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HYPOBARIC HYPOXIA, INTERVENTIONS AND OUTCOMES : A SCOPING REVIEW

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ABSTRAK

Aktivitas pekerjaan di lingkungan dataran tinggi membuat individu mengalami hipoksia hipobarik dan tekanan atmosfer rendah, yang menyebabkan risiko kesehatan yang unik. Memahami dampak fisiologis dari tenaga kerja di ketinggian sangat penting untuk keselamatan pekerja. Ulasan cakupan ini melihat sifat bervariasi dari penelitian hipoksia hipobarik, menyoroti pentingnya dalam memahami respons fisiologis terhadap keadaan hipoksia. Dari 2019 hingga 2024, ekstensi Item Pelaporan Pilihan untuk Tinjauan Sistematis dan Meta-Analisis untuk Tinjauan Pelingkupan (PRISMA-ScR) digunakan untuk melakukan pencarian literatur di PubMed, Perpustakaan Online Wiley, dan publikasi terpilih. Enam puluh lima makalah yang berpotensi relevan ditemukan, 24 di antaranya memenuhi kriteria inklusi. Investigasi yang disertakan, yang diterbitkan antara 2020 dan 2023, mencakup 15 penelitian pada hewan dan dua studi pada manusia. Hipoksia hipobarik intermiten memiliki efek perlindungan pada tingkat molekuler dan fungsional pada 88,24% penyelidikan, terutama dalam hal penurunan indikator stres oksidatif. Penelitian pada manusia telah menunjukkan pelatihan hipoksia intermiten meningkatkan kinerja atletik dan fungsi hemodinamik. Penelitian pada hewan menunjukkan perubahan dalam karakteristik genetik, histologis, dan fungsional di bawah situasi hipoksia hipobarik yang berbeda. Sementara hipoksia hipobarik intermiten tampaknya melindungi fungsi tubuh, efek pada fungsi kognitif tetap tidak diketahui.

Kata kunci **:** hasil, hipoksia hipobarik, intervensi

ABSTRACT

Occupational activities in high-altitude environments expose individuals to hypobaric hypoxia and low atmospheric pressure, leading to unique health risks. Understanding the physiological impacts of high-altitude labor is critical for worker safety. This scoping review looks at the varied nature of hypobaric hypoxia research, highlighting its importance in understanding physiological responses to hypoxic circumstances. From 2019 to 2024, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist was used to conduct literature searches in PubMed, Wiley Online Library, and chosen publications. Sixty-five potentially relevant papers were discovered, 24 of which met inclusion criteria. The included investigations, which were published between 2020 and 2023, included 15 animal and two human studies. Intermittent hypobaric hypoxia had protective effects on molecular and functional levels in 88.24% of investigations, notably in terms of decreasing oxidative stress indicators. Human studies have shown intermittent hypoxia training improves athletic performance and hemodynamic function. Animal studies indicated alterations in genetic, histological, and functional characteristics under different hypobaric hypoxia situations. While intermittent hypobaric hypoxia appears to protect bodily functioning, the effects on cognitive function remain unknown.

Keywords ***:*** *hypobaric hypoxia, interventions, outcomes*

INTRODUCTION

Due to hypobaric hypoxia and falling air pressure, occupational tasks performed at high elevations carry inherent health risks. Various environmental elements present unique obstacles for those engaged in such activities, including mountaineers, miners, aviation or military personnel, and construction workers. Those who labor in these situations are particularly concerned about hypobaric hypoxia, characterized by lower oxygen levels at greater elevations.

While a certain amount of hypoxia could be advantageous for adaptation, excessive acute hypoxia can have negative repercussions that could jeopardize general health and physiological systems. People in occupations such as mining and mountaineering are especially vulnerable to these effects since extended exposure to hypobaric hypoxia can cause altitude sickness, cognitive impairment, and cardiovascular problems. Furthermore, the physical and psychological strain that high-altitude workers frequently endure exacerbates the challenges that hypoxic conditions present.

Understanding the complex interaction between hypobaric hypoxia and human physiology is essential to safeguarding the well-being of those working in high-altitude conditions. By examining the large amount of hypobaric hypoxia literature, this scoping review seeks to understand the various physiological reactions brought on by hypoxic settings. This work highlights the significance of increasing our understanding of hypobaric hypoxia through a thorough examination of the literature, providing insights that could guide the development of efficient methods to decrease associated health dangers in industrial settings.

METHODS

Our protocol was written using Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist. The checklist was created by the EQUATOR (Enhancing the QUAlity and Transparency Of health Research) Network for the development of reporting guidelines in 2018 (1). The search for research articles to be reviewed in this study was done within one week, January 16th to 22nd, 2024, in Central Indonesian Time.

