficial cerebral adaptations that bolster cognitive health. However, in addition to increasing CBF, engaging in aerobic exercise also promotes the upregulation of neuropeptides and vascular growth factors pivotal to maintaining healthy endothelial cells and promoting a regulated CBF [27,28]. Moreover, recent research has started exploring a new avenue of maximizing the benefits of aerobic exercise by identifying methods to promote the greatest increment in CBF. Specifically, unlike in normoxic conditions, evidence suggests that exercising under hypoxic conditions could provide greater benefits towards cognitive function, especially in memory preservation [29–35]. In other words, albeit the direct mechanistic adaptation leading to improvements in cognitive function warrants further research, exercising under a hypoxic condition may bolster a greater cognitive improvement than what is achieved while exercising under normoxic conditions by improving how individuals perform in different tests to assess cognitive performance. In part as to why hypoxia may induce a positive change related to cognitive function relates to its ability to stimulate angiogenesis and the production of red blood cells by inhibiting the enzymatic activity of prolyl hydroxylase domain 2 (PHD2), which in turn promotes the production of erythropoietin (EPO) [27,36,37]. In addition, exposure to hypoxic conditions permits the upregulation of hypoxia-inducible factor (HIF) proteins that are of importance due to their ability to stimulate cerebral and vascular adaptations that lead to an increased CBF [38–41], where increasing CBF is needed to maintain the ability to CA [18–20] and promote the postulated cognitive improvements. However, unless an individual inhales hypoxic gas prior to or while exercising, it is not common to create a hypoxic condition simply by exercising. While inhaling gas to elicit a hypoxic condition is effective [29–35], it limits the ability to apply this in a wide array of settings due to possible limitations in gas accessibility. In addition, the majority of the emphasis has been placed on utilizing gas-induced hypoxia to achieve a greater understanding of CBF regulation in the context of CA, and lesser attention has been placed on assessing how biomarkers that are upregulated during hypoxia could also positively affect CBF over time under this type of training regime.

Cerebral blood flow and breathing pattern

One plausible method to explore the effects of exposure to hypoxic conditions while exercising without the reliance on external gas inhalation is by accounting for the breathing pattern used during exercise. While the breathing pattern utilized during exercise primarily depends on a personal preference, there are 3 different types of breathing patterns, including nasal, oral, and oronasal (both nasal and oral). Based on the type of breathing pattern used, the physiological stress elicited by an exercise bout can differ, which can be reflected in respiratory-related variables that change accordingly to the breathing pattern of use. Physiologically, oxygen uptake (VO_2) is governed by total minute ventilation (V_e), a variable determined by respiratory rate (RR) multiplied by tidal volume (V_t) [42]. A reduction in RR or V_t can lead to a reduction in V_e and, herein, the ability to uptake oxygen. Extrapolated to exercise performance, a common phenomenon during a maximal aerobic effort revolves around hyperventilation, where the rate at which air is moved in and out of the lungs is significantly increased and linked as a limiting factor in aerobic performance due to impaired gas exchange at the alveolar level [43]. In other words, during exercise, the point at

which an individual begins to hyperventilate can be contrasted to the point at which an individual is no longer able to efficiently remove carbon dioxide (CO_2) from their body, also referred to as the ventilatory threshold. To compensate for the excess CO_2 that accumulates in the body past the ventilatory threshold, a common phenomenon includes an innate change in the breathing pattern utilized, where there is a shift from nasal towards oral breathing that facilitates a higher V_e than if nasal breathing was maintained throughout [44,45]. Meaning that at lower exercise intensities, the reliance on the oral cavity for breathing is less because the stimuli provided by carotid bodies and chemoreceptors are lesser than what is elicited during greater exercise intensities due to a rise in the arterial partial pressure of CO2 ($PaCO_2$) [46,47]. A primary outcome of an increased $PaCO_2$ is that to remove CO_2 from the blood. Thus, hyperventilation is stimulated by carotid bodies and chemoreceptors to increase gas exchange within the alveoli. Worth denoting although the presented role for carotid bodies and chemoreceptors is plausible, after decades of work, there is still no shared consensus as to how exactly the central nervous response regulates breathing to match V_e to alveolar demand [48,49]. Yet, to increase V_e and sustain a greater CO_2 removal is only possible if a greater volume of air can be moved in and out of the lungs, as permitted by relying on the oral route rather than the nasopharyngeal route [11]. That is why at greater exercise intensities, as reported to occur past around 70 % of someone's maximal VO_2 [50–52], there is an innate shift to relying more on oral breathing to increase V_e and remove excess CO_2 that is attributed to working muscles and a greater metabolic efflux of CO_2.

