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Review

The Use of Simulated Altitude Techniques for Beneficial Cardiovascular Health Outcomes in Nonathletic, Sedentary, and Clinical Populations: A Literature Review

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Abstract

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Background: The reportedly beneficial improvements in an athlete's physical performance following altitude training may have merit for individuals struggling to meet physical activity guidelines.

Aim: To review the effectiveness of simulated altitude training methodologies at improving cardiovascular health in sedentary and clinical cohorts.

Methods: Articles were selected from Science Direct, PubMed, and Google Scholar databases using a combination of the following search terms anywhere in the article: ''intermittent hypoxia,'' ''intermittent hypoxic,'' ''normobaric hypoxia,'' or ''altitude,'' and a participant descriptor including the following: ''sedentary,'' ''untrained,'' or ''inactive.''

Results: 1015 articles were returned, of which 26 studies were accepted (4 clinical cohorts, 22 studies used sedentary participants). Simulated altitude methodologies included prolonged hypoxic exposure (PHE: continuous hypoxic interval), intermittent hypoxic exposure (IHE: 5–10 minutes hypoxic:normoxic intervals), and intermittent hypoxic training (IHT: exercising in hypoxia).

Conclusions: In a clinical cohort, PHE for 3–4 hours at 2700–4200 m for 2–3 weeks may improve blood lipid profile, myocardial perfusion, and exercise capacity, while 3 weeks of IHE treatment may improve baroreflex sensitivity and heart rate variability. In the sedentary population, IHE was most likely to improve submaximal exercise tolerance, time to exhaustion, and heart rate variability. Hematological adaptations were unclear. Typically, a 4-week intervention of 1-hour-long PHE intervals 5 days a week, at a fraction of inspired oxygen (F_IO_2) of 0.15, was beneficial for pulmonary ventilation, submaximal exercise, and maximum oxygen consumption ($\dot{V}O_{2max}$), but an F_IO_2 of 0.12 reduced hyperemic response and antioxidative capacity. While IHT may be beneficial for increased lipid metabolism in the short term, it is unlikely to confer any additional advantage over normoxic exercise over the long term. IHT may improve vascular health and autonomic balance.

Keywords: chronic disease; hypoxia; intermittent hypoxia; intermittent hypoxic training; inactive; unfit

Introduction

Altitude training has long been used in athletic populations in an attempt to improve competitive performance. However, it is not only athletes and coaches who are interested in adaptations associated with altitude training. The potential for physiological improvement and exercise-enhancing adaptations has meant that altitude-centered intervention has also become a point of interest in nonathletic and clinical cohorts (Burtscher et al., 2010). For example, patients with cardiovascular disease exhibit poor exercise tolerance, which makes any physical activity difficult and short lived. In addition, sedentary individuals, who typically suffer from poor exercise tolerance and fitness levels, would also stand to benefit from treatments designed to improve physical performance.

However, for a nonathletic population, the real-world practicalities of work and family commitments typically prohibit the use of real altitude exposure, restricting these

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users to a variety of simulated altitude models (Wilber, 2001). These simulated protocols either use hypobaric chambers or create a normobaric hypoxic environment through nitrogen dilution (Wilber, 2001), recycling expired air using rebreathers (Sausen et al., 2003), or using a polymeric membrane air separation process to filter out oxygen by devices called ''hypoxicators'' (Serebrovskaya et al., 2003).

While there is little doubt that there are differences between hypobaric and normobaric hypoxia (Levine et al., 1988; Roach et al., 1996; Snyder et al., 2006; Girard et al., 2012; Millet et al., 2012a, 2012b), it is the reduction of oxygen that is the trigger for adaptations associated with the oxygen-sensing transcription factor, the α-subunit of hypoxia-inducible factor-1 (*HIF-1α*) (Mounier and Brugniaux, 2012a, 2012b). For example, activation of *HIF-1α* upregulates genes responsible for angiogenesis, erythropoiesis (Semenza, 2009), iron homeostasis [observed as an increase in hemoglobin (Clark et al., 2009; Saunders et al., 2009)], and altered glucose and energy metabolism (Semenza, 2001).

In addition to these adaptations, physiological changes such as increased chemoreflex sensitivity to hypoxia (Bernardi et al., 2001), increased pulmonary arterial pressure (Zhao et al., 2001), and increased subsarcolemmal mitochondrial expression (Schmutz et al., 2010), which is a subgroup of mitochondria that appears to be most responsive to endurance training (Koves et al., 2005), are observed. While the hematological adaptations (red blood cells and hemoglobin in particular) typically receive most of the credit for improved athletic performance (Levine and Stray-Gundersen, 2005), nonhematological adaptations such as improved muscle buffering capacity, lactic acid tolerance, and greater mitochondrial efficiency (Gore et al., 2007) are increasingly being viewed as equally important (Garvican et al., 2011).

All altitude and simulated altitude training protocols usually involve a relatively brief altitude exposure (typically a few weeks) for the purpose of adapting the body to either enhance sea level performance or reduce the compromise in performance at altitude. Thereafter, the individual returns to sea level for their usual training. As such, the hypoxic exposure is ''intermittent''. However, the ''intermittent'' nature of the hypoxic dosage is highly varied and several different training approaches have been developed.

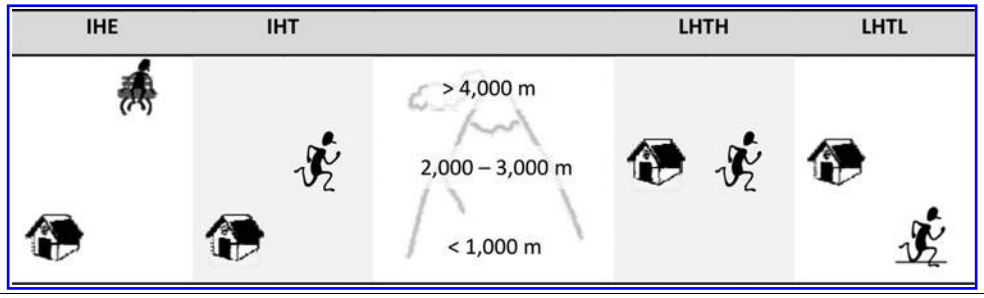
Some popular altitude training methods include the following: live high train high, live high train low (LHTL), intermittent hypoxic training (IHT), and intermittent hypoxic exposure (IHE). Refer to Table 1 for a description of these techniques. Typically, prolonged hypoxic exposure (PHE) such as protocols incorporating a ''live high'' element or protocols incorporating exercise in hypoxia use lower hypoxic dosages (2000–3000 m), while shorter hypoxic exposures, as is used in passive IHE models, use a higher hypoxic dosage (4000 m). At times, a combination of these techniques is used. For example, IHT may be used in conjunction with IHE, whereby participants initially perform 30–60 minutes of exercise in hypoxia followed by another 3 hours of passive hypoxic exposure. Alternatively, additional IHT may be performed in conjunction with the LHTL model (also referred to as ''live high train low and high'').

The purpose of this review is to determine the extent to which simulated altitude has been investigated in nonathletic/sedentary populations and examine the treatments used and findings from the retrieved articles.