To be included in our review, a paper should be original research using primary data, not a review of intermittent hypobaric hypoxia. Peer-reviewed journal papers were included if they met the following criteria: available in free full texts from accessed database, published between 2019-2024, written in English, and involving human or animal subjects. To consider diverse aspects of quantifying those two types of treatment in the aforementioned population, qualitative, quantitative, and mixed methods studies meet our inclusion criteria. Papers were excluded if they did not fit within our conceptual framework of study, including people with specific diseases such as asthma.

From 2019 to 2024, the following bibliographic databases were searched for potentially relevant publications: PubMed and Wiley Online Library. The electronic database search was added by searching Antioxidants journal (https://www.mdpi.com/journal/antioxidants) and Acta Biochimica Indonesiana journal (https://pbbmi.org/newjurnal/index.php/actabioina) websites for other relevant publications. Keywords combined with some truncations and Boolean logic operators used in the PubMed and Wiley Online Library database queries for this review are “intermittent AND hypobaric AND hypoxia”. Filters used in the database are Free full text for text availability, English for article language, and publication date from 2014/02 – 2024. For the central review, only publication from 2019 was included.

When duplication occurs, the one from the PubMed database search is used. The reviewer then evaluated the titles and abstracts, and then the entire text of all papers was discovered thrice to increase consistency.

As mentioned earlier, this scoping review aims to answer the following questions: How is research conducted on intermittent intervention of hypobaric hypoxia? By answering this question, the reviewer could clarify the definition of intermittent hypobaric hypoxia and its impacts in vivo. To address this question, the reviewer employed the following elements: population, intervention, comparator, outcomes, and study design (PICOS). Population: human or non-human mammals. Intervention: intermittent hypobaric hypoxia, as stated explicitly in the title or abstract. Comparator: normoxia and/or continuous hypobaric hypoxia. Outcomes: changes in body systems were observed quantitatively. Study design: primary study. A data-charting form was developed to determine which variables to extract and chart the data. Other than PICOS, the reviewer included authors, year of publication, aim(s) of study, and sample size in the data charting form.

Data synthesis was conducted in line with i) methodological features of included studies, and ii) interventions and outcomes. Finally, the reviewer combined and evaluated data from the included studies and concluded. The synthesis of results and conclusion were based on the research question mentioned above.

RESULTS

Selection of sources of evidence. The literature search yielded sixty-five potentially relevant publications. The reviewer then evaluated each publication based on the year of publication and study design. The evaluation was done thrice in Mendeley Library and each database or website. Twenty-four research articles were then obtained for further review and data extraction. The remaining publications were either unable to be retrieved, unavailable in free full text, did not use English, did not publish as a journal, or did not contain “intermittent” and “hypobaric” and “hypoxia” in the title and abstract. Figure 1 displays a flow diagram of the article selection process (7).

Characteristics of sources of evidence. All the investigations were published between 2020 and 2023 and included fifteen animal and two human studies. Mice or rats were used as experimental models in all animal studies in which the animals were subjected to hypobaric hypoxia conditions, either continuously or intermittently. Meanwhile, human subjects were subjected to hypobaric hypoxia on an intermittent basis. Table 1 summarizes the methodological features of all included studies. Table 2 highlights the treatments and results from the included studies.