In contrast, if nasal breathing was to be utilized for the entire exercise bout, it is possible that the stimulatory effects on cognitive function would be greater than relying on the oral or oronasal route. This is under the premise that cognitive function favors periods of increased CBF/hyperemia. That is because exercising using only nasal breathing has been shown to induce hypoventilation [11,53,54], which is linked to creating a hypercapnic condition resembling the effects of hypoxia [55–57]. Worth mentioning there is no physiological mechanism that would increase the reliance on the nasopharyngeal route while exercising. Instead, nasal breathing is to be induced by manipulating the breathing pattern, such as providing individuals with a mouthguard to serve as a proprioceptive reminder to maintain the mouth closed or utilizing hypoallergenic tape for the same purpose [53]. One of the effects of hypercapnia induced by nasal breathing is the superior ability to increase nitric oxide production in comparison to oral breathing [58], which in turn can favor CBF due to its dilatory effects [59–62]. Furthermore, compared to oral breathing, nasal breathing has advantages in allowing the lungs to fully expand due to a lower RR [63] that does not permit individuals to hyperventilate [53]. Thereof, if individuals hypoventilate during exercise, the effects result in an overall reduction in the exhalation of CO_2 due to nasal breathing reducing the volume of exhaled air, which increases the $PaCO_2$. An increase in $PaCO_2$, referred to as hypercapnia, has been documented as an important condition increasing CBF [12,23,64–68]. Similarly, because hypercapnia causes the upregulation of unique biomarkers attributed to hypoxia [69–71], such as HIF proteins, this type of exercise training focused on nasal breathing paired with moderate-intensity aerobic exercise might be a promising approach to upregulate neuropeptides and growth factors to help develop adaptations that will increase CBF over time and therefore increase the ability to CA [68]. An overview of the postulated effects elicited during moderate-intensity aerobic exercise based on the breathing pattern utilized is illustrated in Fig. 1.

Overview of hypercapnia

In this review, the term hypercapnia is contrasted to hypoxia because they both resemble a physiological status characterized by a decreased availability of oxygen. However, hypoxia and hypercapnia are distinguished from each other because they have independent factors that can drive their occurrence [72]. Note, however, that if either hypoxia or hypercapnia occurs, ultimately, what is being described is representative of an environment where the PaO_2 is decreased and the $PaCO_2$ is increased [72–74]. Therefore, although independent to some extent, hypoxia and hypercapnia are inclusive/permissive of each other. From an applicability point of view, hypoxia is often utilized to describe conditions where a chronic factor, such as a tumor, changes the

