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RESEARCH ARTICLE

Intermittent hypoxia training improves cerebral blood flow without cognitive impairment

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Abstract

Objective: Brief exposure to intermittent hypoxia has been shown to potentially induce protective effects in the body. Animal studies suggest that intermittent hypoxia could increase cerebral blood flow and confer resistance to subsequent hypoxic–ischemic injury, yet clinical investigations are limited. This study aimed to evaluate the impact of a moderate short-term intermittent hypoxia protocol on cerebral blood flow and cognitive performance. **Methods**: Subjects who met the inclusion criteria were recruited to this study and randomized into the intermittent hypoxia group or the control group, which receives intermittent hypoxia training and sham-intermittent hypoxia training, respectively. Cerebral hemodynamics, cognitive performance, cerebral perfusion pressure, and oxygen saturation were assessed before and after the intervention. **Results**: A total of 100 healthy participants were included in this study. Compared to the control group, the intermittent hypoxia group exhibited higher peak systolic blood flow velocity (108.64 ± 22.53 vs. 100.21 ± 19.06, $p = 0.049$) and cerebrovascular conduction index (0.74 ± 0.17 vs. 0.66 ± 0.21, $p = 0.027$), and lower cerebrovascular resistance index (1.41 ± 0.29 vs. 1.54 ± 0.36, $p = 0.044$) following intermittent hypoxia training. Additionally, within-group comparisons revealed that intermittent hypoxia training led to increased cerebral blood flow velocity, elevated cerebrovascular conductance index, and decreased cerebrovascular resistance index ($p < 0.05$). Other indicators including cognitive function, cerebral perfusion pressure, and oxygen saturation did not exhibit significant differences between groups. **Interpretation**: These findings revealed that intermittent hypoxia may represent a safe and effective strategy for improving cerebral blood flow.

Introduction

As the most oxygen-dependent organ, the brain accounts for 20% of resting oxygen consumption in humans, making it exquisitely vulnerable to hypoxia.[1] Long-term chronic exposure or extremely low oxygen concentration might cause dangerous cardiovascular and metabolic consequences.[2] Exposure to either sustained environmental hypoxia as occurs upon ascent to high altitude, or intermittent episodes of systemic hypoxia, such as obstructive sleep apneas (OSA), can trigger multiple damaging processes of the central nervous system (CNS). These processes include the activation of cerebral and systemic inflammation, which is part of the body's immune response to injury but can cause further damage if unchecked. Additionally, hypoxia can activate caspase-mediated neuronal apoptosis, reactive oxygen species (ROS) and nitric oxide (NO) over production, damaging cellular components and contributing to neuronal injury.[3,4] Furthermore, OSA aggravates infarcts and actives tau phosphorylation and mitochondrial permeability transition and is a crucial event in the pathogenesis of cognitive impairment.[5,6]

However, administration of relatively mild hypoxia for shorter periods can produce beneficial and protective effects on physiological function.[7] This approach, often referred to as intermittent hypoxia (IH) training, involves exposure to cycles of low oxygen levels interspersed with normoxic or hyperoxic gas mixtures. The parameters of intermittent hypoxia protocols currently used vary greatly, and the outcomes of IH largely depend on these key determinants, including hypoxic intensity, duration of a single episode of hypoxia, intra-session and inter-session frequency, and the duration of the training carried out, which are collectively called hypoxia "dose".[8] Animal studies have investigated its role in enhancing cerebral blood flow (CBF) and resisting subsequent hypoxic–ischemic brain damage,[9,10] which indicates that IH has the potential to make the brain more resilient to severe hypoxic conditions by activating adaptive physiological responses.

Thus, intermittent hypoxia is believed to elicit adaptive responses without causing pathological injuries when carefully regulated.[11] Despite promising results in animal models, studies on the effects of IH in humans remain understudied. This study aimed to evaluate the effects of a moderated short-term IH regime as previously described[12] on CBF and cognitive performance in healthy participants to determine the efficacy and safety.

Materials and Methods

Participants

Healthy volunteers aged between 18 and 45 years were recruited for the study from March 1, 2023, to September 1, 2023. They underwent clinical assessments before enrollment, including standardized history-taking and neurological examinations, to screen for eligibility based on inclusion criteria. Eligible participants were low-land volunteers with a body mass index (BMI) between 19 and 24.9 kg/m^2. Additional criteria for participants included a resting peripheral oxygen saturation (SpO_2) $\geq$ 90%, cerebral tissue oxygen saturation (ScO_2) between 58% and 82%, heart rate (HR) between 60 and 100 beats per minute, and blood pressure (BP) within the normal range (90–130/60–80 mmHg) as determined during pretrial screening. Individuals who undergo menstrual periods, pregnancy, lactation, current smoking or history of smoking within the past 2 years, alcohol or drug abuse, and long-living at altitudes above 1200 meters as well as high-altitude exposure in the last 6 months were excluded. Participants were asked to abstain from caffeinated beverages, alcohol, and strenuous exercise throughout this study to minimize the confounding effects. Prior to the participation, they were informed about potential risks that might be involved in this procedure and provided written informed consent. This study was performed according to ethics committee approval and was registered on the site ClinialTrials.gov (NCT05733338).