Methods

Science Direct, PubMed (via Medline), and GoogleScholar, were searched using a combination of ''include'' and ''excluding'' terms. In addition to these databases, all *American Physiological Society* journals and the ''*High Altitude Medicine and Biology*'' journals were searched individually. The focus of this literature review is on the health-related adaptive response to short-term, simulated altitude in un-acclimatized, nonathletic/sedentary humans. Excluding factors included studies involving high-altitude natives, permanent or long-stay sojourns to real altitude, mountaineering expeditions, or hypoxia associated with disease states (obstructive sleep apnea, ischemic heart disease, or neonatal hypoxia), single dose, and all animal studies. Inclusion factors comprised the following:

Table 1. Hypoxic Exposure Training Methods



IHE is usually achieved using either a hypobaric chamber or altitude tent, or by delivering a lower F_IO_2 through a hand-held face mask. This method of simulated altitude exposure is distinct from the others in that, there is no physical training performed within or alongside the altitude exposure. Hypoxic exposure can range from several repeated doses of a few minutes of hypoxic exposure interrupted by several minutes of ambient air over 40–90 minutes, or a single dose of several hours. IHT requires that the individual either travels to real altitude for their training program or trains within a hypobaric chamber (hypobaric hypoxia) or altitude tent (normobaric hypoxia), or while inspiring a hypoxic gas delivered through a face mask. The individual then returns to sea level following the exercise. During LHTH, the individual either resides at and trains in real altitude, in a hypobaric chamber (hypobaric hypoxia), or in an ''altitude apartment'' (normobaric hypoxia). The hypoxic exposure is uninterrupted and can range in time from several days to several weeks. However, with LHTL, the individual resides at real altitude, in a hypobaric chamber, in an ''altitude apartment'', or in an ''altitude tent'', but returns to a normoxic environment for training. The hypoxic exposure usually ranges from 8 hours (in the case of altitude tents) to 18–20 hours (in altitude apartments, real altitude, or hypobaric chambers).

F_IO_2, fraction of inspired oxygen; IHE, intermittent hypoxic exposure; IHT, intermittent hypoxic training; LHTH, live high train high; LHTL, live high train low.

an intervention-styled study, individuals ranging from healthy (but sedentary) to diseased states, adult participants, the provision of voluntary written informed consent, and English-speaking, full-text, peer-reviewed academic journal articles. Refer to Figure 1 for all search terms used, and the filtering process. In addition, the reference lists of selected review articles (Muza, 2007; Wilber, 2007; Bärtsch et al., 2008; Burtscher et al., 2010; Astorino et al., 2015) were reviewed and any additional articles were added.

The specificity of population-related search terms (''sedentary'' OR ''untrained'' OR ''inactive'') may have excluded studies where the training status of the population was not specified. So this review should be considered an extensive, rather than an exhaustive review.

A quality assessment protocol adapted from van Tulder et al. (1997) and used in whole body vibration studies (Rehn et al., 2007; Manimmanakorn et al., 2014) was used to assess the quality of the selected journal articles. In short, the quality of the studies was based on the suitability of patient selection, intervention, outcome measurements, timing of the follow-up measurements, and the statistical approach to the study. Each ''yes'' yielded 1 point and was therefore assessed on a 16-point scale using the following qualitative outcome: >11 points: high quality; 7–10 points: moderate; and <6 points: low methodological quality.

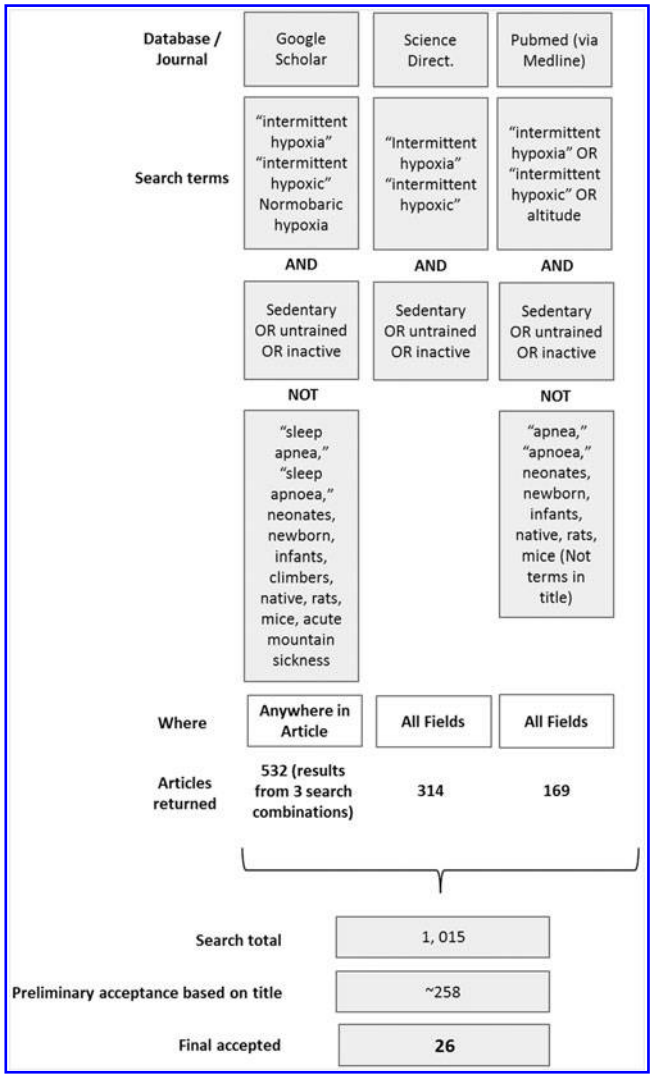


FIG. 1. Overview of database and journal search procedure.

After articles were retrieved and documented, they were then sorted into one of two participant categories:

- Sedentary/untrained
- Clinical

Deciding to include a study of nonathletic, but active participants was, at times, difficult, and the ultimate decision to include the study or not often came down to the wording used by the authors. For example, if participants were described as healthy and explicitly stated noninvolvement in exercise or physical activity, or were ''untrained,'' they were included in the review. In cases where participants were described as healthy, but no explicit physical activity level was recorded, but included a description akin to ''healthy lowlanders, not taking medications and without disease,'' the study was included in a ''healthy/active'' category and was not included in this review. Therefore, there is a possibility that some studies have been misclassified, and have been incorrectly omitted from this review.

Within the IHE protocol, there were two distinct techniques: Those that included one continuous, passive exposure of simulated altitude, usually over 3–4 hours, and those that included short (several minutes) severe hypoxic exposure alternated with a similar duration of ambient air, and repeated for 40–90 minutes. For the sake of clarity, repeated, short intervals of hypoxic air alternated with short periods of breathing normoxic air will be referred to as intermittent hypoxic exposure (IHE), while the sustained periods of passive hypoxic exposure will be referred to as PHE.

Results

The most common reasons for the rejection of articles were as follows: nonintervention studies, reviews/commentaries/debates, real-altitude studies, duplicates, animal studies, case studies, or were irrelevant. Four articles (Ciuha et al., 2015; Stavrou et al., 2015; Debevec et al., 2016; Rittweger et al., 2016) were excluded due to extended confinement (with and without bedrest) akin to long-stay sojourns. Articles ranged in date from 1992 to 2016, and were generally of moderate ($n = 14$, 53.9%) to high ($n = 9$, 34.6%) quality, with only three articles of low quality (11.5%) (Supplementary Table S1; Supplementary Data are available online at www.liebertpub.com/ham)

Studies were male dominant (Table 2) and in the sedentary/untrained group, two distinct age groups were evident: 14 studies ranged in age from 19–29 years and 8 studies ranged in age from 42–64 years.