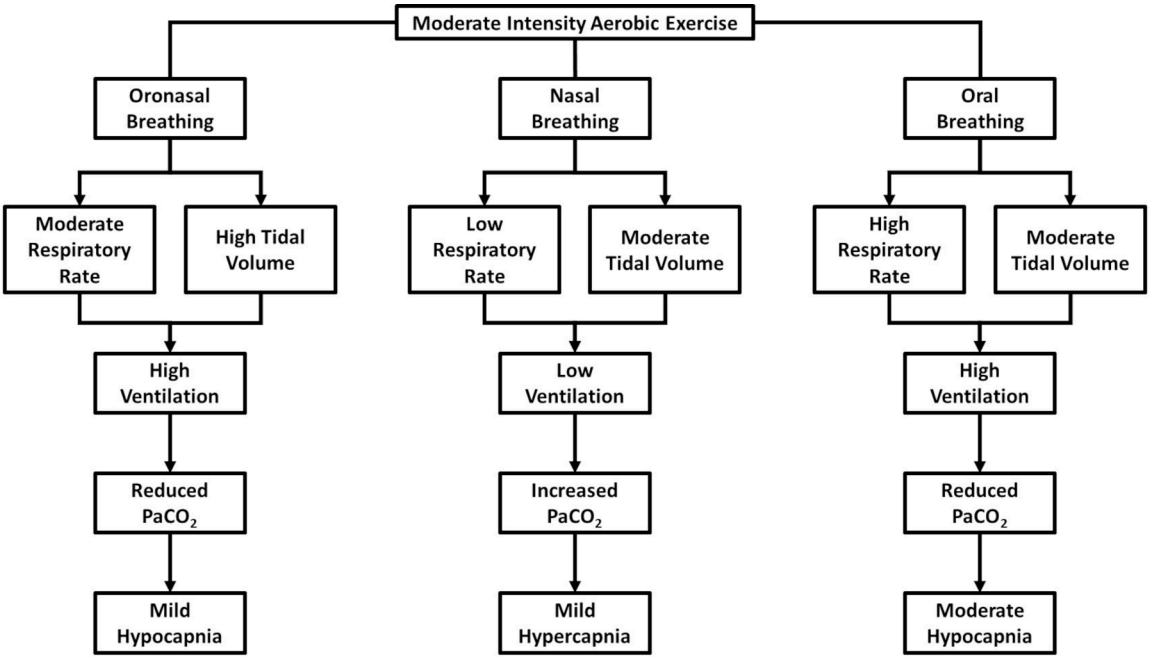

Fig. 1. Overview of the effects elicited during moderate-intensity aerobic exercise based on the breathing pattern utilized. The order of impact is described from low to high impact on a given variable, where: low, mild, moderate, and high indicate the degree of change within the variable compared to the other breathing methods. For example, a box containing the description of "low" indicates that the given breathing pattern compared to the other two elicits a reduction to the variable of interest. Partial arterial pressure of carbon dioxide = $PaCO_2$.

metabolic demands that will deprive a given localized region (tissue) of oxygen and, thereof, elicit a hypoxic condition [75,76]. In contrast, hypercapnia is often utilized to describe factors that can increase $PaCO_2$ due to impaired removal of CO_2 from the bloodstream. While not accounting for all cases, chronic obstructive pulmonary disease, a condition where the alveolar sacks are damaged, is among the main reasons why someone may experience hypercapnia because their gas exchange is compromised [77,78]. Nonetheless, whether the term hypoxia or hypercapnia is utilized to describe a condition of decreased availability of oxygen, it is critical to highlight that the duration and severity of the condition will ultimately determine the impact of the reduced PaO2.

For example, a chronic reduction in PaO_2 is detrimental to all cells. A compensatory mechanism that attempts to correct the reduced PaO_2 revolves around the upregulation of HIF proteins to increase the overall systemic availability of O_2 [79,80]. In contrast, what is being described in this manuscript is a condition of reduced PaO_2 that is transient in nature, i.e., short-lived and rapidly corrected once the stimulus (such as nasal breathing during moderate-intensity aerobic exercise) is removed. The goal is to expose individuals to transient conditions where the decline in PaO_2 will stimulate the upregulation of the HIF proteins that could provide unique exercise adaptations that cannot be achieved under normoxic conditions (homeostatic PaO_2) [74,81]. On the other hand, regarding the degree of severity, the implications of reducing PaO_2 differ based on the extent to which the PaO_2 is reduced. For example, whether the term hypoxia or hypercapnia describes the decline in PaO_2, the severity can be categorized based on mild, moderate, or severe. For example, utilizing the saturation of peripheral oxygen (SpO_2) to assess oxygen availability/saturation, common thresholds include 100 – 95 %, 94 % - 90 %, 89 % - 85 %, and so forth [82]. The severity increases from no severity to high severity as the lower the SpO_2 value drops. Contrasted to PaO_2, a value of 90 % SpO_2, for example would represent on average a PaO_2 of 60 mmHg [83], which is slightly below the recommended range (75–100mmHg) for PaO_2 [84]. Conversely, if SpO_2 and PaO_2 decrease, then the $PaCO_2$ will increase above the normal range of 35–45mmHg [85,86]. In summary, if words such as mild, moderate, or severe are referenced to describe either PaO_2 or $PaCO_2$, the reference is being utilized to describe the severity of the condition (above or below normal expected values). In the context of this manuscript, the postulated benefits of hypercapnia are both described as being occurring/beneficial if the duration is transient and not chronic and the severity is nothing greater than moderate, with plausible benefits under mild severity as well.