Study overview

A double-blind randomized controlled trial was conducted. Eligible subjects were randomly assigned to the IH group or the control group according to a computer-generated random number table. Participants in the IH group were assigned to receive intermittent hypoxia training, which consisted of four 10-min cycles at the fraction of inspired oxygen (FiO_2) of 13% interspersed with 5-min normoxic cycles. They had two sessions per day, separated by intervals of at least 6 h, for 5 days. The cumulative hypoxic time for each participant was 40 min for a single session, totaling 400 min across the trial. Participants in the control group received the sham-IH training (normoxia), which involved normobaric normoxia (FiO_2 = 21%) for 55 min under the same session schedule (Fig. 1). The trial was conducted in an environmentally controlled laboratory with a constant ambient temperature of 22°C.

Neither the participants nor the investigators conducting the outcomes measurements were aware of the trial-group assignments throughout the trial. The primary outcome was the change in cerebral hemodynamic index mean blood flow velocity (MFV). The secondary outcomes include changes in other cerebral hemodynamics, cognitive performance, cerebral perfusion pressure (CPP), mean arterial pressure (MAP), and ScO_2 of participants. Safety endpoints included the occurrence of conditions that met the termination criteria or severe and intolerable discomfort associated with hypoxia, collectively referred to as adverse events in this study.

Measurements

At baseline, all participants had standard assessments of their demographic characteristics and medical history. They also completed evaluations of cerebral hemodynamics, cognitive performance, cerebral perfusion pressure, and cerebral tissue oxygen saturation. Following IH training, all participants underwent the same set of evaluations as at baseline.

Cerebral hemodynamics evaluation

Transcranial Doppler (TCD) ultrasonography, as a noninvasive and relatively inexpensive tool, can accurately assess the hemodynamics of the brain and provide information on cerebrovascular function.[13,14] Therefore,