Table 2. Overview of Participant Profiles in Simulated Altitude Research

Participant group	*No. of studies*	*Male,* n	*Female,* n	*Approximate average age (years ± SD)*
Clinical	4	71	11	50.8 ± 8.2
Sedentary/ untrained	22	463	97	33.1 ± 14.6

Discussion

The effectiveness of simulated altitude in altering health states in a sedentary or clinical population makes up a minority of the overall simulated altitude research field. This review has divided the ''sedentary population'' into clinical participants and sedentary, but otherwise healthy participants. The first part of this review provides an overview of the findings for each simulated altitude study on the health outcomes, and critiques the studies making up the section. In the second part of the discussion, health measures worthy of further exploration are examined.

Clinical populations

There were only four articles examining the effect of IHE in a clinical population, all of which used passive hypoxic exposure (Table 3). Within the IHE protocols, one article focused on interval IHE (Haider et al., 2009) and three focused on PHE (Tin'kov and Aksenov, 2002; del Pilar Valle et al., 2006; Saeed et al., 2012). The studies examining the use of simulated altitude in a clinical population are promising. The three articles examining PHE have found that ~3–4 hour episodes of sustained PHE at a simulated altitude of 2700–4200 m for 2–3 weeks in patients with various forms of heart disease appear to have beneficial effects on blood lipid profile, myocardial perfusion, and exercise capacity. While there appears to be potential for IHE to improve autonomic function in a clinical population, only one study has used this protocol and so, further placebo-controlled (or randomized crossover), double-blind studies are required before more certain conclusions can be made.

Intermittent hypoxic exposure

There was only one study examining the effect of IHE in a clinical population. The aim of Haider et al.'s study was to assess whether IHE could attenuate the decline in cardiovascular autonomic function in patients with chronic obstructive pulmonary disease (COPD) (Haider et al., 2009). Following the 3-week trial, participants receiving IHE demonstrated improved baroreflex sensitivity and a slight (nonstatistically significant) decrease in systolic blood pressure (SBP) compared to baseline data. Heart rate variability (R wave-to-R wave [RR] interval) also increased, suggesting improved parasympathetic modulation of the autonomic nervous system.

Prolonged exposure

The reports of improved exercise tolerance (Saeed et al., 2012), myocardial perfusion (del Pilar Valle et al., 2006), and blood lipid profile (Tin'kov and Aksenov, 2002) in a clinical population following PHE are promising. However, the small number of studies in this population and the different focus in each of the studies make it difficult to assess the repeatability of the respective findings. There are also limitations in each of these studies that cloud the clarity of outcomes in these trials.

The major limitation in these studies has been the lack of a control group. For example, despite a relatively large ($n = 46$) number of participants, Tin'kov and Aksenov (2002) did not include a group receiving a normoxic placebo. Therefore, it is possible that the change in the blood lipid profile over the course of the study could have been attributed to the participant's ongoing use of medication, a change in season (Ockene et al., 2004), change in physical activity level, or diet. Similarly, oral acetazolamide was administered to 11 of the 12 participants in Saeed et al.'s (2012) study before the PHE treatment to prevent altitude sickness. Acetazolamide has been reported to reduce maximum oxygen consumption ($\dot{V}O_{2max}$) (Schoene et al., 1983) and muscle endurance (Fulco et al., 2006) at sea level, which may have provided a training stimulus, resulting in improved strength and $\dot{V}O_{2max}$ following cessation of acetazolamide ingestion. However, as the time course of changes in the blood profile variables almost perfectly matches the changes in the intervention, particularly immediately following the intervention period, and the 3 month follow-up, it is likely that the hypobaric hypoxic treatment was indeed responsible for this change.

The small sample size in the study by del Pilar Valle et al. (2006) was possibly their largest limitation. However, given the high-risk population used in their trial and the absence in participant motivation required for their measurements, their results are likely valid. The improvement in myocardial perfusion was attributed to the improved blood flow from increased angiogenesis and/or increased vasodilation as a result of improved serum nitric oxide following the PHE protocol.

IHT and IHE in sedentary or untrained populations

The results of the studies utilizing sedentary/untrained, but otherwise relatively healthy individuals are summarized in Table 4. The research involving this cohort focused exclusively on IHE, PHE, and IHT training modalities. Overall, the quality of these studies was better than in the clinical groups, with more researchers reporting comparisons relative to control groups.

Intermittent hypoxic exposure

Five studies used IHE as the simulated altitude model, and included populations ranging from participants with mild COPD (or at risk for COPD), who were overweight, to people who were healthy and normally active, but elderly (60–74 years). Most of the studies reported an improvement in exercise tolerance during a submaximal workload (Burtsher et al., 2004; Shatilo et al., 2008; Burtscher et al., 2009; Lizamore et al., 2016), particularly in those with greater disease (Burtsher et al., 2004) or a sedentary nature (Shatilo et al., 2008). Changes in maximal exercise capacity were somewhat harder to detect. Only the elderly men in Burtscher et al.'s (2004) earlier study demonstrated a clear increase in $\dot{V}O_{2max}$ compared to the control group, while their later study (Burtscher et al., 2009) and the study by Lizamore et al. (2016) and Balykin et al. (2004) reported small, not statistically significant changes in $\dot{V}O_{2max}$ following IHE. Despite the lack of change in $\dot{V}O_{2max}$, Burtscher et al.'s later study reported an increase in time to exhaustion following the IHE intervention (Burtscher et al., 2009).

There were several conflicting hematological adaptations in response to the IHE protocol. For example, while some studies report an increase in red blood cells (Burtsher et al., 2004) and hemoglobin (Burtsher et al., 2004; Burtscher et al., 2009), others have noticed no such change (Shatilo et al., 2008). Interestingly, both Shatilo et al.'s (2008) and Burtscher and et al.'s (2009) later study reported small, but not statistically significant decreases in cholesterol, which is in line with the improvement in blood lipid profile following

Table 3. Studies Researching Simulated Altitude Training in a Clinical Population

Authors	*Participant description (cohort, MF, age)*	*Group participant number*	*Frequency (sessions, per week, weeks)*	*Hypoxic dosage*	*Main outcomes*
IHE					
Haider et al. (2009)	Patients with mild COPD symptoms; 10M8F; 51.5 years	IHE: 9 COPD	3–5 minutes of hypoxia: 3 minutes of recovery cycled for 3–5 rotations; 5 sessions/week, 3 weeks.	F_IO_2: 0.15, 0.13, and 0.12 in weeks 1, 2, and 3, respectively	↑ Baroreflex sensitivity and RR interval, slight ↓ in SBP, but NS. ↑ HCVR, but not HVR
		C: 9 (sham)	As above, but with normoxic placebo	F_IO_2: 0.21 in weeks 1–3	Slight ↓in baroreflex sensitivity and RR interval (NS), ⇆ SBP
		Healthy: 14	Baseline data comparison	No treatment	
PHE					
del Pilar Valle et al. (2006)	severe stable CHD, 6M, 66.5 years	PHE[a]: 6	4 hours/session, 1 session/week, 14 sessions	2 hours building up to target, 1 hour at target, 1 hour descent. Starting target 2400 m, ↑ by 250–300 m each, following session until 4200 m	Improved myocardial perfusion, no evidence of impairment
Saeed et al. (2012)	Patients with stable chronic heart failure, 9M3F, 52.5 years	PHE: 12	3–4 hours/session, 10 sessions over 22 days	Started at 1500 m, ↑ by 300 m every session until 2700 m.	↑ $\dot{V}O_{2max}$ (up to 4 weeks after), ↑ exercise time, ↓ 6-minute walk distance, ↑ skeletal muscle strength. Trend to improved LVEF
Tin'kov, Aksenov (2002)	coronary heart disease patients (30 with myocardial infarction, 16 with ischemic heart disease); 46M, 48 years	PHE[a]: 46	3 hours/session, 22 sessions in 22 days	3500 m	↓Total cholesterol and LDL, ↑ HDL (up to 6 months after). ↓ coefficient of atherogenity

[a]Hypobaric hypoxia.

