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Effects of Normobaric Intermittent Hypoxia at Moderate Hypoxia Level on Physiological Responses in Healthy Subjects: A Pilot Study

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Purpose: To reveal the effects of short-term normobaric intermittent hypoxia (IH) at a moderate level on physiological responses, and to assess its safety and feasibility in healthy volunteers. **Methods:** Thirty healthy subjects were recruited to this pilot study and underwent the IH intervention. The IH program consisted of four 10-min hypoxic periods in which volunteers inhaled a gas mixture of 13% oxygen, with 5-min normoxic intervals. Physiological parameters, including blood pressure, heart rate, peripheral oxygen saturation, and cerebral oxygen saturation were monitored continuously during the IH intervention. Intracranial pressure was recorded before and 30 minutes after the intervention. Hypoxia-related adverse events were also assessed. **Results:** All thirty health subjects completed the experiment. No subjects reported unbearable discomfort or adverse events. During the IH intervention, subjects' blood pressures, heart rates, peripheral oxygen saturations, and cerebral oxygen saturations fluctuated within the normal range. The decrease in peripheral oxygen saturation was greater than that in cerebral oxygen saturation. There were no significant differences in systolic blood pressure, tissue oxygen saturation, and intracranial pressure before and after IH intervention. Compared with baseline, there was a reduction in diastolic blood pressure (70.70 ± 12.42 mmHg vs. 74.70 ± 11.30 mmHg, $p = 0.007$) and heart rate (72.13 ± 10.16 bpm vs. 77.80 ± 12.4 bpm, $p < 0.001$) 30 min after exposure to IH. **Conclusion:** Short-term normobaric IH at a moderate level was found to be safe and well-tolerated in healthy volunteers.

Keywords: Intermittent hypoxia, Normobaric, Short-term, Moderate hypoxia, Physiological responses

Introduction

Chronic exposure to severe hypoxia causes multiple adverse health consequences, including sympathetic excitation, activation of systemic inflammation, enhanced oxidative stress, and increased production of vascular adhesion molecules (Timon et al., 2021). Intermittent hypoxia (IH), which is a special hypoxic protocol, is defined as periodic alternating exposures to hypoxia and normoxia (Powel et al., 2000). As a hallmark of sleep apnea, IH was initially considered to be an aggravating factor for cognitive impairment, metabolic dysfunction, and cardiovascular and respiratory diseases (Sanders et al., 2021; Lévy et al., 2011; Zhang et al., 2012). However, several studies have demonstrated that moderate IH exerts beneficial effects, such as modulating and stabilizing hypoxia-inducible factor (HIF)-1, enhancing endothelial function, promoting angiogenesis, suppressing inflammation, and balancing the autonomic nervous system (Lavie et al., 2015; Palazon et al., 2014; Kiers et al.,2018). Currently, IH has transformed into a module for the improvement of exercise performance and high-altitude acclimatization (Viscor et al., 2018; Gangwar et al., 2019). Moreover, IH training has been proposed as being a beneficial nonpharmacological intervention for a wide range of pathophysiological states, such as hypertension, diabetes mellitus, cardiovascular diseases, and emotional disorders (Serebrovska et al.,2017; Lyamina et al., 2011; Mallet et al., 2018; Navarrete-Opaz et al., 2014).

Thus, hypoxia is a double-edged sword, and it potentially plays a role in both pathogenesis and physiological adaptations. The severity and duration of hypoxia, the number of hypoxia/normoxia cycles, the pattern of IH presentation, and the

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cumulative duration of exposure are the pivotal variables that determine the efficacy of IH (Navarrete-Opaz et al., 2014). Moreover, there is a dose–response relationship between the varying degrees of hypoxia and the outcomes of hypoxic exposure (Verges et al., 2015; Törpel et al., 2019).

To date, the existing studies on IH intervention have utilized different exposure protocols and have not provided an optimal regimen for obtaining protective effects. Furthermore, few data are available in the literature regarding the main physiological responses during and after IH. Therefore, the current study aimed to investigate the acute and short-term effects of normobaric moderate IH on physiological responses, to determine the safety and feasibility of the IH intervention, and to identify physiological biomarkers for the early assessment of IH. Additionally, this study introduced noninvasive cranial pressure technology, which can respond to intracranial pressure by the principle of flash visual evoked potential, as another important indicator of safety. Herein, we hypothesized that the IH intervention is safe and toleratable for healthy volunteers, and will not contribute to intracranial elevation as in acute hypoxic exposure.