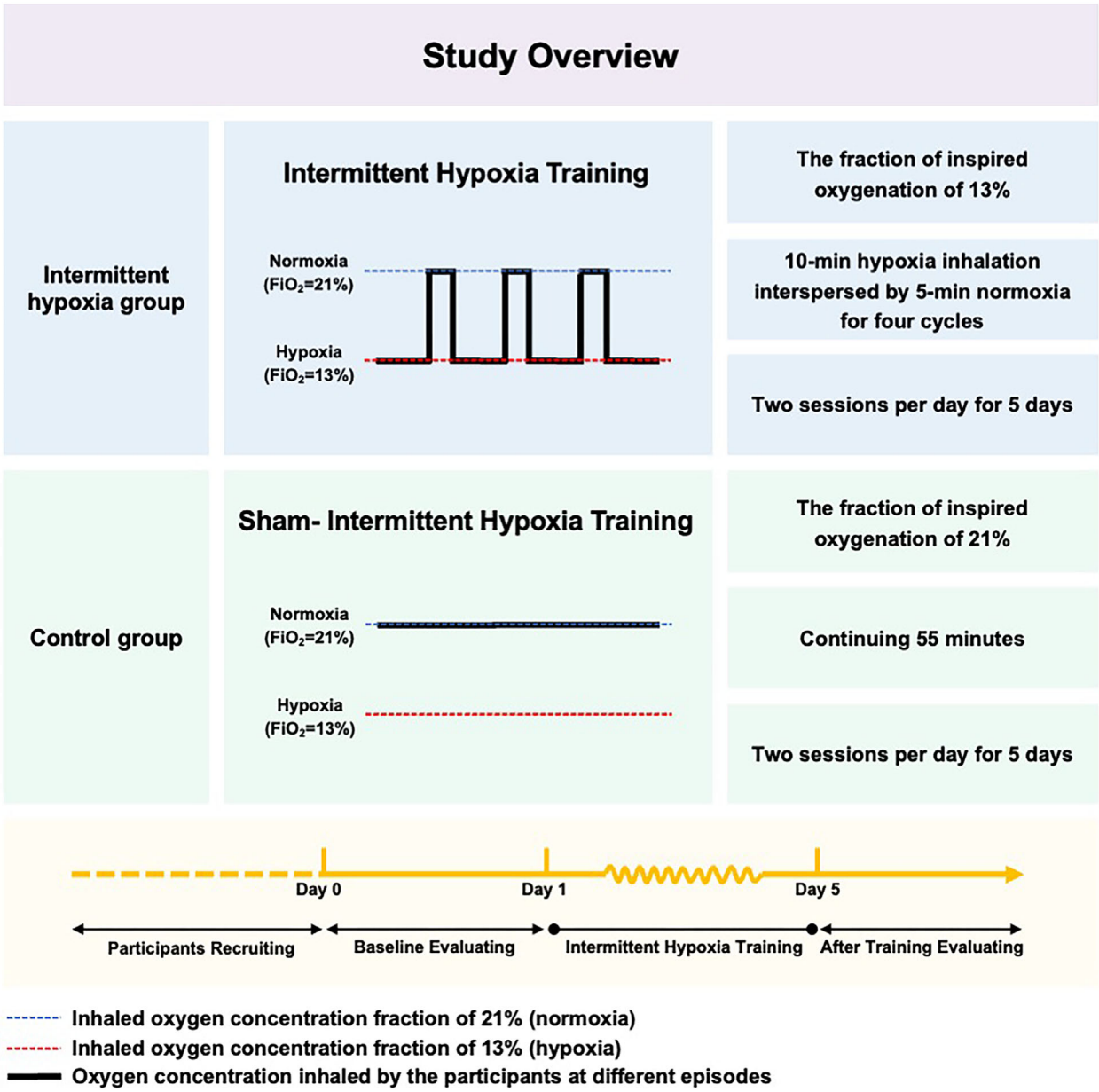

Figure 1. Overview of different training modalities and timeline of this study. Blue dashed line: inhaled oxygen concentration fraction of 21% (normoxia). Red dashed line: inhaled oxygen concentration fraction of 13% (hypoxia). Horizontal black line: oxygen concentration inhaled by the participants at different episodes.

hemodynamic changes were evaluated using TCD in this study. The peak systolic, mean, and end diastolic blood flow velocities at the most proximal segment of the right middle cerebral artery (MCA) (M1 proximal segment for MCA, at 50–60 mm depth) were measured through the temporal windows with a 2 MHz hand-held transducer (HI VISION Ascendus, Hitachi, Ltd., Japan) by an experienced sonographer. The pulsatility index (PI) was calculated according to the formula [peak systolic blood flow velocity (PSV) − end diastolic blood flow velocity (EDV)]/MFV, and the Pourcelot resistivity index (RI) was calculated as (PSV-EDV)/PSV[15]. To minimize the effect of blood pressure on these indicators, cerebrovascular conductance index (CVCi) and cerebrovascular resistance index (CVRi) were calculated as MFV/MAP and reciprocal of CVCi, respectively.[16]

Cognitive performance

Three different neurocognitive tests were performed on a portable computer with BrainFit (Beijing CAS-Ruiyi Information Technology Co., Ltd.). The Digit Span Test (DST) evaluated the working memory and attention. The task required participants to repeat a series of digits of increasing length forwardly (DST) or reversely (DSTR). Each span level had two trials, and the trial ended when the participants erred two consecutive times at a given level. The longest digit span of correct recalls across the task was the final score.[17] The Stroop Color-Word Test (SCWT) Stage 3 was used to assess selective attention, inhibitory control, and speed of mental processing. The participants were required to name color Chinese characters displayed in incongruous colors, such as determining the color of the Chinese character red written in blue ink. The number of correct responses made in 60 sec was recorded as the score.[18] The Trail Making Test (TMT) provided information about processing speed, cognitive flexibility, and executive functioning. It consists of two parts, TMT-A (consecutive numbers) and TMT-B (consecutive order of alternating numbers and letters), which were scored by how long it took to complete the test.[19] All these assessments were taken in a quiet room with only the participants and one investigator present. Low values of DST and SCWT, and high scores of TMT indicated poor cognitive performance.

Cerebral perfusion pressure and mean arterial pressure

A noninvasive intracranial pressure detection analyzer (JYH_ICP_1B_D, Chongqing Zhongli Medical Equipment Co., Ltd., Chongqing, China) was used to assess intracranial pressure (ICP). Arterial blood pressure, including systolic blood pressure (SBP) and diastolic blood pressure (DBP), was noninvasively measured in the radial artery at the level of the heart with monitor apparatus (ePM12, Shenzhen Mindray Bio-Medical Electronics Co., Ltd., Shenzhen, China). MAP was estimated according to the formula: 1/3SBP + 2/3DBP, and CPP was calculated based on the formula MAP-ICP[20].

Cerebral tissue oxygen saturation

Near-infrared spectroscopy (NIRS) is a widely used, noninvasive, and reliable method for measuring regional cerebral oxygen saturation.[21] The regional ScO_2 in the frontal cortex was determined by analyzing specific absorbance patterns of oxygenated and deoxygenated hemoglobin with near-infrared light. The prefrontal cortex ScO_2 of participants was noninvasively monitored using NIRS with a sensor (WORTH, Casibrain Technology Co., Ltd., Beijing, China). Measures of ScO_2 were conducted with participants in a seated position after at least 5 min of rest.