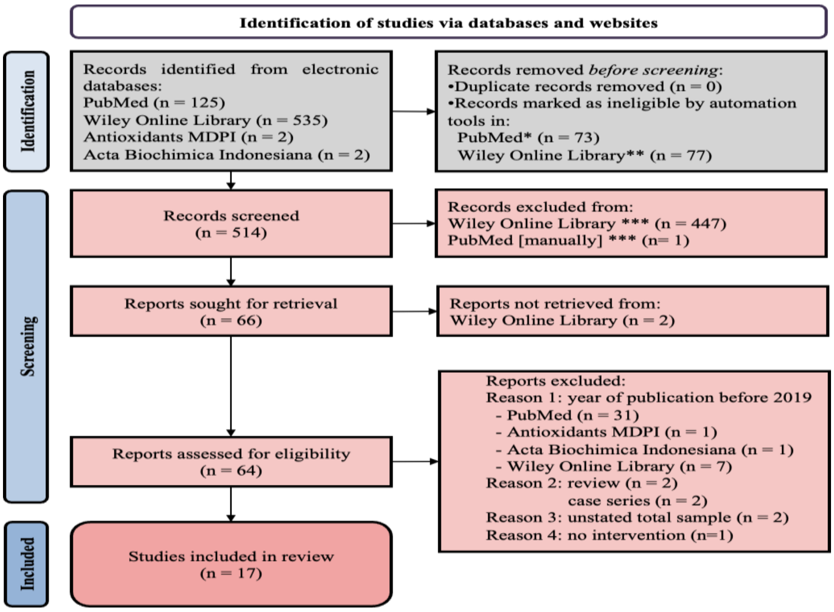

Figure 1. Flow Diagram of The Article Selection Process

Table 1. Methodological Features of The Included Studies

Author (publication year)	Population	Aims of study	Study design
Dewi S et al. (2022) (8)	Wistar rats (6-8 weeks, male)	Investigated the effect of intermittent hypobaric hypoxia (IHH) on malondialdehyde and carbonyl levels of rat skeletal muscle as oxidative stress indicators.	Case control
González-Candia et al. (2022) (9)	Wistar rats (8 weeks, male)	Described the responses of cardiac function toward IHH in rats as animal model.	Case control
Santocildes et al. (2023) (10)	Sprague-Dawley rats (7 weeks, male)	Examined the impact of IHH and cold exposure, separately and concurrently, on rat muscle regeneration.	Case control
Jung et al. (2020)(6)(11)	Human (moderately trained middle and long-distance runners) (adult 24-27 years, male)	Investigated the impact of intermittent interval training in hypobaric hypoxic conditions within six weeks on hemodynamic and autonomic nervous system function, and also on athletic performance.	Case control
Ramos-Romero et al. (2020) (12)	Sprague-Dawley rats (adult with initial body weight 215 g, male)	Investigated how intermittent exposure to cold, hypobaric hypoxia (HH), and their combination affect gut microbiota and metabolites in vivo, as well as their impact on host physiology.	Case control
Pena et al. (2020) (13)	Wistar rats (3 months, male)	Determined the oxidative level, NADPH oxidase expression, and MAPK activation in rats with right ventricular hypertrophy caused by CIHH.	Case control
Liu et al. (2020) (14)	Sprague-Dawley rats (8 weeks, female)	Assessed the impact of IHH on rat female reproductive systems and investigate the underlying mechanisms at the histological, endocrine, and molecular levels.	Case control
Terrizzi et al. (2021) (15)	Wistar rats (adult with body weight ranging 250-300g, male)	Examined how CIHH and continuous HH affects the hypothalamic-pituitary-gonadal axis regulation in male rats.	Case control
Coimbra-Costa et al. (2021) (16)	Sprague-Dawley rats (adult weighing between	Investigated the impact of IHH on preventing brain	Case control

	230-250g, male)	damage from acute severe hypoxia.	
Shati et al. (2022) (17)	Sprague-Dawley rats (12 weeks, male)	Investigated whether intermittent short-duration re-oxygenation may protect the myocardium from hypoxia injury.	Case control
Choudhary et al. (2022) (18)	Balb/c mice (8-10 weeks, male)	Investigated the role of 12/15 LOX in HH-induced mitochondrial integrity disturbance and its correlation with neuronal apoptosis	Case control
Liu et al. (2022) (19)	Sprague-Dawley rats (8 weeks, male)	Investigated the healing mechanisms of CIHH on intervertebral disc degeneration disease in rats	Case control
Utrera et al. (2022) (20)	Wistar rats (adult, male)	Investigated the cycle-dependent biomechanical effects of IHH on the structure and function of the thoracic aorta artery.	Case control
Meyer et al. (2023) (21)	Human (over 50 years, male and female)	Investigated flight oxygenation relationship with ventricular (VE) and supraventricular ectopy (SVE)	Block-randomized crossover
Yaman et al. (2023) (22)	Sprague-Dawley rats (adult 245-312 g, male)	Investigated lung injury due to chronic long-term IHH (CLTIHH) in rat model and the impact of N-methyl-D-aspartate receptors by using receptor antagonist MK-801 (dizocilpine)	Case control
Luo et al. (2023) (23)	ApoE-/- mice on a C57BL/6 background (6-8 weeks 18-22 g, male)	Examined, preliminarily, how continuous HH affects atherosclerosis in high-altitude setting.	Case control
Zhang et al. (2023) (24)	Wistar rats (8 weeks, male)	Investigated the CIHH involvement in osteoporocis induced by spinal cord injury in rat model	Case control