Materials and Methods

Subjects

Healthy, nonsmoking volunteers were recruited to this study. Subjects who were eligible for the study were sea-level (< 300 m) residents who had not traveled to places of altitude > 1,000 m or who had been exposed to hypoxic conditions within the previous six months. The following inclusion criteria were used: (1) aged from 18- to 45-years-old; (2) body mass index (BMI) between 19.0-24.9 kg/m2; and (3) resting peripheral oxygen saturation of more than 90%, cerebral oxygen saturation between 58-82%, heart rate between 60 bpm and 100 bpm, and blood pressure within the normal range (90-130/60-80 mmHg). Subjects with contraindications to IH were not eligible for this study. The following exclusion criteria were used: (1) a history of cardiovascular, cerebrovascular, pulmonary, hepatic, dermatologic, or hematologic diseases; (2) a history of substance abuse; (3) currently taking medications or using medical devices; (4) currently being pregnant, breastfeeding, or trying to get pregnant; and (5) hypertension, diabetes mellitus, obesity, sleep apnea, and neurological disorders. An initial medical assessment was performed, including a brief clinical examination and a 12-lead electrocardiogram. Volunteers with eligible medical histories that were reviewed by a physician were included. Furthermore, subjects were required to abstain from alcohol, caffeine, and intense exercise for a minimum of 48 hours prior to the study.

All of the subjects were provided with detailed information on the study process, and they signed written informed consent for participating in this study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Institutional Review Board of Xuanwu Hospital, Capital Medical University.

Design

This study used a within-subject, repeated measures design to determine physiological responses to short-term IH in healthy volunteers. In the present study, IH exposure of the subjects was performed by breathing hypoxic gas mixtures with a reduced fraction of inspired oxygen (FiO_2) under a normobaric environment. To achieve hypoxia or normoxia, the subjects inhaled air through a face mask connected with the plastic tubing of a hypoxicator. This apparatus mixes ambient air with nitrogen to obtain the desired partial pressure of inspired oxygen. During the recovery periods, the subjects took off the mask to breathe the ambient air (normoxia). The intervention program was performed by trained physicians. During IH intervention, subjects laid in the supine position in bed at rest and stayed awake in a quiet environment. The marked hypoxia-related sensation of the subjects was recorded, and the subjects could remove the mask if uncomfortable symptoms occurred, such as dizziness, headache, and palpitation.

The IH intervention protocol was obtained from previous studies in human subjects (Navarrete-Opaz et al., 2014; Baker et al., 2018; Baillieul et al., 2017) with the following modifications: the total duration was approximately 55 min, and the IH protocol consisted of 4 moderate hypoxic periods, each lasting 10 min (normobaric hypoxia at 13% FiO_2, simulated altitude of 3,800 m) with 5-min normoxic intervals.

Procedures

Clinical assessments. Exposure to normobaric hypoxia leads to hypoxemia and symptoms that resemble ascent to high altitude. In the normobaric environment, hypoxia-related symptoms may occur, such as headache, lightheadedness, nausea, fatigue, and sleep disturbances, which are collectively known as acute mountain sickness (AMS) (Lawley et al., 2014). At baseline, 30 min, and 3 days after the IH intervention, the subjects completed the Lake Louise Score (Savourey et al., 1995; Roach et al., 2018) (LLS; 0-12 scores) to evaluate their uncomfortable symptoms caused by hypoxia, including headache, gastrointestinal disturbance, fatigue, weakness, and dizziness. Sleep quality was assessed at baseline, on the night of the IH intervention, and 3 days after the intervention by using the Insomnia Severity Index (ISI) (Morin et al., 2011) with scores ranging between 0 and 28. The total score was interpreted as follows: no clinically significant insomnia (0-7), subthreshold insomnia (8-14), moderate insomnia (15-21), and severe insomnia (22-28).

Physiological parameter monitoring. Physiological parameters, including peripheral oxygen saturation (SpO_2), heart rate (HR), electrocardiogram (ECG), and brachial arterial blood pressure (BP), were continuously monitored during the intervention by using a multiparameter monitor (HC-2010®, HealthCare NewTech Co., Ltd., Beijing, China). Cerebral tissue O_2 saturation (ScO_2) was paralleled with cerebral blood flow (Van Lieshout et al., 2003), and the monitoring of ScO_2 can provide an extra safety measure of the hemodynamic changes of the subjects during hypoxic challenge. Regional ScO_2 was noninvasively monitored by using near-infrared spectroscopy (NIRS; BRS-1®, Casibrain Technology Co., Ltd., Beijing, China) via sensors placed on the bilateral sides of the forehead (Guo et al., 2006). Continuous-wave NIRS relies upon the relative transparency of tissue to infrared light and the oxygen-dependent absorption characteristics of hemoglobin to determine oxyhemoglobin and deoxyhemoglobin measurements, the sum of which represents total hemoglobin (Fryer et al., 2019). Left prefrontal cortex hemodynamics were assessed at the location between Fp1 and F3 according to the international 10-20 EEG system with an interoptode distance of 3.5 cm. These parameters were recorded at baseline, every five mins during the intervention, and 30 minutes following completion of the procedure.