Postulated benefits from aerobic exercise training using nasal breathing

Regular exercise will increase CBF if the common oronasal type of breathing is utilized. However, the argument towards utilizing nasal breathing during moderate-intensity aerobic exercise revolves around the likelihood of stimulating a hypercapnic condition that will provide a greater increment in CBF than oronasal breathing would. Considering cognitive function, increasing CBF can help maintain a healthy and functioning brain by promoting cerebrovascular angiogenesis [20,87–90]. From a total blood volume, an increased flow will increase the shear rate against cerebral arteries and stimulate the proliferation of endothelial cells [91,92]. In diseases characterized by neurodegeneration, a major feature is a damaged endothelial wall that disrupts the integrity of the blood-brain barrier (BBB) [93,94]. As a countermeasure, stimulating endothelial cell proliferation can help prevent an excess infiltration of molecules, such as pro-inflammatory cytokines, that should not actively cross into the brain because they can promote neurodegeneration and the disruption of the BBB. In addition, the overarching rationale to stimulate cerebrovascular angiogenesis is to increase tissue perfusion that will provide neurons and glial cells with the necessary environment to proliferate and adapt [95]. It is important to denote that chronic hypercapnia is not good for cells, but exposure to transient insults is a promising therapeutic approach because it provides a temporary stimulus that does not cause a toxic, harmful environment for cells [68,96]. Therefore, periodic nasal breathing during moderate-intensity aerobic exercise holds the potential to provide transient hypercapnic insults that, in theory, result in greater cerebrovascular adaptations and may be a more effective approach to promote cognitive improvements than if oronasal breathing is utilized. That is why the postulated framework of nasal breathing during exercise is warranted to be further studied via well-controlled studies.

Another consideration is that nasal breathing during exercise allows for greater air filtration and equalizes the air to body temperature, providing the lungs with cleaner air that can reduce the risk of infections [97–100]. In addition, trained athletes who receive additional training to use nasal breathing are reported to become capable of exerting themselves and achieving a similar respiratory (VO_2) training adaptation as someone breathing via the oral or oronasal route [11,53,101–104]. Adaptations to nasal breathing could also be explored as an avenue to help individuals with obstructive sleep-disordered breathing (SDB). SDB is characterized by the inability to inhale via the nasopharynx route, which deprives the brain and tissues of oxygen due to a lack of overall V_e while sleeping [105]. SDB is linked to a decline in cognitive function, a lack of restfulness, waking up tired, snoring during the night, headaches, and weight gain, among many other symptoms [105–111]. Common treatments for SDB include losing weight or, more acutely, using an external respirator known as continuous positive air pressure (CPAP) device that forcefully opens the nasopharynx while sleeping to improve the symptoms of SDB [112,113]. However, it is postulated that among preventative strategies towards SDB, exercising via nasal breathing may provide adaptations that could help improve conditions like SDB that greatly benefit from improvements in nasopharyngeal airflow [114–118].