Termination criteria

Termination criteria included SpO_2 of 80% or lower; BP equal to or greater than 160/100 mmHg; HR greater than 100 beats per minute or an increase of 10% or more from the baseline; any ECG signs of myocardial ischemia or malignant arrhythmia; respiration rate greater than 40 breaths/min; or participant-reported unbearable discomfort, such as shortness of breath, dizziness, or headache. If any of these conditions were observed or other adverse reactions occurred, the hypoxic intervention was terminated immediately. Participants were instructed to breath ambient air, with supplemental oxygen (2 L/min) provided if necessary. Participants were permitted to leave once indicators returned to normal or symptoms improved significantly.

Statistical analysis

The sample size calculation involved setting the significance level of $\alpha = 0.05$ and a power $(1 - \beta)$ of 0.90. A 1:1 sample size ratio between the treatment to control was used $(k = 1)$. The allowable difference between groups was set at 0%, with a standard deviation (SD) of 10% assumed for this study. And a 6% change in CBF was considered as the clinically meaningful difference in view of the existing literature about nonpharmacological strategies for CBF.[22–24] To account for an estimated 5% dropout rate, a sample size of 50 participants per group was determined. The data were presented as mean ± SD. Comparisons between the two groups were made using Student's *t*-tests (normal distribution) or the Mann–Whitney U tests (non-normal distribution). The paired *t*-tests were used to compare the differences between before and after training within groups. Repeated-measures analysis of variance was performed on the complete outcome data to account for potential errors introduced by within-group repeated measurements across multiple parameters. The statistical significance level was set at $p < 0.05$. Statistical analyses were conducted using SPSS software (version 26.0).

Results

This study included 100 healthy participants, 50 in the IH group and 50 in the other. The 5-day training program

was well tolerated by all participants, and no adverse events as described above were reported. Demographic characteristics including gender, age, body mass index, and heart rate between the two groups were of no significant difference (Table 1).

Effects of IH on cerebral hemodynamics

There was no significant difference in PSV, EDV, MFV, PI, RI, CVCi, and CVRi between the two groups at baseline (Table 2). After the 5-day IH training, the IH group exhibited higher values of PSV than the control group (108.64 ± 22.53 vs. 100.21 ± 19.06, $p = 0.049$). Additionally, values of CVCi in the IH group were significantly higher and CVRi were lower than that in the control group (0.74 ± 0.17 vs. 0.66 ± 0.21, $p = 0.027$; 1.41 ± 0.29 vs. 1.54 ± 0.36, $p = 0.044$; respectively). Within-group analysis revealed that compared with to baseline, the values of PSV, MFV, and CVCi in the IH group were significantly higher, while the CVRi value was significantly lower ($p < 0.05$) (Fig. 2). Additionally, there were statistically significant differences in the changes in parameters of PSV, EDV, MFV, and CVCi before and after training between the two groups ($p < 0.05$) (Fig. 3).

Table 1. Demographic characteristics.

	IH group	Control group	*p*
Age (years, mean ± SD)	35.56 ± 6.70	35.36 ± 5.64	0.872
Male-to-female ratio	25:25	26:24	0.841
Body mass index (kg/m^2, mean ± SD)	23.84 ± 3.23	23.95 ± 3.16	0.854
Heart rate (beats per minute, mean ± SD)	82.02 ± 11.22	77.74 ± 10.88	0.056
Mean arterial pressure (mmHg, mean ± SD)	93.59 ± 8.89	96.29 ± 9.99	0.158
Cerebral tissue oxygen saturation (%, mean ± SD)	66.80 ± 2.56	67.18 ± 2.97	0.494

IH, intermittent hypoxia; SD, standard deviation.

Effects of IH on cognitive performance

Scores of DST, DSTR, TMT, and SCWT showed no differences between the two groups at baseline and post-training ($p > 0.05$) (Table 3). Compared with the baseline, both IH training and the sham-IH training did not decrease the participants' cognitive performance ($p > 0.05$).

Effects of IH on cerebral perfusion pressure and mean arterial pressure

At baseline, there were no significant differences in CPP and MAP between the two groups (CPP: 83.52 ± 9.07 vs. 87.04 ± 10.18, $p = 0.071$; MAP: 93.59 ± 8.89 vs. 96.29 ± 9.99, $p = 0.158$), with no differences were found after the training (CPP: 84.29 ± 11.41 vs. 85.33 ± 11.71,

Table 2. Cerebral blood flow velocity between groups at baseline and after the training.

Time points	Parameters	Values		*p*
		IH group	Control group	
Baseline	PSV (cm/s)	100.17 ± 14.29	100.79 ± 19.94	0.860
	EDV (cm/s)	44.77 ± 9.04	45.81 ± 10.55	0.599
	MFV (cm/s)	63.23 ± 9.73	64.14 ± 13.05	0.698
	PI	0.89 ± 0.18	0.87 ± 0.15	0.531
	RI	0.55 ± 0.08	0.54 ± 0.06	0.621
	CVCi (cm/s/mmHg)	0.68 ± 0.12	0.64 ± 0.20	0.271
	CVRi (mmHg/cm/s)	1.51 ± 0.26	1.56 ± 0.34	0.394
After Training	PSV (cm/s)	108.64 ± 22.53	100.21 ± 19.06	0.049*
	EDV (cm/s)	48.84 ± 13.74	45.13 ± 9.76	0.127
	MFV (cm/s)	68.77 ± 16.12	63.49 ± 12.06	0.070
	PI	0.88 ± 0.15	0.87 ± 0.16	0.795
	RI	0.55 ± 0.06	0.55 ± 0.07	0.798
	CVCi (cm/s/mmHg)	0.74 ± 0.17	0.66 ± 0.21	0.027*
	CVRi (mmHg/cm/s)	1.41 ± 0.29	1.54 ± 0.36	0.044*