Intracranial pressure (ICP) was measured by using a noninvasive cranial pressure detector (Welcom®, Chongqing Hiwelcom Iatrical Apparatus Co., Ltd., Chongqing, China) at baseline and 30 min after IH intervention. The N2 wave is considered a cortical phenomenon (Nag et al., 2019). In addition, there is a good relationship between ICP elevation and an increase in latency of the N2 wave of the visual evoked response. In this study, ICP was measured by using flash visual evoked potentials (FVEP) (Price et al., 2020), which were recorded three times within 15 minutes, and the mean was calculated to analyze the N2 wave.

Safety endpoints. The hypoxic intervention was stopped if any

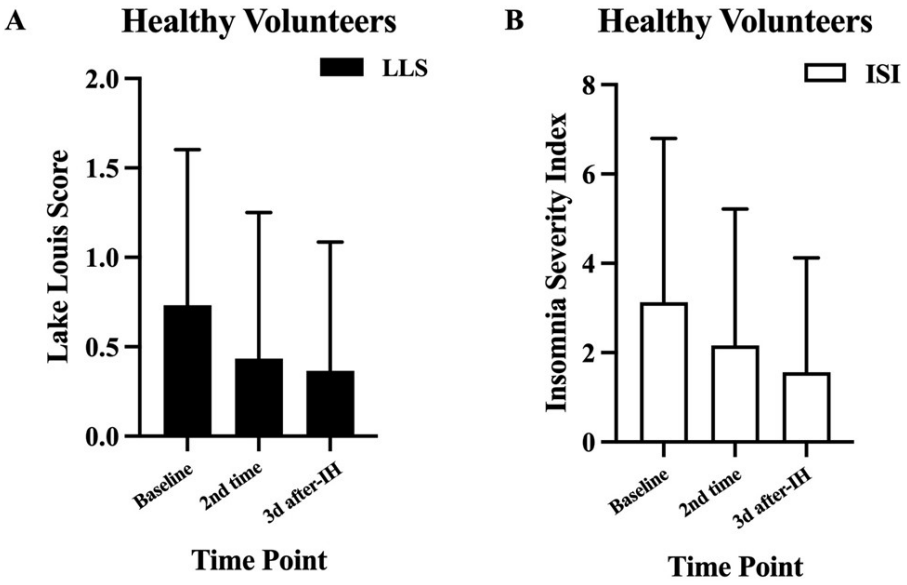

Figure 1. The pre-IH and post-IH Lake Louise Score (LLS, 1A) and Insomnia Severity Index (ISI, 1B) of the subjects (mean ± SD). "2nd time" means 30 min after the IH intervention in 1A; and on the night of the IH intervention in 1B.

of the following conditions were observed: SpO_2 of 80% or less; BP equal to or greater than 160/100 mmHg; HR greater than 100 bpm 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.

Statistical analysis

Statistical analyses included summary statistics presented as the mean ± standard deviation (SD) for the continuous variables. Paired t tests were used to identify statistically significant differences in physiological parameters between pre-IH baseline and post-IH results within the same subjects. To dynamically observe the effect of the intervention on the subjects' vital signs, we used one-way analysis of variance to compare the measured parameters at each time point with the baseline. Changes in LLS and ISI scores at three time points were assessed via one-way analysis of variance and Welch's test, respectively. Additionally, the incidences of hypoxia-related symptoms were analyzed via Fisher's exact test. In all of the cases, p values below 0.05 were considered to be statistically significant. Analysis was performed with IBM SPSS Software 26.0 (IBM, Armonk, NY, USA).

Results

A total of thirty (14 females and 16 males) healthy adults aged 23-39 years were recruited in our study. The average values of age, weight, height, and body mass index (BMI) were 28.97 ± 0.84 years, 66.57 ± 2.62 kg, 169.17 ± 1.52 cm, and 23.01 ± 0.59 kg/m^2, respectively. This 10-minute hypoxia and 5-minute normoxia cyclic bout was repeated four times during the experiment. All of the subjects completed the protocol with good tolerance. Moreover, no significant discomfort or adverse effects were observed during the experiment.

Effects of IH on hypoxia-related symptoms

At baseline, seven (23.3%) subjects suffered from varying degrees of headache. The incidences decreased over time (p = 0.218). Three (10.0%) subjects reported headaches 30 min after IH intervention, and 2 (6.67%) subjects had persistent slight headaches 3 days after the IH intervention. No subject reported gastrointestinal disturbance, fatigue, weakness, or dizziness. In terms of the LLS, there was a decreasing trend at 30 min and three days after IH intervention compared with baseline (0.73 ± 0.87 vs. 0.43 ± 0.82 vs. 0.40 ± 0.72, p = 0.216) (Figure 1A).