Another potential benefit of promoting a hypercapnic condition during exercise revolves around the possibility of stimulating peripheral blood mononuclear cells (PBMCs). First, it must be distinguished that under conditions of neuroinflammation, such as Alzheimer's and Parkinson's disease, an increased infiltration of immune cells is linked to a greater permeability in the BBB and a decline in cognitive function [93,119–121]. Among the common pro-inflammatory mediators secreted by PBMCs, such as interleukin-6 and tumor necrosis factor alpha, the ability to also secrete monocyte chemoattractant protein-1 possess a direct link to the disruption of the BBB integrity [93,122]. Acknowledging that PBMCs might have a pervasive effect influencing neuroinflammation, recent evidence has demonstrated that PBMCs can be conditioned to change their phenotype [123–125]. Specifically, their action can be conditioned to hold an anti-inflammatory phenotype that is characterized by an upregulation in the secretion of growth factors that stimulate tissue repair and cellular proliferation. This was shown in-vitro where PBMCs cultured under hypoxic, rather than normoxic conditions became highly expressive of two main growth factors compared to the normoxic PBMCs. Specifically, hypoxia-conditioned PBMCs upregulated vascular endothelial growth factor and transforming growth factor-beta [126,127]. Because of their upregulated growth-factor secretion, it is stipulated that they can cross the BBB [126] and have an angiogenic stimulatory role that will have benefits related to increased neuronal and glial cell activity. While there is also some evidence indicating that PBMC conditioning during exercise is possible [124,128,129], more research is warranted to fully determine if it is plausible to condition the phenotype of PBMCs via exposure to transient exercise-induced hypercapnia, such as postulated to be induced via nasal breathing under moderate-intensity aerobic exercise.

Lastly, another important factor to be mentioned revolves around body composition, where exposure to transient hypercapnia may provide potential benefits not seen during normoxic conditions. Specifically, moderate-intensity aerobic exercise programs that utilized intermittent hypoxia for 8 to 12 weeks with 3 sessions per week demonstrated a significant reduction in body fat percentage in

overweight/obese male and female participants compared to their normoxic training counterparts [130,131]. Additional benefits reported to be significantly greater during hypoxic aerobic exercise training in relation to body composition included increased insulin sensitivity, skeletal muscle and bone mass preservation, increased aerobic capacity, improved vascular health, lower blood pressure, reduced cholesterol, reduced appetite, and improved mood [132–140]. Altogether, a compelling body of evidence suggests that engaging in moderate-intensity aerobic exercise while using nasal breathing may provide greater benefits than seen during oral or oronasal breathing. The benefits include but are not limited to an increased CBF, improved nasopharyngeal airflow, greater anti-inflammatory activity, and healthier body composition. However, caution should be taken, as better understanding is needed regarding which populations might benefit from this training method the most, what the possible contraindications for its application could be, and what are the underlying mechanistic adaptations that occur both acutely and after a long-term intervention.

Assessment of cerebral blood flow during aerobic exercise

When examining the effect that exercise has on increasing CBF, utilizing an objective method that can rapidly assess changes in CBF is of uttermost importance because CBF is continuously changing. Unless measured while someone is exercising, it is impossible to estimate how much CBF increased during an exercise bout. This is under the context that the goal is to identify a type of exercise intervention that is capable of increasing CBF as much as possible. For example, in the early times of CBF assessment, a common method to estimate CBF was utilizing the Fick principle based on the rate of disappearance of inert nitric oxide tracers [141], but a limitation was that it lacked specificity in outlining the regional CBF and that it relied on the assumption of a symmetrical venous outflow which proved to be inconsistent [142,143]. Additionally, the utilization of magnetic resonance imaging would provide an accurate representation of regional CBF but would require individuals to be motionless, making it unusable for exercise. In contrast, functional near-infrared spectrometry devices (fNIRs) are becoming more popular and effective for the assessment of CBF. However, there are some limitations to fNIRs usage during exercise due to their sensitivity to excess noise caused by the artifact's motion and potential signal interference produced by bright environments or excess hair. In addition, the infrared light used by fNIRs cannot penetrate deep into the skull; therefore, it only represents cortical CBF [144]. A brief overview of the strengths and weaknesses of these methods is presented in Table 1.