Data were presented as mean ± standard deviation.
CVCi, cerebrovascular conductance index; CVRi, cerebrovascular resistance index; EDV, end diastolic velocity; IH, intermittent hypoxia; MFV, mean flow velocity; PI, pulsatility index; PSV, peak systolic velocity; RI, Pourcelot resistivity index.
*$p < 0.05$.

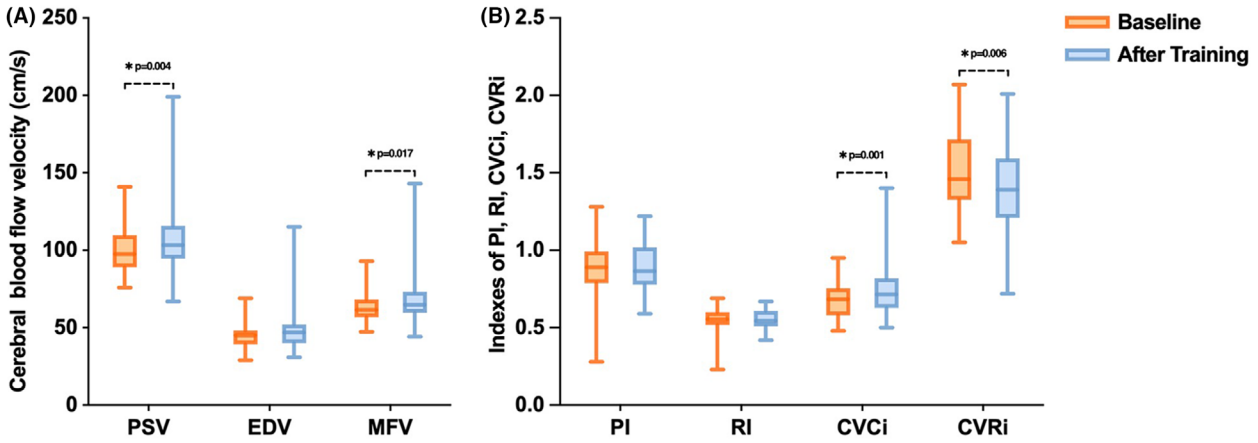

Figure 2. Indicators of cerebral hemodynamics between baseline and after the training within the IH group (A: cerebral blood flow velocity, B: indexes of PI, RI, CVCi, CVRi). CVCi, cerebrovascular conductance index; CVRi, cerebrovascular resistance index; EDV, end diastolic velocity; MFV, mean flow velocity; PI, pulsatility index; PSV, peak systolic velocity; RI, Pourcelot resistivity index. Error bars represent min to max. *$p < 0.05$ (Repeated-measures analysis of variance).

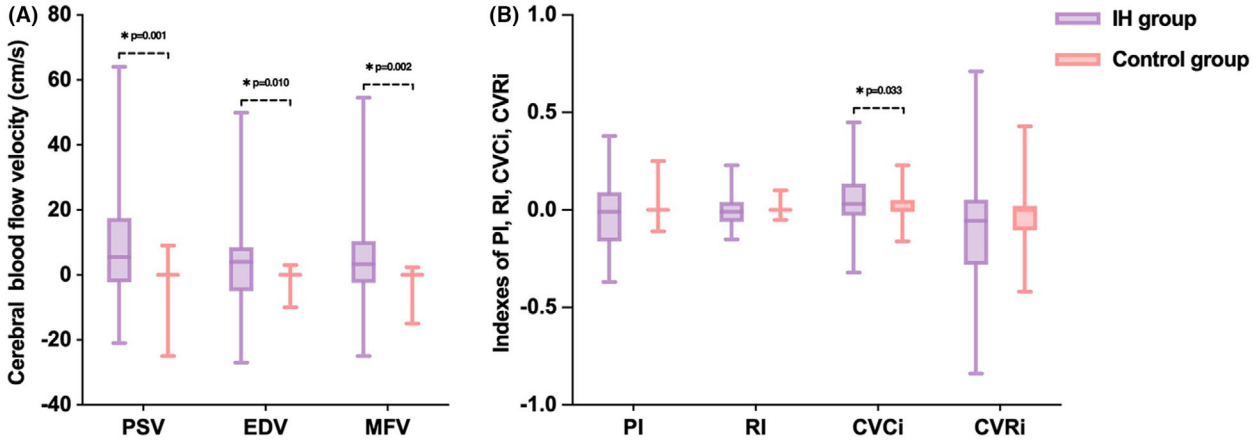

Figure 3. Changes in indicators of cerebral hemodynamics from baseline to after training between groups (A: cerebral blood flow velocity, B: indexes of PI, RI, CVCi, CVRi). CVCi, cerebrovascular conductance index; CVRi, cerebrovascular resistance index; EDV, end diastolic velocity; IH, intermittent hypoxia; MFV, mean flow velocity; PI, pulsatility index; PSV, peak systolic velocity; RI, Pourcelot resistivity index. Error bars represent min to max. *$p < 0.05$ (Student's *t*-tests or Mann–Whitney *U* tests).