Regarding sleep quality, there was no subject report of moderate or severe insomnia. The incidences of subthreshold insomnia at baseline, on the night of intervention, and three days after the intervention were 16.7% (n = 5), 10% (n = 3), and 6.67% (n = 2), respectively (p = 0.592). There were no significant differences in ISI scores at the three time points (3.13 ± 3.67 vs. 2.17 ± 3.05 vs. 1.57 ± 2.56, p = 0.170) (Figure 1B).

Effects of IH on Blood Pressure and Heart Rate

Changes in BP and HR during the hypoxia-normoxia cycles are presented in Figure 2. The mean values of systolic blood pressure (SBP), diastolic blood pressure (DBP), and HR fluctuated from 108.2 to 113.1 mmHg, 70.7 to 74.7 mmHg, and 72.1 to 78.4 bpm, respectively. After IH intervention, there were significant reductions in DBP (74.70 ± 11.30 mmHg vs. 70.70 ± 12.42 mmHg, p = 0.007) and HR (77.80 ± 12.44 bpm vs. 72.13 ± 10.16 bpm, p < 0.001) from baseline to 30 min after the intervention, but no significant effect was observed on SBP (113.13 ± 14.50 mmHg vs. 110.67 ±14.94 mmHg, p = 0.063).

Effects of IH on Tissue Oxygenation

During hypoxia within each cycle, both SpO_2 and ScO_2 in all of the subjects steadily decreased until the normoxic interval, during which they nearly returned to baseline prior to each successive cycle (Figure 3). The mean values of SpO_2, left prefrontal cortex ScO_2, and right prefrontal cortex ScO_2 fluctuated from 96.7% to 99.5%, 67.8% to 71.1%, and 68.1% to 71.2%, respectively. The subjects' SpO_2 significantly decreased during hypoxia exposure compared with the pre-IH baseline (F = 7.072, p < 0.001). A decreasing trend of ScO_2 during the hypoxic periods was observed, but without statistical significance (left: F = 0.803, p = 0.648; right: F = 0.495, p = 0.917). Moreover, there were no significant differences in SpO_2 (99.47 ± 0.97% vs. 99.50 ± 0.68%, p = 0.856) and ScO_2 (left: 70.93 ± 5.03% vs. 71.07 ± 4.88%, p = 0.825; right: 71.67 ± 6.74% vs. 70.26 ± 7.23%, p = 0.158) between the baseline and the measurements at 30 min after the intervention.

Effect of IH on intracranial pressure

Compared with the pre-IH baseline, there was a reduction in ICP after the IH intervention (86.50 ± 17.48 mmH_2O vs.

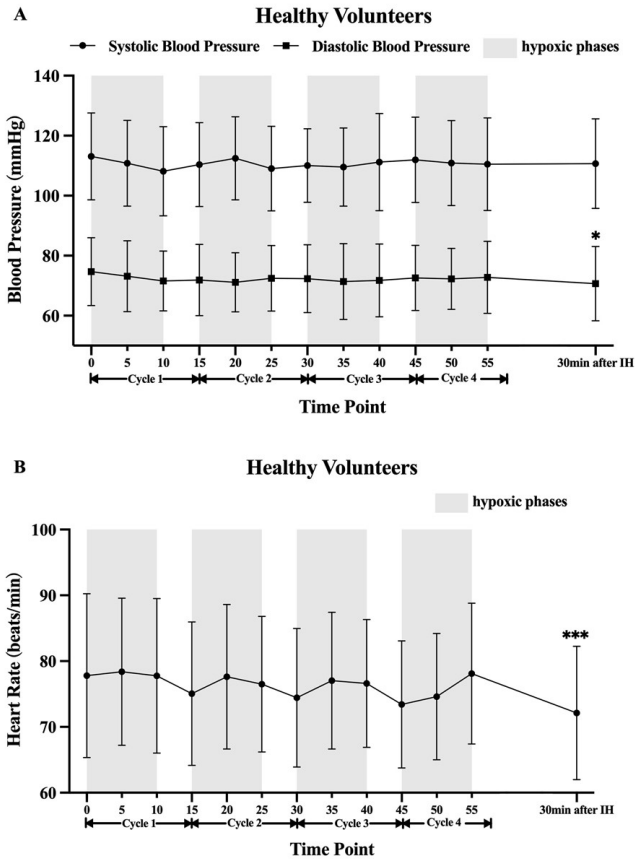

Figure 2. The effects of intermittent hypoxia (IH) on blood pressure (BP, 2A) and heart rate (HR, 2B) in healthy volunteers. Gray areas indicate hypoxic phases. *p < 0.05, ***p < 0.001, 30 min after IH vs. baseline (paired t-test).