↑, increase; ↓, decrease; ⇆, no change; C: control; sham: normoxic placebo; COPD: chronic obstructive pulmonary disease; F, female; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HCVR, hypocapnic ventilatory response; HVR, hypoxic ventilatory response; M, male; NS, not significant ; PHE, prolonged hypoxic exposure; RR, R wave-to-R wave interval, average distance between RR peaks; SBP, systolic blood pressure; $\dot{V}O_{2max}$, maximum oxygen consumption.

Table 4. Studies Relating to Simulated Altitude in a Sedentary/Untrained Population

Authors	*Participant description (cohort, MF, Age)*	*Group*	*Frequency (sessions, per week, weeks)*	*Hypoxic severity*	*Main Outcome*
IHE					
Balykin et al. (2004)	Healthy, sedentary, overweight, no disease, 11M, 18–20 years	C: cycling (100 W)	30 minutes/day, 3 days/week, 4 weeks	Sea level	Very small changes, only resting $\dot{V}O_2$ and $\dot{V}CO_2$ worthwhile, ↓ strain index of ANS (not significant)
	As above; 9M; 18–20 years	IHE	5 minutes of hypoxia alternated with 5 minutes of recovery, 10 sessions, over 22 days	F_IO_2: 0.10	↓ SNS, ↑ PNS, ↓ strain index of ANS, ↑ physical work capacity
	As above; 9M; 18–20 years	IHE before exercise	As above, followed by C exercise. 10 IHE and 10 C exercise sessions	F_IO_2: 0.10	⇆ SNS, ↑ PNS, ↓↓strain index of ANS, ↑ physical work capacity, better than IHE alone
	As above; 10M; 18–20 years	IHT: cycling (100 W)	30 minutes/day, 3 days/week, 10 sessions	F_IO_2: 0.10	⇆ ANS changes between IHE + Exercise and IHE only, but greater ↑ in physical work capacity
	As above; 8M; 18–20 years	IHE alternated with IHT	IHE and IHT protocols alternated, as described above	F_IO_2: 0.10	Improved ANS balance and physical work capacity (less than combination groups). Greater improvement in anthropometric data.
Burtscher et al. (2004)	Normally active, half with and half without prior myocardial infarction, 8M, 59 years	IHE	3–5 minutes of hypoxia cycled with 3 minutes normoxia repeated for 3–5 cycles, 5 days/week, 3 weeks	F_IO_2: 0.14, 0.12, and 0.10 in weeks 1, 2, and 3	↑RBC and Hb, ↑submaximal efficiency and tolerance. ⇆ peak workload, but ↑ efficiency
	As above, 8M, 61 years	C	As above, but normoxic placebo	F_IO_2: 0.21	↓RBC, ⇆ other bloods, small changes in submaximal and maximal exercise
Burtscher et al. (2009)	Normally active (2 hours/week), with chronic obstructive pulmonary symptoms, 5M4F, 51 years	IHE	3–5 minutes of hypoxia alternated with 3 minutes of normoxia, cycled for 3–5 repetitions, 5 days/week, 3 weeks	F_IO_2: 0.15, 0.13, and 0.12, in weeks 1, 2, and 3	↓SBP, DBP, ↑forced expiratory volume, Hb, and plasma volume, ↑exercise time compared to C
	As above, 5M4F, 52 years	C	As above, but normoxic placebo	F_IO_2: 0.21	↓ SBP, DBP, arterial O_2 saturation, ↑triglycerides
Lizamore et al. (2016)	Less than 30 minutes of physical activity/day, otherwise healthy. 3M5F, 56 years	IHE	5 minutes hypoxia alternated with 5 minutes normoxia cycled 6 times, 4 days/week, 4 weeks.	F_IO_2: week 1: 0.21, $F_IO_2$wk 2: 0.16, $F_IO_2$wk 3: 0.13, $F_IO_2$wk 4: 0.10–0.12	Improved rMSSD. Likely ↓ in submaximal exercising HR. ⇆ exercising capacity
	As above, 2M6F, 56 years	C	As above	Sea level	⇆ rMSSD, submaximal exercise or exercise capacity

(*continued*)

TABLE 4. (CONTINUED)

Authors	*Participant description (cohort, MF, Age)*	*Group*	*Frequency (sessions, per week, weeks)*	*Hypoxic severity*	*Main Outcome*
Shatilo et al. (2008)	Healthy active seniors; 14M; 67 years	IHE	5 minutes of hypoxia alternated with 5 minutes of normoxia cycled 4 times, for 10 days	F_IO_2: 0.12	⇆ Hemodynamic indices or work capacity. ↑ skin blood flow during submaximal exercise and hyperemic recovery time
	Sedentary seniors; 21M; 61 years	IHE	As above	As above	↓ Blood pressure, ↑ submaximal work and anaerobic threshold. ↓ HR and BP during submaximal exercise. ↑ skin blood flow. ↑ improvements compared to active group
PHE					
Gatterer et al. (2015)	Obese participants, 4M12F, 50 years	IHT: cycle ergometer or cross trainer or treadmill at 65%–70% maximal HR (+10 bpm if working on cross trainer or treadmill). Then PHE for 90 minutes.	90 minutes/day IHT, followed by 90 minutes of PHE, 2 days/week, 8 months (52 sessions)	IHT: F_IO_2: 0.14 (3500 m) PHE: F_IO_2: 0.122 (4500 m)	Improved body weight, BMI, waist: hip circumference, SBP and peak power output
	As above; 6M10F, 52 years	C: as above in normoxia	As above, but normoxic placebo	Sea level	As above
Katayama et al. (1998)	Healthy, no regular physical activity, no cardiorespiratory disease or medication; 7M; 19 years	IHT[a]: 2×15 minutes cycling (5 minutes of recovery between) at 40% sea level max; remainder PHE[a]	2 hours/day, 6 sessions in 6 days	30 minutes up to 4500 m; 1 hour at 4500 m, 15 minutes back to sea level	⇆HVR or HCVR, ↑ $\dot{V}O_{2peak}$
	As above; 6M; 19.5 years	PHE[a] (rest)	As above	As above	↑ HVR, but ⇆HCVR or $\dot{V}O_{2peak}$
Ricart et al. (2000)	4WD members; 5M4F; 45 years	PHE[a]	2 hours/day, 7 days/week, 2 weeks	Hypobaric, 5000 m	↑ SaO_2 and expired minute volume (↑ tidal volume). ⇆ Resting variables, packed cell volume or Hb after 2 weeks.
Wang et al. (2007b)	Healthy, nonsmokers, no medications, disease free; 10M; 24 years	PHE: Moderate (15%)	1 hour/day, 5 days/week, 8 weeks	F_IO_2: 0.15; 2733 m	Lower ↑ in hypoxia and exercise induced eosinophil and neutrophil platelet aggregation, interleukin-1β, and malondialdehyde levels
	As above; 10M, 23 years	PHE: Severe (12%)	As above	F_IO_2: 0.12	As above, but also ↑ plasma interleukin 6 and interleukin 10