$p = 0.656$; MAP: 93.32 ± 11.04 vs. 94.10 ± 11.49, $p = 0.730$) (Fig. 4). It was found that IH training did not lead to obvious fluctuations in MAP and CPP values ($p > 0.05$).

Effects of IH on cerebral tissue oxygen saturation

The ScO_2 values for the IH group and control group at baseline were 66.80 ± 2.56 and 67.18 ± 2.97, respectively ($p = 0.494$), and there was no significant difference between groups after training (66.82 ± 2.64 vs. 66.96 ± 3.10, $p = 0.808$).

Discussion

The main result of this study was that intermittent hypoxia training improves CBF as evidenced by increasing the cerebral blood flow velocity and cerebrovascular conduction index and decreasing cerebrovascular resistance index, without impairing the cognitive function and increasing the cerebral perfusion pressure.

The brain is one of the most metabolically active organs, which consumes 15–20% of the body's nutrients and energy supply in the resting state. Cerebral perfusion is the process of delivering blood to the brain tissue, which is determined by both CBF and the pressure

Table 3. Cognitive performance between groups at baseline and after the training.

Time points	Items	Scores		*p*
		IH group	Control group	
Baseline	DST	9.30 ± 2.14	9.08 ± 1.44	0.548
	DSTR	7.68 ± 2.00	7.26 ± 2.40	0.344
	SCWT	36.66 ± 6.88	36.36 ± 7.20	0.832
	TMT-A	24.03 ± 7.25	25.17 ± 9.11	0.493
	TMT-B	38.90 ± 21.78	34.30 ± 12.88	0.201
After training	DST	8.98 ± 1.52	9.06 ± 1.53	0.794
	DSTR	7.94 ± 1.77	7.54 ± 2.22	0.321
	SCWT	37.80 ± 7.12	39.50 ± 7.60	0.251
	TMT-A	22.62 ± 5.67	21.93 ± 6.37	0.571
	TMT-B	32.38 ± 9.42	29.81 ± 8.45	0.153

Data were presented as mean ± standard deviation.
DST, Digit Span Test; DSTR, Digit Span Test reverse; IH, intermittent hypoxia; SCWT, Stroop Color-Word Test; TMT-A, part A of Trail Making Test; TMT-B, part B of Trail Making Test.

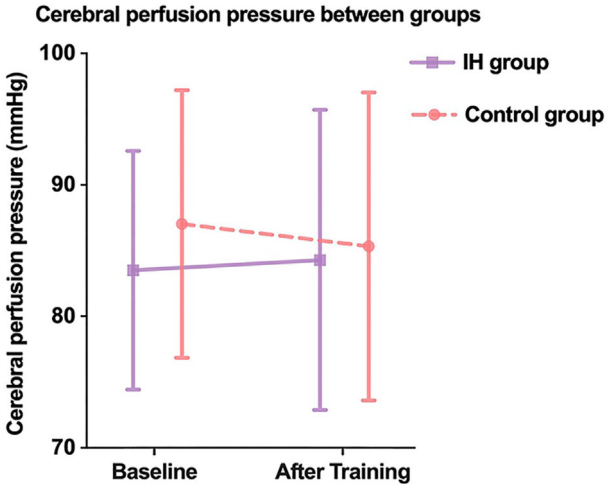

Figure 4. Cerebral perfusion pressure between groups at baseline and after training, IH: Intermittent hypoxia.

driving this flow, known as cerebral perfusion pressure. As the brain has no endogenous energy storage, it is dependent upon cerebral perfusion to constantly replenish oxygen and energy substrates and to remove waste products. Therefore, sufficient cerebral perfusion is essential for supporting normal brain function and navigating acute and chronic diseases.[25] As a paramount factor for maintaining cerebral perfusion, CBF should respond to changes in blood gas status and protect the brain from fluctuations of circulating arterial pressure.[26] It has been established that hypoxia is accompanied by an increase in CBF, which is probably due to the increase in blood flow velocity, the dilation of cerebral arterioles, and vascular angiogenesis. It is thought to be a compensatory mechanism serving to maintain oxygen supply in the presence of arterial hypoxemia.[27,28] However, obstructive sleep apnea, characterized by chronic intermittent hypoxia, is a risk factor for cardiovascular and cerebrovascular disease or neurodegenerative diseases.[29] Although patients with OSA may experience a short-term increase in cerebral blood flow velocity during sleep apnea (that is, chronic intermittent hypoxia), current research suggests that OSA may impair cerebral circulation by affecting resting cerebral blood flow and cerebral blood flow regulation. Increased sympathetic vasodilatory activity, reduced endothelial function, and increased arterial stiffness might be the underlying mechanisms.[30]