83.00 ± 14.57 mmH_2O, p = 0.05). Thus, short-term normobaric moderate hypoxia did not result in acute intracranial hypertension.

Discussion

In this pilot study, we assessed the acute and short-term physiological responses to normobaric moderate IH intervention in healthy volunteers. No adverse events occurred, and all of the subjects tolerated the IH intervention well. During the IH intervention, subjects' blood pressure, heart rate, peripheral oxygen saturation, and cerebral oxygen saturation measurements fluctuated within the normal range. Moreover, IH induced reductions in DBP and HR 30 minutes after the IH intervention.

Intermittent hypoxia has been a topic of considerable research for decades. However, a comprehensive understanding of IH and its biological effects remains unclear. Intermittent hypoxia has dichotomous effects in multiple systems, which may be attributed to varied experimental paradigms adopted by investigators. Whether IH is detrimental or beneficial mainly relies on the exposure patterns (Baker et al., 2018). The 5-min normoxic duration is in accordance with the half-life of 5-8 min of HIF-1α (Berra et al., 2001) and was based on previous IH protocols with normoxic periods lasting 3-5 min (Nagel et al., 2020).

There were no significant complications or serious adverse events caused by our moderate IH protocol. No subjects reported dizziness, palpitation, dyspnea, or other hypoxia-related symptoms during the IH intervention. The incidences and severities of headaches and sleep disorders after IH intervention did not significantly differ compared with baseline. But the declining tendency did indicate that IH may be a strategy to counter damage induced by hypoxia, which needs to be further confirmed.

As sensitive indicators of hypoxia, BP, HR, tissue oxygen saturation, and ICP were measured to evaluate the safety of IH intervention (Kjeld et al., 2021). These physiological parameters were strictly monitored, because the changes would reflect the body's tolerance to hypoxia. The subjects' BP, HR, SpO_2, and ScO_2 values fluctuated within the normal range. Thirty minutes after four cycles of hypoxia-normorxia intervention, there were reductions in DBP and HR in healthy volunteers, which were consistent with the results of previous studies (Lyamina et al., 2011). The antihypertensive effect exerted by IH depends on increased endothelial nitric oxide (NO) production, decreased sympathetic activity, enhanced antioxidant defenses, and improved water and sodium metabolism (Lyamina et al., 2011; Navarrete-Opazo et al., 2014; Muangritdech et al., 2020).

Acute hypoxia decreases arterial O_2 saturation and content, which results in diminished O_2 delivery to and utilization by body tissues. Regional ScO2 decreases along with a reduction in the partial pressure of end tidal O_2 during acute hypoxia (Zhang et al., 2010). In our study, the decrease in SpO_2 was greater than that in ScO_2. The present data indicated that the O_2 extraction rate during hypoxia was well maintained in cerebral tissue compared with that in peripheral tissues, thus suggesting that regional cerebral tissue was protected during brief IH exposure. Zhang et al. (2010) found that repeated short sessions of IH training augmented arterial hemoglobin-O_2 dissociation and systemic O_2 delivery during hypoxia, which consequently improved the O_2 extraction rate in regional cerebral tissue. Chacaroun et al. (2020) demonstrated that the changes in ScO_2 were attributed to increased local cerebral blood volume and improved cerebrovascular reactivity to hypoxia (Chacaroun et al., 2020). We also observed no differences in SpO_2 and ScO_2 before and after IH intervention. In fact, a few minutes of exposure to hypoxia stabilizes HIF-1, which activates erythropoietin (EPO) gene transcription and production. EPO