(*continued*)

TABLE 4. (CONTINUED)

Authors	*Participant description (cohort, MF, Age)*	*Group*	*Frequency (sessions, per week, weeks)*	*Hypoxic severity*	*Main Outcome*
Wang et al. (2007a)	Healthy, nonsmokers, no medications, disease free; 10M; 24 years	PHE: Moderate (15%)	1 hour/day, 5 days/week, 4 weeks	F_IO_2: 0.15; 2733 m	↑ pulmonary ventilation and oxygen uptake
	As above; 10M, 23 years	PHE: severe (12%)	As above	F_IO_2: 0.12	As above, but also ↑ exercising BP, ↑ plasma malondialdehyde and nitric oxide, ↓hyperemic arterial response (hemodynamic function), venous compliance, and endothelium-dependent vasodilation. ↓ Plasma antioxidant and Vitamin E
	As above, 10M, 24 years	C	As above	F_IO_2: 0.21	No change.
Wang et al. (2010)	Healthy, nonsmokers, no medications, disease free; 12M; 23 years	IHT: cycling 50% maximal heart rate reserve	30 minutes/day, 5 days/week, 4 weeks	F_IO_2: 0.15; 2733 m	↓ Stroke volume, hyperemia, and reoxygenation suppression induced by F_IO_2: 0.12. ↑perfusion and O_2 extraction in F_IO_2: 0.12 exercise
	As above; 12M; 23 years	IHT: 50% max work at FiO2: 15%	As above	F_IO_2: 0.15; 2733 m	As above, but also better improvement in aerobic capacity than normoxic exercise.
	As above; 12M; 23 years	C: sedentary normoxic	As above	Sea level	No worthwhile change
	As above; 12M; 21 years	C: normoxic cycling (50% maximal work rate)	As above	Sea level	No worthwhile change
	As above; 12M; 21 years	PHE	As above	F_IO_2: 0.15; 2733 m	No worthwhile change
IHT					
Balykin et al. (2004)	Healthy, sedentary, overweight, no disease, 11M, 18–20 years	C: Cycling (100 W)	30 minutes/day, 3 days/week, 4 weeks	Sea level	Very small changes, all NS except resting $\dot{V}O_2$ and $\dot{V}CO_2$, ↓in strain index of ANS (NS)
	As above; 9M; 18–20 years	IHE	5 minutes of hypoxia alternated with 5 minutes of recovery, 10 sessions, over 22 days	F_IO_2: 0.10	↓ SNS, ↑ PNS, ↓ strain index of ANS, ↑ physical work capacity
	As above; 9M; 18–20 years	IHE before exercise	As above, followed by C exercise. 10 IHE and 10 C exercise sessions	F_IO_2: 0.10	⇆ SNS, ↑ PNS, ↓↓strain index of ANS, ↑ physical work capacity, better than IHE alone
	As above; 10M; 18–20 years	IHT: cycling (100 W)	30 minutes/day, 3 days/week, 10 sessions	F_IO_2: 0.10	⇆ANS changes between IHE + Exercise and IHE only, but greater ↑ in physical work capacity
	As above; 8M; 18–20 years	IHE alternated with IHT	IHE and IHT protocols alternated, as described above	F_IO_2: 0.10	Improved ANS balance and physical work capacity (less than combination groups). Improvement in anthropometric data.

(*continued*)

TABLE 4. (CONTINUED)

Authors	*Participant description (cohort, MF, Age)*	*Group*	*Frequency (sessions, per week, weeks)*	*Hypoxic severity*	*Main Outcome*
Engfred et al. (1994)	Untrained, healthy participants, 4M3F, 26 years	IHT: Cycle ergometer, 70%; $\dot{V}O_{2max}$ at altitude	45 minutes/day, 5 days/week, 5 weeks	Hypobaric hypoxia. 2500 m	↑ $\dot{V}O_{2peak}$, ⇆ noradrenaline, adrenaline, growth hormone, beta-endorphin, glucagon, and insulin between groups. ⇆ Erythropoietin, 2,3-diphosphoglycerate between before and after.
	As above, 4M3F, 27 years	As above, at 70% $\dot{V}O_{2max}$ at sea level	As above	As above	As above
	As above, 4M3F, 26 years	As above,	As above	Sea level	As above, but highest ↑ in endurance
Emonson et al. (1997)	No regular physical activity, nonsmokers and no contraindications, 9M, 28 years	IHT: Cycle ergometer at HR corresponding to 70% $\dot{V}O_{2max}$ at altitude	45 minutes/day, 3 days/week, 5 weeks	Hypobaric hypoxia: 554 mmHg (72.4 kPa) 2500 m	↑ SL $\dot{V}O_{2peak}$ and TTE. ⇆ Peak blood lactate during endurance test
	As above, 9M, 30 years	As above, but in normoxia, at an HR corresponding to 70% $\dot{V}O_{2max}$ at sea level	As above	Sea level: 750 mmHg (100 kPa)	As above.
Friedmann et al. (2003)	Recreationally active or untrained, 10M, 25 years	IHT: Low resistance, high repetition leg strength training	40 minutes/day, 3 days/week, 4 weeks	F_IO_2: 0.12 (4500 m)	As below, but also correlation between hypoxic markers and glycolytic enzyme mRNA linked to hypoxia-specific adaptation. No practical benefit of IHT
	As above, 9M, 24 years	C: normoxic low resistance, high repetition leg strength training	As above, but normoxic placebo	Sea level	↑ Strength endurance capacity, but ⇆ muscle cross sectional area, fiber-type distribution or fiber cross sectional area. High interindividual variation in mRNA analyses.
Gatterer et al. (2015)	Obese participants, 4M12F, 50 years	IHT: cycle ergometer or cross trainer or treadmill at 65%–70% maximal HR (+10 bpm if working on cross trainer or treadmill). Then PHE for 90 minutes.	90 minutes/day IHT, followed by 90 minutes of PHE, 2 days/week, 8 months (52 sessions)	IHT: F_IO_2: 0.14 (3500 m) PHE: F_IO_2: 0.122 (4500 m)	Improved body weight, BMI, waist: hip circumference, SBP, and peak power output
	As above; 6M10F, 52 years	C: as above in normoxia	As above, but normoxic placebo	Sea level	As above

(*continued*)

TABLE 4. (CONTINUED)