Table 2. Interventions and Outcomes

Study	Design	Population	Intervention	Comparator	Outcomes
Dewi S et al. (2022)(8)	Case control	25 Wistar rats (6-8 weeks, male), allocated [equally] into five groups (4 intervention groups, 1 control group)	Exposed to an altitude of 25,000 feet within 5 minutes using hypobaric chamber in	normobaric conditions (n=5)	- The malondialdehyde (MDA) levels in: ○ Group I was considera

			once (group I), twice (II), thrice (III), and four (IV) times, with a 7-day interval		bly higher compared to normobaric group (p= 0.008) ○ Group II, III, and IV were lower compared to group I - The carbonyl level in: ○ Group I was significantly higher compared to normobaric group (p=0.000) ○ Group II was higher than Group I compared to normobaric group ○ Group III and IV was higher compared to normobaric group, but lower compared to group I and II
González-Candia et al. (2022) (9)	Case control	12 Wistar Kyoto rats (8 weeks, male), randomly divided into 2 equal groups (1 intervention group, 1 control group)	Exposed to one cycle which consists of one shift of HH (428 Torr equivalent to 4600 of altitude, 4 days) followed by one shift of normoxia (750 Torr, 4 days). Intervention group, n=6	Normobaric normoxia (NN group), 750 Torr, n=6	- Echocardiography: by the 4th cycle, there was a higher ejection and a shortening fraction of the left ventricle function - Histology of the heart: Cardiac tissue showed lower expression of

			(IHH group) was exposed to 4 cycles.		antioxidant proteins. - Molecular biology assays of the heart (cardiac oxidative stress biomarkers, antioxidant enxymes, and NLRP 3 inflammasome panel expression): IHH leads to lower levels of IL-1β, TNF-α, and oxidative stress markers than normobaric hypoxic controls.
Santocildes et al. (2023) (10)	Case control	Sprague-Dawley rats (7 weeks, male), randomly assigned to 5 groups (3 intervention groups, 2 control groups)	All rats were surgically wounded in one gastrocnemius and treated for four hours/day within 9 or 21 days: - COLD group: exposed to 4^{0}C intermittently - HYPO group: exposed to IHH with an internal pressure of 577±3hPa mimicking 4500m of geographical height, comparable to 11.5% O_2 concentration at sea	Control (CTRL) group: passive recovery in normoxia at 23^{0}C after surgically wounded in one gastrocnemius Additional control (CTRL_0): injured then after 24 h were assessed for the functional test	Muscle regeneration: - Histological and functional evidence: ○ faster (histological evidence after 9 days, functional evidence in 21 days) in COLD and COHY compared to CTRL.

		level, or over half (55%) of the sea level oxygen availability. - COHY group: exposed to cold and hypobaric hypoxia (4500m) intermittently and simultaneously		○ Earlier full recovery from injury, within 9 days, than COLD and COHY - Molecular signaling: ○ - in the pSer473 Akt/total Akt ratio after 9 days in COLD, HYPO and COHY à faster regeneration ○ - in the pThr172 AMPKα/total AMPKα ratio in the gastrocne

					mius of HYPO à regeneration
Jung et al. (2020) (11)	Case control	20 athletes, moderately trained middle and long-distance runners (adult 24-27 years, male), divided into 2 groups	Hypoxic training group, HTG (n=10): residing at sea level but training in 526-mmHg hypobaric hypoxia with frequency of training was 90 min, 3 days per week, within 6 weeks	Normoxic training group, NTG (n=10): residing and training at sea level	- Body composition: no significant difference - Athletic performance (e.g., maximal oxygen uptake): improved more significantly in HTG - Hemodynamic function (e.g. oxygen uptake, and cardiac output) during submaximal exercise: improved more in HTG - Autonomic nervous function (e.g., SD and root mean square of successive differences, high frequency, and low/high frequency): improved more in HTG - Immune function: steady within the usual range before and after training in HTG and NTG
Ramos-Romero et al. (2020) (12)	Case control	52 Sprague-Dawley rats (adult with initial body weight 215 g, male), randomly divided into 4 groups	- Cold-exposed (COLD) group; exposed to 4 ^{0}C, 4 h/day within 21 days - Hypobaric hypoxia (IHH) group; using hypobaric chamber	Control (CTL) group	IHH: increased hemoglobin, red and white cell counts and Enterobacteriales, and reduced body and adipose tissues weights and Lactobacilliales. COHY: counteracted the hypoxia-induced weight loss as well as the increase in white blood cells, reducing the Bacteroidetes:Firmicutes ratio and