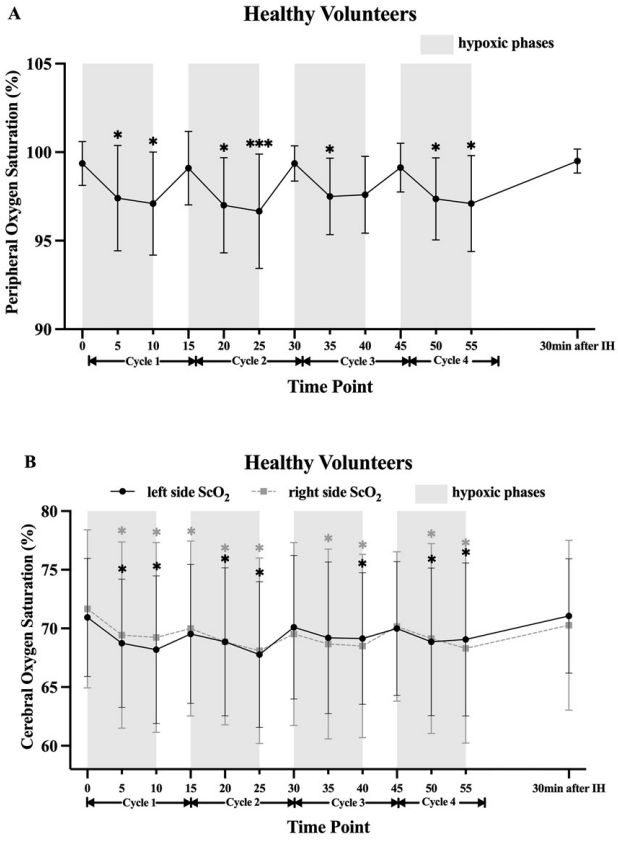

Figure 3. The effects of intermittent hypoxia (IH) on peripheral oxygen saturation (SpO_2, 3A) and cerebral oxygen saturation (ScO_2, 3B). During the hypoxic periods, both SpO_2 and ScO_2 decreased steadily until the normoxic intervals, where they nearly returned to the baseline prior to each successive cycle. The decrease in SpO_2 was greater than that in ScO_2. Gray areas indicate hypoxic phases. *p < 0.05, ***p < 0.001, significantly different from the normoxic baseline (paired t tests).

is a glycoprotein that regulates red blood cell production and consequently restores oxygen supply to tissues (Semenza et al., 2004). Burtscher et al. (2009) found that repeated sessions of an IH protocol consisting of three to five hypoxic periods (each lasting 3-5 min with 3-min normoxic intervals) increased red blood cell count and hemoglobin concentration, which was likely due to a hypoxia-related stimulation of erythropoiesis (Burtscher et al., 2009).

Oxygen is an active stimulus of cerebral vasoconstriction and vasodilation, and hypoxia can induce intracranial hypertension. There have been few studies on the hypoxia tolerance of the human brain and how IH might affect the brain. Animal studies have shown that ICP acutely but mildly increases and remains elevated at least over the first 6 h under hypoxic conditions (DiPasquale et al., 2016). Acute moderate to severe hypoxia results in profound cerebral vasodilatation and elevated cerebral arterial and venous blood volume. The initial increase in ICP may be associated with increased cerebral blood volume, and elevated sagittal sinus pressure may contribute to the maintenance of elevated ICP (Lawley et al., 2016). In the current study, the IH program did not cause increased ICP, which could lead to headaches, brain edema, and acute mountain sickness. These findings further suggest that the IH program is safe and feasible.

There were also some limitations of this study. First, this study only investigated some acute and short-term responses to the IH intervention, and other potential adaptations, such as hematological and metabolic changes and cardiorespiratory responses, remain to be investigated. Second, to identify potential physiological biomarkers for monitoring the beneficial and deleterious effects of IH, we focused on acute and short-term physiological adaptations to IH. The long-term effects of IH intervention also need to be further evaluated. Third, the sample size of this study was relatively small, and future studies with larger sample sizes in an older populations and patients with chronic illnesses are required to demonstrate the findings and to obtain a better understanding of the effects of IH intervention as a therapeutic tool, as well as the underlying nonhematological mechanisms for adaptation.

Conclusion

The findings of this study provide specific insight into healthy volunteers' physiological responses to IH. Short-term normobaric IH intervention at a moderate hypoxia level consisting of 4 hypoxic periods (with each period lasting 10 min with 5-min normoxic intervals) was safe and well tolerated in healthy volunteers. Additionally, the IH program may decrease diastolic blood pressure and heart rate in healthy subjects. The potential benefits of intermittent hypoxia preconditioning need to be confirmed in future studies.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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References

Baillieul S, Chacaroun S, Doutreleau S, Detante O, Pépin JL, Verges S (2017) Hypoxic conditioning and the central nervous system: A new therapeutic opportunity for brain and spinal cord injuries? Exp Biol Med (Maywood) 242:1198-1206. [PubMed: 28585890]

Baker TL, Johnson SM, Watters JJ (2018) Special issue title: "Intermittent hypoxia: Pathologic killer or healing tonic?" Respir Physiol Neurobiol 256:1-3. [PubMed: 29933051]

Berra E, Roux D, Richard DE, Pouysségur J (2001) Hypoxia-inducible factor-1 alpha (HIF-1 alpha) escapes O(2)-driven proteasomal degradation irrespective of its subcellular localization: nucleus or cytoplasm. EMBO Rep 2:615-20. [PubMed: 11454738]

Burtscher M, Haider T, Domej W, Linser T, Gatterer H, Faulhaber M, Pocecco E, Ehrenburg I, Tkatchuk E, Koch R, Bernardi L (2009) Intermittent hypoxia increases exercise tolerance in patients at risk for or with mild COPD. Respir Physiol Neurobiol 165:97-103. [PubMed: 19013544]