Paradoxically, if the parameters of intermittent hypoxia are controlled well, it can yield beneficial effects across multiple physiological systems.[31,32] Since different hypoxic "doses" exist, the outcomes of hypoxic exposure are influenced by a dose–response relationship, with varying degrees of hypoxia producing different effects. Accumulating evidence suggests that mild to moderate hypoxia (FiO_2 = 9–16%), short durations (3-10 min per episode), and 3–15 episodes per day generally result in positive effects without inducing pathology.[8,11] The IH protocol used in this study is based on these findings and previous studies. Furthermore, our group's prior animal study found that hypoxic "dose" with a 13% oxygen concentration can induce favorable neuroprotective effects, and the safety and feasiblity of the IH protocol used in this study (four cycles of 10-min hypoxia at 13%, separated by 5 min of normoxia) were validated in our previous pilot study.[9,12]

Therapeutic mild to moderate IH has shown significant advantages for its safety and ease of administration, which should not be confused with OSA modeling chronic IH. Patients with OSA experience recurrent apnea or hypoventilation due to upper airway obstruction during sleep, leading to chronic and pathological intermittent hypoxia, which is a known risk factor for systemic diseases, metabolic dysfunction, and cognitive impairment. In contrast, IH training of short-term, mild to moderate hypoxia can increase the resistance to hypoxic injury, which are being used as nonpharmacological strategy to manifest cardio and neuroprotection, improve metabolic status, and other pathological conditions. The protocols of OSA and IH training are substantially different. In this study, we aimed to evaluate the effectiveness of the identified IH protocol in enhancing cerebral blood flow in healthy subjects. To ensure safety, we monitored cognitive function, cerebral perfusion pressure, and cerebral oxygenation – parameters that are commonly impaired in patients with OSA.

TCD is a rapid, noninvasive, real-time method for measuring cerebrovascular function, and the measurement

of blood flow velocity by TCD has become an important tool for the assessment of CBF in humans.[33,34] Although CBF could be influenced by multiple factors such as vessel diameter and blood viscosity, studies have shown that the cerebral blood flow velocity of the MCA remains a reasonable index of CBF in different situations. In view of the increased blood flow velocity and unaltered CPP of the current study, we concluded that the intermittent hypoxia enhanced CBF without decreasing cerebral perfusion pressure. The mechanism by which intermittent hypoxia increases CBF involves several physiological responses. During hypoxia, the body initiates a series of adaptive processes to maintain adequate oxygen delivery to the brain, a process known as autoregulation. Intermittent hypoxia induces compensatory changes, including hypoxic cerebral vasodilation, to maintain adequate cerebral oxygen delivery. Research have shown that cyclic IH can enhance shear-mediated dilation of the internal carotid artery, which may also serve as an indicator of cerebrovascular endothelial function and cerebrovascular health. Additionally, periodic IH increases cerebral blood velocity, thereby improving oxygen delivery to the brain during hypoxic episodes. Our finding was in line with these previous studies.[35,36] In addition, animal studies also concluded that IH induces cerebral angiogenesis by activating the expression of hypoxia-inducible factor 1 and its target genes, this activation leads to increased levels of vascular endothelial growth factor, erythropoietin, and brain-derived neurotrophic factor.[9] While the increase in CBF observed in our study is a key outcome, it should not be assumed to be inherently positive or negative without considering the broader physiological context.

Cerebral blood flow might also be influenced by the changes in systemic arterial blood pressure of hypoxemia and/or hypercapnia during the training process.[37] Thus, additional information about changes in cerebrovascular function as measured by CVCi and CVRi was applied in this study, to eliminate the direct effects of changes in arterial blood pressure on CBF.[38,39] In addition, in contrast to cerebral hemodynamics, the use of CVCi and CVRi may better reflect the physiological process of vasomotor reactivity during hypoxemia and/or hypercapnia.[38] This study showed an unaltered MAP with enhanced cerebrovascular conductance, which was in accordance with previous studies.[35] These findings suggested that IH training resulted in increased cerebral blood flow as indicated by enhanced cerebrovascular conductance and reduced cerebrovascular resistance.

Since persistent or severe hypoxia may cause cognitive impairment, neurocognitive tests including DST, SCWT, and TMT were used to assess the safety of the IH protocol in the present study. These tests were used to evaluate different aspects of cognitive function, such as processing speed, executive function, and attention. And we found that there were no significant changes in cognitive function after intermittent hypoxia in healthy participants. As a result, the safety of the IH protocol is underscored by the absence of cognitive decline among these participants, which implies that IH can be applied without detrimental effects on cognitive health. However, previous studies have demonstrated that therapeutic IH could improve cognitive function in geriatrics and patients with mild cognitive impairment,[40–42] such results in the present study may be attributed to the fact that our participants were healthy volunteers, which may have a ceiling effect.