			with target pressure equivalent to 4,000 m of altitude achieved slowly over ~15 min, sustained for 4 h/day then gradually recovered to the normal barometric pressure over 15 min. This intermittent exposure was done for 21 days. - Cold plus hypoxia (COHY) group		normalizing the populations of Enterobacteriales and Lactobacilliales.
Pena et al. (2020) (13)	Case control	20 Wistar rats (3 months, male), randomly divided into two experimental groups	CIH group: 2 days exposure to HH alternating with 2 days exposure to normobaric normoxia (NX) for 30 days	Normobaric normoxia (sea level control group) n=10	CIH group: developed right ventricular hypertrophy, upragulated lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1), Nox2, and p22phox, increased lipid peroxidation, stabilization of HIF1α, and activation of p38α.
Liu et al. (2020) (14)	Case control	40 female Sprague-Dawley rats (8 weeks), randomly divided into two experimental groups	IHH: 20 rats were subjected to hypoxia at a simulated altitude of 5000 m in a hypobaric chamber for 8 hours (9:00 a.m.-17:00 p.m.) daily, for 2 weeks.	Control group (n=20) did not receive any treatment	The length of the diestrus phase increased considerably with IHH exposure. Following IHH exposure, estrogen levels increased while luteinizing hormone and progesterone levels declined. IHH-exposed rats also showed altered expression of ER, PR, and LHR. IHH exposure significantly reduced GSH-Px and T-SOD activity while increasing MDA

					content.
Terrizzi et al. (2021) (15)	Case control	30 adult male Wistar rats (weight ranging 250-300g), randomly divided into three experimental groups	Chronic intermittent hypoxia (CIH) involves exposure to discontinuous hypoxia (600 mbar, corresponding to 4,000 meters of simulated altitude) in a simulated high-altitude chamber for 18 hours per day, 5 days a week, within 30 days (approximately 50% of the total duration is hypoxia). Chronic Continuous Hypoxia (CCH) involves continuous exposure to the same ambient pressure in a simulated high-altitude chamber for 23.5 hours per day, seven days a week, within 30 days (nearly 100% of the experimental period is hypoxia condition)	Control group (C): normoxia	Male rats with hypoxia may have infertility due to overexpression of negative regulators of GnRH and luteinizing hormone production: - Intermittently treated rats showed increased levels of Rfrp3 (a negative regulator of GnRH and LH release) compared to controls. - Continuous hypoxia led to elevated levels of Kiss1 (a neuropeptide that increases GnRH release). - Intermittent hypoxia in rats resulted in decreased plasma luteinizing hormone and testosterone levels, as well as lower body weight compared to other groups.
Coimbra-Costa et al. (2021) (16)	Case control	44 adult male Sprague-Dawley rats (weighing between 230-250 g), randomly divided into four experimental groups	- Acute Severe Hypoxia (ASH) group: rats were subjected to normobaric hypoxia in constant flow chamber of 93% N2 and 7% O2 during 6-hour session, then decapitated immediately	NOR: normoxic group	ASH rats displayed astrocytes with phenotypic forms consistent with severe diffuse reactive astrogliosis, elevated oxidative stress indicators, and increased apoptotic proteins. Those three effects were decreased and prevented in rats preconditioned with IHH, coupled with

			after the exposure (without any time for reoxygenation) - Intermittent Hypobaric Hypoxia (IHH) group: rats were subjected to HH for 8 days, with 4-hour periods per day. A hypobaric chamber was used to imitate an altitude of meters. - IHH + ASH group: rats were subjected to intermittent hypobaric hypoxia followed by a normobaric acute severe hypoxic session, then were decapitated soon after hypoxia to prevent reoxygenation.		EPO upregulation and NF-κB downregulation
Shati et al. (2022) (17)	Case control	18 Sprague-Dawley male rats (12 weeks), randomly divided into three experimental groups	Hypoxia group: rats were subjected to a hypobaric chamber (405 mmHg) to simulate hypoxia at 5,000 m, for 14 days. Intermittent short-duration re-oxygenation: rats were subjected to a hypobaric chamber and then exposed to room air three times a day, for 14 days	Normoxia: exposed to room air as control	Hypoxia increased the oxidative stress biomarkers malondialdehyde and decreased antioxidant supreoxide dismutase. Hypoxic hearts showed higher levels of TNF-α and IL-6 in the myocardium. Histological results of hypoxic rats: cardiac myofibrils revealed muscle fiber disorder, sarcoplasm vacuolation, nucleus pyknosis, and intercellular gaps enlargement. Intermittent short-duration reoxygenation improves heart