Chacaroun S, Borowik A, Doutreleau S, Belaidi E, Wuyam B, Tamisier R, Pépin JL, Flore P, Verges S (2020) Cardiovascular and metabolic responses to passive hypoxic conditioning in overweight and mildly obese individuals. Am J Physiol Regul Integr Comp Physiol 319:R211-R222. [PubMed: 32609532]

DiPasquale DM, Muza SR, Gunn AM, Li Z, Zhang Q, Harris NS, Strangman GE (2016) Evidence for cerebral edema, cerebral perfusion, and intracranial pressure elevations in acute mountain sickness. Brain Behav :e00437. [PubMed: 27099800]

Eren F, Yilmaz SE (2022) Neuroprotective approach in acute ischemic stroke: A systematic review of clinical and experimental studies. Brain Circ 8: 172-179.

Fryer S, Stone K, Dickson T, Wilhelmsen A, Cowen D, Faulkner J, Lambrick D, Stoner L (2019) The effects of 4 weeks normobaric hypoxia training on microvascular responses in the forearm flexor. J Sports Sci 37:1235-1241. [PubMed: 30558476]

Gangwar A, Pooja, Sharma M, Singh K, Patyal A, Bhaumik G, Bhargava K, Sethy NK (2019) Intermittent normobaric hypoxia facilitates high altitude acclimatization by curtailing hypoxia-induced inflammation and dyslipidemia. Pflugers Arch 471:949-959. [PubMed: 30980137]

Guo H, Tierney N, Schaller F, Raven PB, Smith SA, Shi X (2006) Cerebral autoregulation is preserved during orthostatic stress superimposed with systemic hypotension. J Appl Physiol (1985) 100:1785-92. [PubMed: 16424075]

Kiers D et al (2018) Short-Term Hypoxia Dampens Inflammation in vivo via Enhanced Adenosine Release and Adenosine 2B Receptor Stimulation. EBioMedicine 33:144-156. [PubMed: 29983349]

Kjeld T, Isbrand AB, Linnet K, Zerahn B, Højberg J, Hansen EG, Gormsen LC, Bejder J, Krag T, Vissing J, Bøtker HE, Arendrup HC (2021) Extreme Hypoxia Causing Brady-Arrythmias During Apnea in Elite Breath-Hold Divers. Front Physiol 12:712573. [PubMed: 34925050]

Lavie L (2015) Oxidative stress in obstructive sleep apnea and intermittent hypoxia--revisited--the bad ugly and good: implications to the heart and brain. Sleep Med Rev 20:27-45. [PubMed: 25155182]

Lawley JS, Alperin N, Bagci AM, Lee SH, Mullins PG, Oliver SJ, Macdonald JH (2014) Normobaric hypoxia and symptoms of acute mountain sickness: Elevated brain volume and intracranial hypertension. Ann Neurol 75:890-8. [PubMed: 24788400]

Lawley JS, Levine BD, Williams MA, Malm J, Eklund A, Polaner DM, Subudhi AW, Hackett PH, Roach RC (2016) Cerebral spinal fluid dynamics: effect of hypoxia and implications for high-altitude illness. J Appl Physiol (1985) 120:251-62. [PubMed: 26494441]

Lee H, Yun HJ, Ding Y (2021) Timing is everything: Exercise therapy and remote ischemic conditioning for acute ischemic stroke patients. Brain Circ 7:178-186. [PubMed: 34667901]

Lévy P, Tamisier R, Minville C, Launois S, Pépin JL (2011) Sleep apnoea syndrome in 2011: current concepts and future directions. Eur Respir Rev 20:134-46. [PubMed: 21881142]

Lyamina NP, Lyamina SV, Senchiknin VN, Mallet RT, Downey HF, Manukhina EB (2011) Normobaric hypoxia conditioning reduces blood pressure and normalizes nitric oxide synthesis in patients with arterial hypertension. J Hypertens 29:2265-72. [PubMed: 21897291]

Mallet RT, Manukhina EB, Ruelas SS, Caffrey JL, Downey HF (2018) Cardioprotection by intermittent hypoxia conditioning: evidence, mechanisms, and therapeutic potential. Am J Physiol Heart Circ Physiol 315:H216-H232. [PubMed: 29652543]

Morin CM, Belleville G, Bélanger L, Ivers H (2011) The Insomnia Severity Index: psychometric indicators to detect insomnia cases and evaluate treatment response. Sleep 34:601-8. [PubMed: 21532953]