Authors	*Participant description (cohort, MF, Age)*	*Group*	*Frequency (sessions, per week, weeks)*	*Hypoxic severity*	*Main Outcome*
Geiser et al. (2001)	Healthy untrained, 10M, 23 years	IHT: high-intensity (80% $\dot{V}O_{2peak}$) hypoxia	30 minutes/day, 5 days/week, 6 weeks	3850 m	↑ $\dot{V}O_{2peak}$ and maximal power tested in hypoxia and normoxia. ↑↑ Mitochondrial volume density. ↑ knee extensor muscle volume and capillary length density (length of capillary in 1 mm^3)
	As above, 8M, 23 years	IHT: low-intensity (67% $\dot{V}O_{2peak}$) hypoxia	30 minutes/day, 5 days/week, 6 weeks	3850 m	↑$\dot{V}O_{2peak}$. ↑ Maximal power, but less so than high-intensity groups. ↑ mitochondrial volume density
	As above, 8M, 25 years	C: high-intensity (80% $\dot{V}O_{2peak}$) normoxia	As above, but normoxic placebo	600 m	↑ $\dot{V}O_{2peak}$. ↑ maximal power (more so than low intensity.) ↑ mitochondrial volume density
	As above, 7M, 29 years	C: low-intensity (67% $\dot{V}O_{2peak}$) normoxia	As above, but normoxic placebo	600 m	↑$\dot{V}O_{2peak}$. ↑ maximal power, but less so than high-intensity groups; ↑ mitochondrial volume density
Kayayama et al. (1998)	Healthy, no regular physical activity, no cardiorespiratory disease or medication; 7M; 19 years	IHT[a]: 2×15 minutes cycling (5 minutes of recovery between) at 40% sea level max; remainder PHE[a]	2 hours/day, 6 sessions in 6 days	30 minutes up to 4500 m; 1 hour at 4500 m, 15 minutes back to sea level	⇆HVR or HCVR, ↑ $\dot{V}O_{2peak}$
	As above; 6M; 19.5 years	PHE[a]	As above	As above	↑ HVR, but ⇆HCVR or $\dot{V}O_{2peak}$
Masuda et al. (2001)	Sedentary adults, 7M, 20 years	IHT: 60% $\dot{V}O_{2max}$ for first 3 sessions, thereafter 70% $\dot{V}O_{2max}$ at altitude	60 minutes/day, every other day for 8 weeks (28 sessions)	Hypobaric hypoxia: 560 torr 2500 m	↑$\dot{V}O_{2max}$, ⇆ muscle myoglobin concentration or muscle fiber composition. ↑ Citrate synthase and capillary: fiber ratio.
	As above	60% $\dot{V}O_{2max}$ for first 3 sessions, thereafter 70% $\dot{V}O_{2max}$ at sea level	As above	Sea level	As above
Mao et al. (2011)	Healthy, nonsmoker, no medication or history of disease: 12M; 22 years	IHT: cycling at 60% work rate	30 minutes/day, 5 days/week, 5 weeks	F_IO_2: 0.15; 2733 m	↓ erythrocyte health and durability under shear stress. ↑ Eryptotic response to hydrogen peroxide
	As above; 12M; 22 years	C: cycling at 60% work rate	As above	F_IO_2: 0.21; (sea level)	⇆ Erythrocyte rheological properties under rest or exercise.

(*continued*)

TABLE 4. (CONTINUED)

Authors	*Participant description (cohort, MF, Age)*	*Group*	*Frequency (sessions, per week, weeks)*	*Hypoxic severity*	*Main Outcome*
Nishiwaki et al. (2011)	Postmenopausal women, sedentary/recreationally active, no hormone replacement therapy; 8F; 56 years	IHT[a]: 30 minutes of swimming 50% $\dot{V}O_{2peak}$, PHE remainder	2 hours/day, 4 days/week, 8 weeks	2000 m	↓ brachial pulse wave velocity; ↑ flow mediated dilation and peak diameter
	As above; 8F; 56 years	C: 30 minutes of swimming	30 minutes/day, 4 days/week, 8 weeks	Sea level	No worthwhile changes
Pesta et al. (2011)	Healthy sedentary: 7M; 29 years	IHT: endurance training	35–55 minutes/day, 3 days/week, 10 weeks	F_IO_2: 0.13.5, 4000 m	↑ Fatty acid oxidation capacity per muscle mass mainly due to qualitative mitochondrial change, and partly due to tissue density.
	As above; 8M; 28 years	C: endurance training, normoxia	As above, but normoxic placebo	Sea level	↑ Physiological oxidative phosphorylation and key mitochondrial changes.
	Healthy sedentary; 7M; 24 years	IHT: strength training	12–17 minutes/day, 3 days/week, 10 weeks	F_IO_2: 0.135, 4000 m	As above
	As above; 3M; 24 years	C: strength training	As above, normoxic placebo	Sea level	As above.
Vogt et al. (2001)	Untrained, 7M, 23 years	IHT: high intensity (4–6 mmol blood lactate)	30 minutes/day, 5 days/week, 6 weeks	3850 m	↑ $\dot{V}O_{2peak}$ and maximal power output; ↑ *HIF-1α* and splice variant *HIF-1α*^{736}; ↑ myoglobin and vascular endothelial growth factor mRNA.
	Untrained, 8M, 25 years	C: High intensity as above	As above, but normoxic placebo	Sea level	↑ $\dot{V}O_{2peak}$ and maximal power output
	Untrained, 7M, 23 years	IHT: low intensity (2–3 mmol blood lactate)	30 minutes/day, 5 days/week, 6 weeks	3850 m	↑ $\dot{V}O_{2peak}$ and maximal power output ↑*HIF-1α* and splice variant *HIF-1α*^{736}
	Untrained, 8M, 29 years	C: Low intensity as above	As above, normoxic placebo	Sea level	↑ $\dot{V}O_{2peak}$ and maximal power output
Wang et al. (2010)	Healthy, nonsmokers, no medications, disease free; 12M; 23 years	IHT: cycling 50% maximal heart rate reserve	30 minutes/day, 5 days/week, 4 weeks	F_IO_2: 0.15; 2733 m	↓ Stroke volume, hyperemic and reoxygenation suppression induced by F_IO_2: 0.12. ↑perfusion and O_2 extraction in F_IO_2: 0.12 exercise
	As above; 12M; 23 years?	IHT: 50% max work at FiO2: 15%	As above	F_IO_2: 0.15; 2733 m	As above; also more ↑aerobic capacity than normoxic exercise.
	As above; 12M; 23 years	C: sedentary normoxic	As above	Sea level	No worthwhile change
	As above; 12M; 21 years	C: normoxic cycling (50% maximal work rate)	As above	Sea level	No worthwhile change
	As above; 12M; 21 years	PHE	As above	F_IO_2: 0.15; 2733 m	No worthwhile change

(*continued*)

TABLE 4. (CONTINUED)

Authors	*Participant description (cohort, MF, Age)*	*Group*	*Frequency (sessions, per week, weeks)*	*Hypoxic severity*	*Main Outcome*
Wang et al. (2014)	Healthy, nonsmokers, no medications, disease free. 20M; 22 years	IHT: PHE then 60% $\dot{V}O_{2max}$ at FiO2: 15%	30 minutes of PHE, 30 minutes of IHT/day, 5 days/week, 5 weeks	F_IO_2: 0.15; 2733 m	Greater ↑ in aerobic capacity, cardiac output and oxygenation of vastus lateralis during exercise. ↑ Mobilization and function of circulating progenitor cells. ↑ Production of angiogenic factors.
	As above; 20M; 22 years	PHE	30 minutes/day, 5 days/week, 5 weeks	F_IO_2: 0.15; 2733 m	
Wiesner et al. (2010)	Sedentary, overweight, healthy, 10M14F; 42 years	IHT: Treadmill (65% maximal HR)	1 hour/day, 3 days/week, 4 weeks	2740 m	↓ Workload during training; ↑ $\dot{V}O_{2peak}$ and time to exhaustion; greater improvement in respiratory quotient and lactate at anaerobic threshold and body composition.
	As above, 8M13F, 42 years	C: Treadmill (65% maximal heart rate)	As above, normoxic placebo	Sea level	↑ $\dot{V}O_{2peak}$ and time to exhaustion

[a]Hypobaric hypoxia.