					histological, ultrastructural, and oxidant/antioxidant characteristics during hypoxia.
Choudhary et al. (2022) (18)	Case control	Male Balb/c mice (8-10 weeks), randomly divided into four experimental groups	Hypoxia (H), corresponding to an altitude of 25,000 feet for 6 hours every day within 3 days; The ascension to the required height and fall to sea level were both at 700 feet per minute and the chamber temperature was kept constant at 26 ± 2 ◦C. Hypoxia treated with Baicalein (HBA, 10 mg/ kg bw) intra-peritoneally for all three-day 30 min before induction of HH	Normoxia (N): did not get any treatments Normoxia treated with Baicalein (NBA, 10 mg/kg bw)	Treatment with baicalein (12/15 LOX inhibitor) dramatically decreased intra-hippocampal 12(S)HETE (12/15 LOX metabolite), which had previously increased due to hypoxia induction. Following HH, 12/15 LOX becomes embedded on the mitochondrial periphery, leading to mitochondrial integrity loss, increased cytochrome-c in the cytosol, and increased activity of Caspase-3, Caspase-9, and Bax/Bcl-2 expression ratios.
Liu et al. (2022) (19)	Case control	48 adult male Sprague-Dawley rats (8 weeks), randomly divided into three groups	Experimental group (CIHH-IDD; n=16): rats were treated with CIHH prior to receiving the same treatment	Control group (CON; n=16): did not undergo any therapies	- CIHH-IDD animals showed considerably decreased intervertebral disc height degradation

			as IDD rats. The CIHH treatment: for 28 days at a simulated altitude of 3,000 meters and 5 hours each day, the PO_2 level was 108.8 mmHg (in low pressure oxygen chamber). Degenerative group (IDD; n=16): tail discs were punctured after 28 days of regular feeding.		compared to IDD rats ($P<0.05$). - CIHH-IDD rat serum showed greater expression levels of bFGF, TGFβ1, and HIF-1α compared to IDD rat serum ($P<0.05$). - Optical microscopy demonstrated moderate disc degeneration in CIHH-IDD animals. - In CIHH-IDD rat intervertebral disc tissues, protein expression levels of bFGF, TGFβ1, and collagen II were higher than those in IDD rats. However, overexpression of collagen I protein was blocked.
Utrera et al. (2022) (20)	Case control	18 adults male Wistar rats, randomly divided into three groups	- Short-term intermittent hypobaric hypoxia (STH; n=6) for four cycles, with normobaric pressure equals to 570 m.a.s.l and changes of simulating altitude increases	Normobaric normoxia (n=6)	- Hypoxia increases longitudinal stretch while reducing circumferential residual strain of the aorta. - During the early phases of IH (STH group), stiffening occurs, resulting in a significant

			of 150 m per minute until 4600 m.a.s.l. Each cycle consists of 4 days of hypobaric hypoxia followed by 4 days of normobaric normoxia. - Long-term intermittent hypobaric hypoxia (LTH; n=6) for 10 cycles After the experimental regimen, 6-month-old animals were killed with an anesthetic overdose (Sodium Thiopentone 150 mg -kg−1 IP) and the aorta artery was removed for biomechanical, functional, and histological testing.		rise in high strain elastic modulus (E2) and a rising trend in low strain elastic modulus (E1). In contrast, the LTH group had greater control-like mechanical behavior. - The STH group has vascular fibrosis, higher elastin levels, and more collagen fibers.
Meyer et al. (2023) (21)	Block-randomized crossover	Humans not displaying any active health symptoms (over 50 years, male and female); including individuals with stable heart problems (moderate coronary artery disease or congestive heart failure-- diagnosed according to New York Heart	From December 2007 to June 2008, groups of participants were observed in a hypobaric chamber (flight conditions equal to 7000 feet altitude) for 2 days, with 1 day of rest in between. The exposure condition was unknown to		The occurrence of VE did not vary by condition, however SVE was more prevalent under flying conditions (OR ratio = 1.77, 95% CI: 1.21, 2.59 for SVE couples). During flying circumstances, rates of VE and SVE increased (RR ratio = 1.25, 95% CI: 1.03, 1.52 for VE couplets, RR ratio = 1.76, 95% CI: 1.39, 2.22 for SVE