An alternative approach to measure CBF during exercise would be to utilize ultrasound sonography. Anatomically, CBF originates from the aortic arch. Located on the right side of the neck, the innominate, also known as the brachiocephalic artery, is the first branch of the aorta. The brachiocephalic artery separates into the subclavian and the common carotid artery (CCA). Stemming from the right subclavian artery is the right vertebral artery which delivers blood to the brain. The subclavian artery extends to the arm as it becomes the axillary artery. Both CCA and vertebral arteries provide the blood supply to the brain. The same applies to the left side of the neck, except that the left side has no brachiocephalic branch, and instead, the left CCA is deeper because it arises directly from the aortic arch [145]. However, to be specific, the CCA bifurcates into both external (ECA) and internal (ICA) carotid arteries, where the ECA provides blood supply to the surface regions of the head while the ICA penetrates deeper and provides blood directly to the brain [146]. Between the vertebral arteries and the ICAs, the brain receives all its required blood supply. During exercise, assessing the ICAs is easier to visualize (most superficial) compared to the vertebral arteries (Fig. 2A), providing an ideal window that can be accessed anteriorly or laterally at the C3-C5 vertebral level to assess CBF via ultrasound sonography.

The benefits of utilizing ultrasound sonography during exercise to assess CBF in the ICA revolve around the ability to attain clear, immediate, direct, and accurate images that permit the assessment of CBF at different exercise intensities. While low frequencies (2–5 MHz) permit the assessment of deep anatomical structures, a higher frequency (10–13 MHz) is recommended for assessing the ICA. Utilizing B-mode paired with color doppler and pulse wave doppler imaging makes it possible to assess the ICA to estimate CBF during low to maximal aerobic efforts if special considerations are accounted for. For example, the color doppler box must be positioned as close as possible to the ICA, in alignment with the vessel wall ~2 cm distal to the origin of the ICA (after the CCA bifurcation) to avoid turbulent blood flow. It is recommended that the size of the box is reduced to prevent excess frames that would freeze/lag the image during movement, as during exercise. Furthermore, the maximal Doppler shift (v = max) occurs at a 0° angle when the ultrasound beam is parallel to the flow of the blood vessel, meaning that it is recommended to maintain a 60° pulse wave doppler angle to get an accurate estimate of blood flow. The assessment of both ICA and ECA via ultrasound sonography during exercise is illustrated in Fig. 2B. Noteworthy, only two critical components of ultrasound sonography imaging have been highlighted in this review, but there is an in-depth review by Revzin et al. that outlines thorough considerations on how to optimize the collection of images [147].

Table 1
Overview of common methods utilized to quantify cerebral blood flow.

Method	Safety	Strengths	Limitations
Fick Principle	Non-invasive and requires no radiation	Representation of CBF in relation to the metabolic demand for oxygen	The non-symmetrical venous outflow reduces the accuracy of the prediction
Magnetic Resonance	Non-invasive and requires radiation	The high spatial resolution of regional CBF	Requires individuals to be motionless, therefore, cannot be employed during exercise
Functional Near-infrared Spectrometer	Non-invasive and requires no radiation	Portable continuous monitoring of localized perfusion based on the positioning of electrodes/quantity of channels	Represents cortical perfusion based on hemoglobin saturation that can also be affected by excess environmental noise, such as light
Ultrasound Sonography	Non-invasive and requires no radiation	Direct measurement of CBF based on flow velocities that are analogous to blood volume	Not portable and requires a high degree of expertise to be utilized and correctly interpret the measured flow velocities during exercise

CBF = cerebral blood flow.

Future recommendations

Overall, there is strong foundational work elucidating that exposure to transient hypercapnia induced via moderate-intensity aerobic exercise using nasal breathing might be an avenue to promote a wide array of health benefits. However, a greater understanding of the impact that using nasal breathing has on overall health will increase the applicability of this exercise modality to make the benefits of transient hypercapnia more accessible. Alongside this, there is great interest in further examining the post-intervention changes following a nasal breathing aerobic exercise intervention on sleep quality and PBMCs. Suppose this modality of training does induce a transient hypercapnic exposure. In that case, it is plausible that after an intervention, individuals who underwent the nasal breathing condition will have improved sleep quality and a phenotype change within their PBMCs that indicates an immune-specific adaptation to the training. It is also necessary to examine the resultant weight loss to determine if body fat percentage and cardiometabolic markers improve after an aerobic exercise intervention