Cerebral perfusion pressure, the difference between MAP and ICP, represents the net pressure gradient that drives blood, oxygen, and nutrient delivery to the brain. Several sustained hypoxic conditions, such as high-altitude exposure and stroke, may lead to increased ICP, which in turn leads to a decreased CPP.[5,43] While current research indicates that noninvasive ICP monitoring does not yet achieved the accuracy and reliability needed to fully replace traditional invasive methods in clinical setting, it shows significant potential in research contexts. Its application in these settings offers a low-risk and cost-effective alternative, making it a valuable tool for exploratory studies and long-term monitoring, where the precision of invasive methods is not essential.[44] In this study, participants' CPP levels evaluated by noninvasive ICP detection analyzer did not fluctuate significantly before and after IH training, suggesting that this IH protocol used is safe in terms of maintaining stable CPP. This stability is crucial, as it indicates that the pressure gradient required to deliver essential nutrients and oxygen to the brain remains unaffected, ensuring continued cerebral health and function.[45]

Cerebral tissue oxygen saturation, a measure of hemoglobin saturation in mixed arterial, venous, and capillary blood in cerebral tissue, reflects integrated information about cerebral oxygen supply and consumption. Our present study found that values of ScO_2 remained stable after IH training, demonstrating well-maintained cerebral oxygen homeostasis of the balance between oxygen delivery to the brain and cerebral metabolic rate of oxygen, which further indicated that intermittent hypoxia is a safe modality to improve CBF.

Although the absolute differences in CBF observed in our study are modest, their clinical relevance should be considered within the context of specific disease states. For instance, in ischemic stroke, even a small increase in CBF can significantly impact patient outcomes.[46,47] Similarly, in conditions characterized by chronic cerebral hypoperfusion, such as vascular dementia and Alzheimer's disease, slight improvements in CBF have been associated

with enhanced cognitive performance and may contribute to slowing the progression of cognitive decline.[48] In view of these, intermittent hypoxia training exerts great therapeutic potential as a simple, noninvasive, and nonpharmacological intervention for certain clinical conditions.[11] It appears that IH might be applied to patients with ischemic cerebrovascular diseases to increase CBF and improve cerebrovascular function on the premise of safety. Nevertheless, the optimal IH protocol for safe and efficiently applying to patients in a clinical setting needs to be further investigated. And the clinically meaningful change in CBF for disease states need to be confirmed in future study.

There are several limitations in this study. Firstly, both the assessment indicators and study duration were limited. Blood flow velocity alone may not fully capture changes in cerebral blood flow during intermittent hypoxia training. And repeated cognitive assessment within a short timeframe might mask any actual decline in cognitive function, potentially affecting the study's outcomes. Future studies should employ more objective and comprehensive evaluation methods, such as perfusion magnetic resonance imaging for a better assessment of cerebral blood flow, and electrophysiological techniques to evaluate cognitive function.[49,50] Furthermore, extending the study duration will be necessary to assess the sustainability of the observed changes. Secondly, the mechanism of increased blood flow velocity was not further explored in this study and the study focused on healthy individuals. As a safe and promising way to improve cerebral blood flow, we intend to carry out in patients with cerebrovascular diseases in future studies. It is also important to note that the impact of intermittent hypoxia on CBF is complex and can vary depending on the specific conditions. Although the findings offer valuable insights, further research is needed to thoroughly understand the mechanisms underlying the effects of intermittent hypoxia on CBF.

In conclusion, this study demonstrated that this short-term IH protocol (13% hypoxia interspersed by normoxia for 5 min, 4 cycles per session, twice a day for 5 days) improved cerebral blood flow with increased blood flow velocity, increased cerebrovascular conductance, and decreased cerebrovascular resistance in healthy volunteers, without impairing cognitive function, cerebral perfusion pressure, and cerebral oxygenation. The efficacy of IH may be influenced by various factors including hypoxic intensity, frequency, cycle, and duration, while the IH strategy that induces the optimal protective effect has not yet been identified. It was shown that this IH protocol is a safe and effective intervention for enhancing cerebral blood flow, suggesting that IH could potentially serve as a nonpharmacological strategy to optimize cerebral vascular function in the elderly and in patients with cerebrovascular disease.

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Conflict of Interest

The authors declared no conflicts of interest regarding the research, authorship, and/or publication of this article.

Author Contributions

XJ and YW: Supervision, Conception and design, Acquisition of data, Analysis and interpretation of data, Drafting, Review and editing the article. QZ and QW: Conception and design, Acquisition of data, Analysis and interpretation of data, Drafting, Review and editing the article. FJ and DH: Conception and design, Acquisition of data, Drafting, Editing the article.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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