		Association guidelines; n = 13), 14 smokers and 14 non-smokers without cardiac problems.	participants, and the order of exposure was randomly assigned to each group. On the first day in the chamber, 30 of 41 participants received the flying condition. A participant who received the control condition on the first day was unable to continue the trial due to a documented work conflict. Participants were allowed to act as they would on a flight, including sleeping, reading, watching movies, walking, and talking freely. The investigator tracked participants' VE (ventricular ectopy) and SVE (supraventricular ectopy) every 5 minutes during flying and control circumstances to assess their frequency and presence.		couplets). The frequency and severity of ectopy increased with flight length.
Yaman et al. (2023) (22)	Case control	32 male adult Sprague-Dawley rats (245-312 g), randomly divided into four groups	- Chronic long-term IHH (CLTIHH) group: rats were placed	Control group: normoxia condition	- The CLTIHH groups showed substantial increases in both oxidant and

		into the low-pressure chamber, stabilized at 430 mmHg (equivalent to an altitude of 4572 m.a.s.l) by an adjustable valve and a dry vacuum pump, which conducted 5 h a day (09:00 am to 02:00 pm) - CLTIHH + SALINE group: rats were placed in the same situation as the previous group and given saline injection *ip* daily (0.5 mL) to rule out possible effects of injection stress - CLTIHH + MK-801 group: rats were placed in the same circumstances as the CLTIHH group		inflammatory indices, with the exception of the group that received MK-801. - Histological examinations showed lung injury and fibrotic alterations in the CLTIHH group. MK-801, an NMDAR antagonist, effectively reduces lung damage and fibrosis.

			and given MK-801 (dizocilpine, 0.3 mg/kg, 0.5 mL in volume/w saline intraperitoneally) everyday. The injections alternated between the left and right sides. After anesthetized with sodium pentobarbital ip, rats were euthanized by cervical dislocation after the blood collected by cardiac puncture.		
Luo et al. (2023) (23)	Case control	ApoE-/- mice on a C57BL/6 background (6-8 weeks 18-22 g, male), randomly divided into two groups	Continuous hypobaric hypoxia (CHH) group : spent 4 weeks in a hypobaric room with 10% oxygen and 364 mmHg air pressure, equivalent to 5,800 m.a.s.l.	Control group: normoxia condition	- Four weeks of CHH exposure led to increased atherosclerotic lesions and impaired plaque stability (p=0.0017). - In the CHH group, plaque smooth muscle cells and collagen levels reduced, but plaque macrophages and lipid levels rose dramatically (p<0.001). - The CHH group had increased levels of CD31 (p=0.0379)

					and endomucin (p=0.0196) in their plaques, which corresponded with angiogenesis development.
Zhang et al. (2023) (24)	Case control	Wistar rats (8 weeks, male), randomly divided into four groups	Wistar rats' T9-T10 spinal cords were transectioned to create a model of SCI. After SCI, those rats received CIHH therapy (6 hours per day, PB = 404 mmHg, Po2 = 84 mmHg) for 7 weeks: 1) Spinal cord injury group (SCI), 2) SCI plus CIHH group (SCI + CIHH).	Sham operated group and CIHH treatment group	- X-ray and micro-CT scans showed lower bone mineral density (BMD), bone volume to tissue volume, volumetric BMD, trabecular thickness, number, and connectivity in SCI+CIHH group compared to sham rats. - CIHH therapy substantially restored the increased trabecular bone pattern factor, trabecular separation, and structural model index in the distal femur and proximal tibia of SCI rats. - Histomorphometry revealed that CIHH therapy improved bone formation in SCI rats by increasing osteoid production

			and decreasing the number and surface of TRAP-positive osteoclasts. - In SCI rats, osteoblastogenesis-related biomarkers (e.g., procollagen type 1 N-terminal propeptide, osteocalcin in serum, ALP and OPG mRNAs in bone tissue) decreased while osteoclastogenesis-related biomarkers (e.g., scleorostin in serum, RANKL and TRAP mRNAs in bone tissue) increased, according to ELISA and real-time PCR results. The deviations of the aforementioned biomarkers have been improved by CIHH treatment. - CIHH's protective effects may be partly mediated via the HIF-1a signaling pathway.

Findings from Human Studies

Hypoxia training dramatically increased athletic performance, including maximum oxygen absorption. During submaximal exercise, athletes trained in hypoxia conditions showed better hemodynamic function (e.g., oxygen uptake, pulse, and cardiac output) and autonomic nervous system function. The study included a 5-day pre-test phase (3 testing days + 1 rest day), a 6-week training period for each environmental condition, and a 5-day post-test. The post-test period began three days following the final training session. The hypoxic state was tested intermittently in a chamber with an oxygen pressure of 526 mmHg, approximating an altitude of 3000 meters (11). One of the studies employed a simulated altitude of 4,000 meters for 1 h/day, 5 days a week, within 6 weeks (16). Meanwhile, in the non-athlete population, one study included in this review found that the frequency and severity of ectopy (supraventricular ectopy) increased with flight time(21).