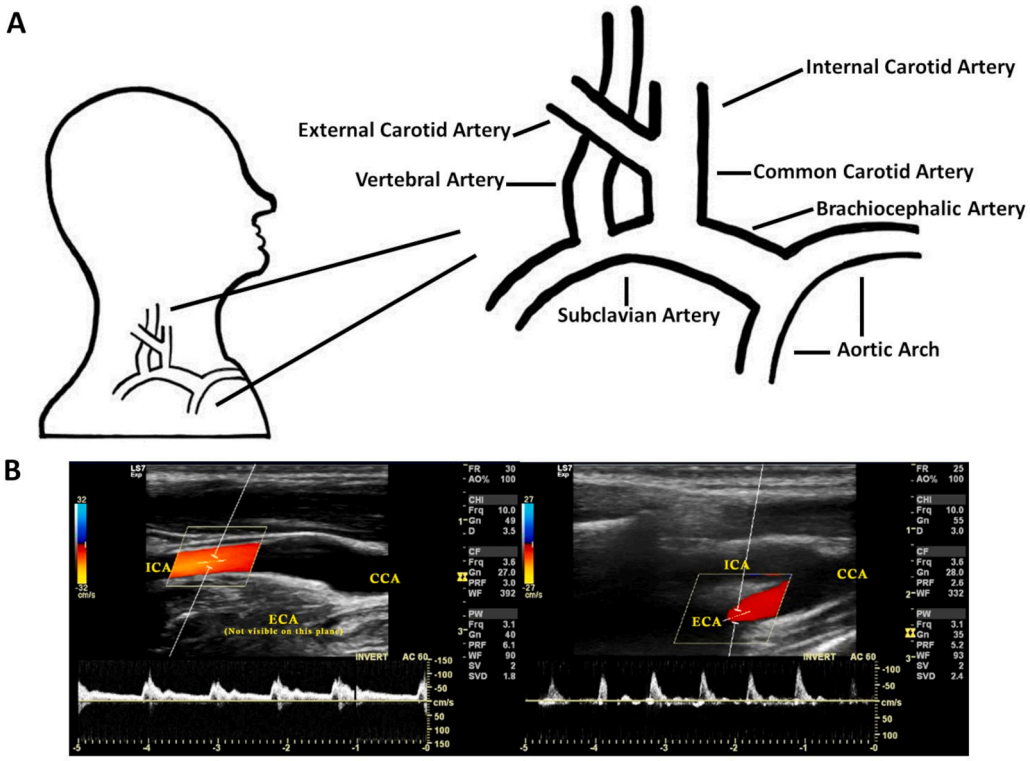

Fig. 2. Representation of the superior arterial branching stemming from the aortic arch that supplies blood to the head (A). Representation of the commonly assessed arteries during exercise to assess cerebral blood flow (B). Common carotid artery = CCA; External carotid artery = ECA; Internal carotid artery = ICA.