ANS, autonomic nervous system; BP, blood pressure; DBP, diastolic blood pressure; Hb, hemoglobin; HCVR, hypocapnic ventilatory response; *HIF-1α*, hypoxic inducible factor-1; HR, heart rate; HVR, hypoxic ventilatory response; $\dot{V}O_2$, volume of oxygen consumption; PNS, parasympathetic nervous system; RBC, red blood cells; rMSSD, root mean square of successive difference; SNS, sympathetic nervous system; $\dot{V}CO_2$, volume of carbon dioxide; wk, week.

PHE in a clinical population (Tin'kov and Aksenov, 2002). However, the decrease in cholesterol in the test group in Burtscher et al.'s (2009) study was similar to the decrease in the control group and therefore these results are equivocal and add doubt to the assumed intervention-based changes in the clinical cohort (Burtscher et al., 2009).

The IHE intervention also appeared to reduce systemic stress. Balykin et al. (2004) and Lizamore et al. (2016) demonstrated improved heart rate variability following the hypoxic exposure intervention, indicating improved sympathetic/parasympathetic balance. This was also reflected in the reduced systolic blood pressure (Shatilo et al., 2008; Burtscher et al., 2009) reported by others. The study by Balykin et al. (2004) primarily investigated the effectiveness of different IHE protocols with and without the use of exercise. The IHE protocols used in conjunction with exercise training (either simultaneously or sequentially) were more effective regarding exercise capability (see discussion regarding ''Intermittent hypoxic training''). Typically, participants receiving IHE appear to tolerate hypoxia well. The most frequently reported side effects include dizziness, shortness of breath, and chest discomfort (Shatilo et al., 2008; Lizamore et al., 2016). However, there may be some risk to blood pressure in severe hypoxia (fraction of inspired oxygen [F_IO_2] ≤0.12) intervals lasting more than 7 minutes (Shatilo et al., 2008), whereas 5-minute intervals were tolerated well. There have also been some reports of tinnitus following IHE (Shatilo et al., 2008). Interestingly, in both Burtscher et al.'s studies (Burtsher et al., 2004; Burtscher et al., 2009) and in the study by Lizamore et al. (2016), side effects were also observed in the control groups who reported feeling dizzy or sleepy during the hypoxic exposure. The side effects also seem to be highly individual, with some participants reporting no side effects and others frequently reporting discomfort (Lizamore et al., 2016). Therefore, researchers should consider the sensitivity of their participants to hypoxia before enrolling them in the study.

All the IHE studies made use of a control group of sorts (while Shatilo et al. (2008) did not use a placebo group, they did examine the same intervention in sedentary compared to active participants; Balykin et al. (2004), on the other hand, only used sedentary participants, but compared a range of different simulated altitude techniques). Of note is that, while some of the hematological parameters are unclear, there were no negative health outcomes attributed to the IHE interventions (such as increased SBP, or a decline in exercise tolerance). Intermittent hypoxic exposure appears to present a reasonable possibility of health benefit, particularly for those with limited exercise ability. Care should be taken to carefully monitor side effects during the hypoxic exposures; however, symptoms of discomfort seem to readily abate upon return to normoxic conditions.

Prolonged hypoxic exposure

Only the studies by Wang et al. (2007a, 2007b, 2010) and Gatterer et al. (2015) have used normobaric PHE, while the others used hypobaric hypoxia. Wang et al. focused primarily on how hypoxic severity (FIO_2 of 0.12 vs. 0.15) affects hemodynamic control (Wang et al., 2007a, 2010) and eosinophil- and neutrophil- platelet aggregation, and the cytokine response to strenuous exercise (Wang et al., 2007b), as well as exercise tolerance and ability.

The results of Wang et al.'s studies are extremely useful in gauging an appropriate dosage of PHE in both session duration and session intensity. For example, 4 or 8 weeks of 1-hour-long PHE, 5 times/week using an FIO_2 of 0.15 resulted in improved pulmonary ventilation, submaximal exercise performance, and $\dot{V}O_{2peak}$, but not maximal exercise time or maximal work rate (Wang et al., 2007a, 2007b). However, these measures were not statistically significant following 30 minutes of PHE at an F_IO_2 of 0.15 (Wang et al., 2010). However, lowering the F_IO2 to 0.12 for 60 minutes tended to worsen the hyperemic response after 4 weeks (Wang et al., 2007a). In addition to the reduced hyperemic response, the group receiving an F_IO_2 of 0.12 demonstrated an increase in lipid peroxidation, decrease in vitamin E levels, and a decrease in vascular endothelial function, which was attributed to a decrease in antioxidative capacity (Wang et al., 2007a).

Contrastingly, 8 weeks of the same PHE protocol at an F_IO_2 of 0.12 or 0.15 resulted in a reduction in the proinflammatory cytokine and thrombo-inflammatory responses to strenuous exercise, but only the group receiving an F_IO_2 of 0.12 demonstrated a substantial increase in circulatory anti-inflammatory cytokines IL-6 and IL-10 during hypoxia and exercise, and at rest (Wang et al., 2007b). Wang et al. (2010) noted no significant difference between PHE and normoxic controls on exercise ability. While the effects of hypobaric PHE are likely to improve hypoxic sensitivity (Katayama et al., 1998) and acclimatization through increased ventilation and SpO_2 during hypoxic exercise (Ricart et al., 2000), there is insufficient literature available to comment on its effectiveness as a means of improving exercise tolerance or health in a sedentary population. Overall, a normoxic PHE protocol of >4 weeks for 1 hour/day, 5 days/week at an F_IO_2 of 0.15 is likely to be the safest PHE model for a sedentary/untrained population. While this protocol may improve submaximal performance and $\dot{V}O_{2peak}$, it is unlikely to confer any performance change in maximal exercise ability.

Intermittent hypoxic training

When researchers have used identical exercise intensity protocols in hypoxic, compared to normoxic conditions, the participants training in hypoxia have demonstrated superior aerobic capacity following as little as 6–10 IHT sessions (Katayama et al., 1998; Balykin et al., 2004) for as long as 4–5 weeks (Wang et al., 2010; Mao et al., 2011) of IHT (30 minutes/day and 5 days/week). However, other researchers have demonstrated no improvement in sea level performance compared to the control group following 5–6 weeks of IHT (between 67% and 80% $\dot{V}O_{2peak}$) for 30–45 minutes/day, 5 days/week (Engfred et al., 1994; Emonson et al., 1997; Geiser et al., 2001; Vogt et al., 2001), and no clear advantage following longer interventions of 10 weeks of IHT (Pesta et al., 2011) or more (Gatterer et al., 2015).

Interestingly, even when there is little change in exercise performance, there are likely to be hypoxia-related adaptations at the cellular level (Geiser et al., 2001; Vogt et al., 2001; Friedmann et al., 2003). For example, despite positive correlations between mRNA levels of vascular endothelial growth factor (VEGF) and myoglobin, and between phosphofructokinase and lactate dehydrogenase following IHT (but not before), there was no additional advantage of strength training in hypoxia compared to normoxia (Friedmann et al., 2003). Other structural alterations reported as a

consequence of IHT include significant increases in muscle volume of knee-extensors, capillary length density, which is the capillary length in 1 mm^3 (Tomanek, 2013), and mitochondrial volume density (Geiser et al., 2001; Vogt et al., 2001), and elevated mRNA concentrations of the *HIF-1α* (Vogt et al., 2001), that is, *HIF-1α* is a subunit of hypoxia-inducible factor-1, which is responsible for upregulating genes that act to reduce the hypoxic stress and include the promotion of erythropoietin and VEGF (Wenger and Gassmann, 1997).