Findings from Non-Human Studies

Most investigations used a case-control approach. Almost all studies included male rats or mice. The animal models ranged from Wistar and Sprague-Dawley rats to Balb-c mice. With simulating altitudes ranging from 3000 to 7620 m.a.s.l., the studies found changes in molecular (for example, oxidative stress), histological, and functional parameters, also pathological evidence. Some studies compare intermittent and continuous hypobaric hypoxia interventions. The intersession of intermittent hypobaric hypoxia intervention ranges from hours (6 hours) to days (7 days)(8–10,12–20,22–24).

Synthesis of Results

The scoping analysis identified 17 relevant articles on hypobaric hypoxia published between 2020 and 2023. We organized research by behavior type and described their populations, aims of study, study designs, interventions, comparator, and overall results. We identified original articles and tallied the number of papers possibly fulfilling our inclusion criteria. Most of the research (88.24%) uses hypobaric hypoxia, which was given intermittently to investigate its impact on molecular and functional levels. From those 17 studies, it can be concluded that intermittent hypobaric hypoxia appears to safeguard numerous body functions. Furthermore, 8 out of 17 articles investigated the effects of hypobaric hypoxia on molecular parameters in oxidative stress.

DISCUSSION

Individuals working in high-altitude locations face particular obstacles and risks to their health. Mountaineers, miners, aviation or military personnel, and construction workers are among the jobs that expose people to hypobaric hypoxia and low atmospheric pressure. Therefore, understanding the impacts of high-altitude occupation is critical for protecting the health and well-being of workers in these settings. Conversely, a tolerated hypoxic situation at a particular time range promotes the protective effect. This scoping review's findings emphasize the multidimensional character of hypobaric hypoxia research. The importance of research focusing on physiological aspects emphasizes the necessity of understanding responses to hypoxic circumstances (1,2,4,5,25).

Working at high elevations, typically classified as elevations exceeding 2,500 meters, will impact the worker's health and general well-being. The key concern is hypoxia. Organ function begins to decline when oxygen transport is substantially disrupted. This condition can result in acute mountain sickness and cerebral edema. High-altitude cerebral edema (HACE) is frequently associated with fatigue, ataxia, and impaired mental state (2). This condition is a serious consequence of hypoxia and can be fatal if not treated immediately.

Meanwhile, headache, dizziness, nausea, and exhaustion are common acute mountain sickness symptoms that appear within the first 6–12 hours post-exposure. This consequence can be prevented with oral treatment and does not typically require prompt descent or oxygen supplementation (3).

Moreover, in a study included in this review, the frequency and severity of ectopy increased with flight length, which equals hypoxia duration (21). On the other hand, another study found intermittent hypobaric hypoxia increases athletic performance and hemodynamic and autonomic nervous, including immunological function (11). We may infer, from included and related studies, that moderate and intermittent hypobaric hypoxia is more protective than severe acute hypoxia (5,11,21,26,27).

If performance alterations are noticed due to hypoxia or intermittent hypobaric hypoxia, underlying molecular changes must have occurred (1,4,5,28,29). Compared to the group that received acute hypobaric hypoxia, rats treated with intermittent hypobaric hypoxia showed a reduction in oxidative stress indicators, notably malondialdehyde (MDA) levels (8). Another study also shows that intermittent hypobaric hypoxia leads to lower levels of IL-1β, TNFα, and oxidative stress indicators than normobaric hypoxic controls (9). IL-1β and TNFα are pro-inflammatory cytokines; the first regulates immunological and inflammatory responses, while the latter promotes systemic inflammation. Based on the two investigations and numerous other research included in this scoping review, it can be concluded that intermittent hypobaric hypoxia exposure induces a protective molecular response, notably in terms of oxidative stress (8–10,13–19,24). Another study also shows the effect of intermittent hypobaric hypoxia on oxidative stress status and antioxidant enzyme activity (30,31). Yet, our scoping review does have certain limitations. The effects of hypobaric hypoxia, particularly intermittent exposure, on cognitive function were not adequately addressed in the research assessed utilizing the applicable techniquen.

CONCLUSION

To the authors' knowledge, no previous research has described hypobaric hypoxia in a scoping review. Intermittent hypobaric hypoxia has protective impacts on human and animal subjects that may be quantified both molecularly and performance-wise. Overall, this scoping review emphasizes the need for more study to unravel the processes underlying hypobaric hypoxia’s molecular, physiological, and cognitive impacts and to investigate novel therapies to minimize its negative repercussions. Future studies should also strive to overcome geographical gaps in study coverage and take into account the many groups that may be impacted by hypobaric hypoxia, such as people living at high elevations and those exposed to hypoxic circumstances in the workplace.

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