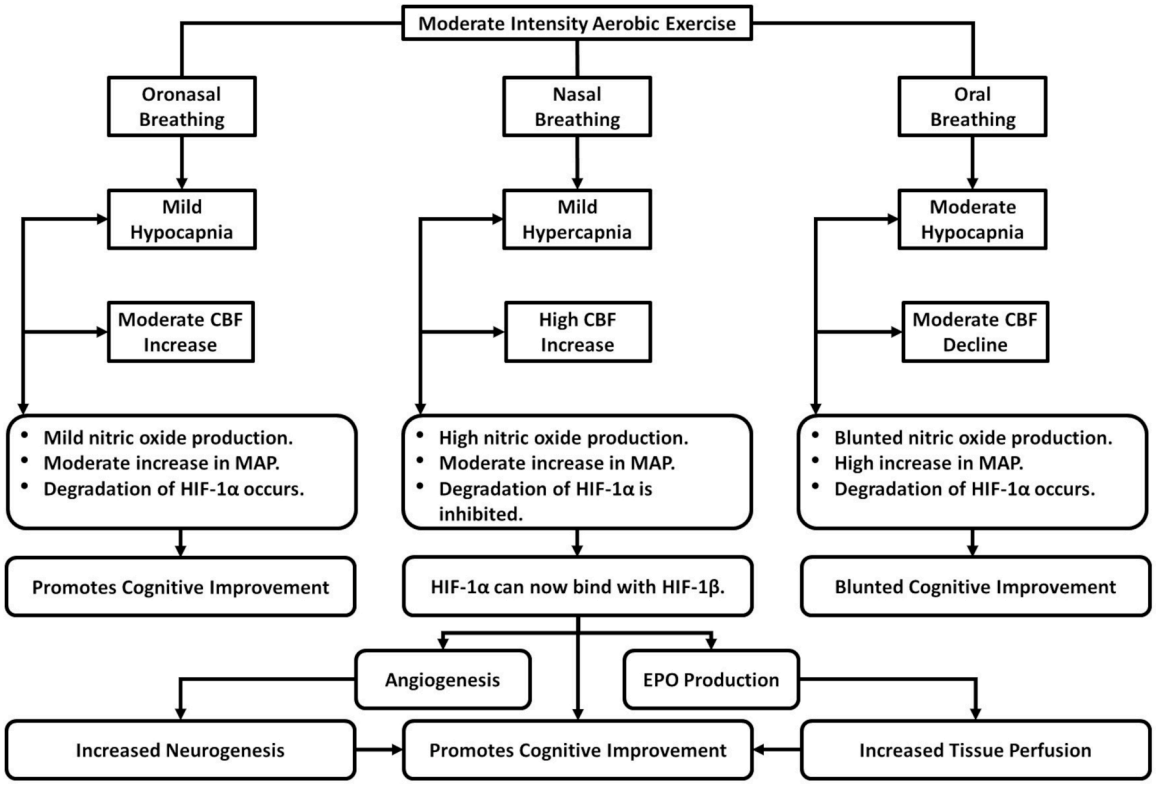

Fig. 3. Overview of the postulated benefits achieved during moderate-intensity aerobic exercise based on the breathing pattern utilized. The order of impact is described from low to high impact on a given variable, where: low, mild, moderate, and high indicate the degree of change within the variable compared to the other breathing methods. For example, a box containing the description of "low" indicates that the given breathing pattern compared to the other two elicits a reduction to the variable of interest. Cerebral blood flow = CBF; Mean arterial pressure = MAP; Hypoxia-inducible factor 1-alpha/beta = HIF-1α/β; Erythropoietin = EPO.

that employs nasal breathing. Within the scope of this review, nasal breathing may serve as an avenue to maximize the ability to increase CBF during exercise. The overarching goal is to increase CBF to prevent cognitive decline in individuals at risk of dementia. However, a great degree of work is needed before making conclusive recommendations. Although the theory supports the utilization of nasal breathing (Fig. 3), more research will permit to understand its applicability, safety, and expected adaptations after acute and long-term aerobic exercise interventions, where special interest should be given to moderate-intensity aerobic exercise due to its ability to stimulate a maximal CBF during exercise.

Conclusions

The utilization of nasal breathing during moderate-intensity aerobic exercise is a promising approach to elicit a transient hypercapnic condition that provides greater increments in CBF than during normoxic conditions. The benefit of stimulating a transient hypercapnic condition is to stimulate adaptations attributed to periods of hypoxia, such as angiogenesis, that can bolster the maintenance and improvements in cognition over time. Moreover, a greater emphasis is warranted on assessing biomarkers that are upregulated under hypoxic conditions to disseminate the extent to which utilizing nasal breathing during a moderate-intensity aerobic exercise bout can upregulate angiogenic growth factors. This will permit to expand from the applied perspective, such as identifying increments in CBF while utilizing nasal breathing, to a mechanistic aspect by examining the interaction and adaptations at a cellular level. Albeit not all-inclusive, a suggested target is to examine how PBMCs are conditioned under episodes of transient hypercapnia, as the former has shown to adapt to the latter and enhance their ability to withstand inflammatory stress by upregulating their transmembrane expression of anti-inflammatory related surface receptors. All in all, nasal breathing is a novel approach to elicit a transient hypercapnic state during regular aerobic exercise with numerous beneficial adaptations and strengthening exercise performance benefits.

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Nothing to report.

Declaration of Competing Interest

Nothing to report.

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