Muangritdech N, Hamlin MJ, Sawanyawisuth K, Prajumwongs P, Saengjan W, Wonnabussapawich P, Manimmanakorn N, Manimmanakorn A (2020) Hypoxic training improves blood pressure, nitric oxide and hypoxia-inducible factor-1 alpha in hypertensive patients. Eur J Appl Physiol 120:1815-1826. [PubMed: 32524226]

Nag DS, Sahu S, Swain A, Kant S (2019) Intracranial pressure monitoring: Gold standard and recent innovations. World J Clin Cases 7:1535-1553. [PubMed: 31367614]

Nagel MJ, Jarrard CP, Lalande S (2020) Effect of a Single Session of Intermittent Hypoxia on Erythropoietin and Oxygen-Carrying Capacity. Int J Environ Res Public Health 17:7257. [PubMed: 33020411]

Navarrete-Opazo A, Mitchell GS (2014) Therapeutic potential of intermittent hypoxia: a matter of dose. Am J Physiol Regul Integr Comp Physiol 307:R1181-97. [PubMed: 25231353]

Palazon A, Goldrath AW, Nizet V, Johnson RS (2014) HIF transcription factors, inflammation, and immunity. Immunity 41:518-28. [PubMed: 25367569]

Powell FL, Garcia N (2020) Physiological effects of intermittent hypoxia. High Alt Med Biol 1:125-36. [PubMed: 11256564]

Price DA, Grzybowski A, Eikenberry J, Januleviciene I, Verticchio Vercellin AC, Mathew S, Siesky B, Harris A (2020) Review of non-invasive intracranial pressure measurement techniques for ophthalmology applications. Br J Ophthalmol 104:887-892. [PubMed: 31704702]

Roach RC, Hackett PH, Oelz O, Bärtsch P, Luks AM, MacInnis MJ, Baillie JK; Lake Louise AMS Score Consensus Committee (2018) The 2018 Lake Louise Acute Mountain Sickness Score. High Alt Med Biol 19:4-6. [PubMed: 29583031]

Sanders CB, Knisely K, Edrissi C, Rathfoot C, Poupore N, Wormack L, Nathaniel T (2021) Obstructive sleep apnea and stroke severity: Impact of clinical risk factors. Brain Circ 7:92-103. [PubMed: 34189352]

Savourey G, Guinet A, Besnard Y, Garcia N, Hanniquet AM, Bittel J (1995) Evaluation of the Lake Louise acute mountain sickness scoring system in a hypobaric chamber. Aviat Space Environ Med 66:963-7. [PubMed: 8526833]

Semenza GL (2004) O2-regulated gene expression: transcriptional control of cardiorespiratory physiology by HIF-1. J Appl Physiol (1985) 96:1173-7; [PubMed: 14766767]

Serebrovska TV, Portnychenko AG, Drevytska TI, Portnichenko VI, Xi L, Egorov E, Gavalko AV, Naskalova S, Chizhova V, Shatylo VB (2017) Intermittent hypoxia training in prediabetes patients: Beneficial effects on glucose homeostasis, hypoxia tolerance and gene expression. Exp Biol Med (Maywood) 242:1542-1552. [PubMed: 28758418]

Timon R, Martínez-Guardado I, Camacho-Cardeñosa A, Villa-Andrada JM, Olcina G, Camacho-Cardeñosa M (2021) Effect of intermittent hypoxic conditioning on inflammatory biomarkers in older adults. Exp Gerontol 152:111478. [PubMed: 34256114]

Törpel A, Peter B, Hamacher D, Schega L (2019) Dose-response relationship of intermittent normobaric hypoxia to stimulate erythropoietin in the context of health promotion in young and old people. Eur J Appl Physiol 119:1065-1074. [PubMed: 30756167]

Van Lieshout JJ, Wieling W, Karemaker JM, Secher NH (2003) Syncope, cerebral perfusion, and oxygenation. J Appl Physiol (1985) 94:833-48. [PubMed: 12571122]

Verges S, Chacaroun S, Godin-Ribuot D, Baillieul S (2015) Hypoxic Conditioning as a New Therapeutic Modality. Front Pediatr 3:58. [PubMed: 26157787]

Viscor G, Torrella JR, Corral L, Ricart A, Javierre C, Pages T, Ventura JL (2018) Physiological and Biological Responses to Short-Term Intermittent Hypobaric Hypoxia Exposure: From Sports and Mountain Medicine to New Biomedical Applications. Front Physiol 9:814. [PubMed: 30038574]

Zhang P, Downey HF, Shi X (2010) Acute intermittent hypoxia exposures enhance arterial oxygen delivery. Exp Biol Med (Maywood) 235:1134-41. [PubMed: 20660087]

Zhang SX, Wang Y, Gozal D (2012) Pathological consequences of intermittent hypoxia in the central nervous system. Compr Physiol 2:1767-77. [PubMed: 23723023]