None of the studies reported any beneficial erythropoietic response as a consequence of 4–6 weeks of IHT (Engfred et al., 1994; Geiser et al., 2001; Wang et al., 2010; Mao et al., 2011). Indeed, Mao et al. (2011) demonstrated accelerated aging, decreased size, a reduction in the ability of erythrocytes to deform under stress, and increased eryptotic (or suicidal cell death) response to hydrogen peroxide in cells, following IHT. These findings raise concern over the appropriateness of IHT interventions in groups or clinical populations with blood disorders that may become further compromised following IHT.

However, potentially valuable adaptations for a sedentary population that were reported following IHT include improved autonomic balance and increased lipid metabolism as evidenced by a lower RER during exercise (Balykin et al., 2004), which was possibly responsible for the 13% decrease in body fat compared to little change following normoxic exercise (Balykin et al., 2004). However, the value of adding hypoxia to a long-term weight loss exercise program was negligible in a recent study (Gatterer et al., 2015).

In Gatterer et al.'s study, both the IHT groups (one working at the same absolute intensity as the normoxic control group and the other at a relative intensity factoring in the added altitude stress) demonstrated similar fitness and body composition changes as the normoxic control group. The authors noted that given the similar fitness and body composition outcomes at lower absolute exercise intensity (in the relative hypoxic group), the IHT may be worthwhile in a cohort unable to physically perform a higher level of physical activity. Otherwise, there was no added advantage of IHT over regular exercise training in an obese population (Gatterer et al., 2015). Nishiwaki et al. (2011) reported improvements in vascular health (decreased pulse wave velocity and improved flow-mediated vasodilation) following hypobaric IHT, but not normoxic exercise. Further research should examine whether these improvements in vascular health can be repeated following normobaric hypoxia.

Key areas for future research in a sedentary or clinical population

In the sedentary and clinical populations, IHT does not appear to be particularly more effective than normoxic training in improving exercise capacity (Vogt et al., 2001; Friedmann et al., 2003; Pesta et al., 2011; Gatterer et al., 2015); however, the effects on vascular health are promising (Nishiwaki et al., 2011; Shi et al., 2013). Contrastingly IHE appeared to be effective in inducing beneficial adaptations, such as improved submaximal aerobic fitness and exercise tolerance (Burtsher et al., 2004; Shatilo et al., 2008; Burtscher et al., 2009), autonomic modulation (Balykin et al., 2004), and blood lipid profile (Tin'kov and Aksenov, 2002).

Autonomic modulation and systolic blood pressure

A decline in autonomic function may be linked to numerous risk factors for cardiovascular disease, and indeed even precede the risk factors themselves (Thayer and Lane, 2007). With this in mind, the potential for hypoxic exposure treatments to improve autonomic balance in a sedentary population warrants further investigation.

While there is an increase in sympathetic activity with hypoxia (Lizamore et al., 2016) as evidenced by an increase in heart rate variability, systolic blood pressure, and heart rate with hypoxia (Rodway et al., 2007), the ''training effects'' of this sympathetic activation appears to result in reduced basal sympathetic activity (Lizamore et al., 2016). Indeed, a decrease in resting (Shatilo et al., 2008) and exercising (Burtsher et al., 2004) systolic blood pressure has been observed following an IHE protocol at an F_IO_2 of 0.12 (particularly in a sedentary population). The improvements in autonomic regulation (Balykin et al., 2004; Haider et al., 2009; Lizamore et al., 2016) appear to be particularly effective in an unhealthy population (overweight and at risk of or with mild COPD), compared to their more healthy counterparts (Bernardi et al., 2001). However, these improvements do not appear to be associated with PHE (Wang et al., 2007a). Therefore, when selecting a mode of hypoxic intervention for a sedentary population, an IHE protocol (rather than PHE) may be preferential in a sedentary population who may be at risk of high BP.

Blood lipid profile and vascular health

High-density lipoprotein (HDL), low-density lipoprotein (LDL), and total cholesterol are important considerations in the assessment of a person's overall cardiovascular risk (New Zealand Guidelines Group, 2003). However, the effect of hypoxic intervention in these measures is conflicting. For example, Tin'kov et al. reported decreased total cholesterol and LDL and a corresponding increase in HDL following PHE (Tin'kov and Aksenov, 2002); however, Gatterer et al. (2015) reported no real differences in these measures between their groups receiving IHT + PHE and normoxic exercise. Furthermore, placebo-controlled trials examining the differences in hypoxic dose on blood lipid profile would be valuable. For example, two recent studies have demonstrated an improvement in vascular health following IHT protocols in both postmenopausal women and healthy young men (Nishiwaki et al., 2011; Shi et al., 2013). However, Wang et al. (2007a) have reported a decrease in hemodynamic function following a PHE of 60 minutes (F_IO_2 of 0.12), but not following 60 minutes at an F_IO_2 of 0.15 (Wang et al., 2007a; Wang et al., 2010), which suggests that the severity of the hypoxic stimulus should pass a minimum threshold, but not be excessive (for the sedentary or clinical population, ''excessive'' may be an F_IO_2 below 0.12 for an hour or more).

An improvement in flow-mediated dilation and arterial compliance was noted following 2 hours of IHT+PHE at a simulated altitude of 2000 m (IHT: 30 minutes of swimming at 50% $\dot{V}O_{2peak}$ + 90 minutes of PHE) (Nishiwaki et al., 2011) or 50 minutes of IHT (60% HR_{max}) + 30 minutes of PHE at a simulated altitude at ~2400 m, or an F_IO_2 of 0.155 (Shi et al., 2013). However, 60 minutes of PHE at an F_IO_2 of 0.12 had a detrimental effect on hemodynamic function (Wang et al., 2007a). An IHE protocol may provide a good

balance between short intervals of severe hypoxia sufficient to improve arterial function, but regular alternation with ambient air may prevent distress or maladaptation.

Dosage

Katayama et al. have investigated various alterations and adjustments between the different hypoxic delivery modalities. In doing so, Katayama's research group has established that, there is no added advantage to using a 3-hour exposure compared to 1 hour of hypoxia for enhancing hypoxic ventilatory chemosensitivity, 14 days are better than 7 days for enhancing central hypercapnic ventilatory chemosensitivity, and an F_IO_2 of 0.123 is better than 0.15 for improving resting (but not exercising) hypoxic chemosensitivity (Katayama et al., 2005; Katayama et al., 2007; Katayama et al., 2009). However, most of these studies have been conducted in well-trained cohorts, using the PHE model, and were focused on acclimatization. Further research regarding dosage is needed in a sedentary population. Furthermore, no researchers have investigated the differences in the frequency of hypoxic exposures per week. As there are no additional advantages to a longer session compared to a shorter session (1 hour compared 3 hours), or IHE to PHE (Koehle et al., 2007), a 60-minute IHE session may prove most beneficial for a sedentary population. In addition, IHE is unlikely to cause any increase in systolic blood pressure (Foster et al., 2005) and may avoid the reduction in hemodynamic function with 60 minutes of PHE at an F_IO_2 of 0.12.

Key points and further research from literature review

- The effects of simulated altitude on health outcomes in a sedentary or clinical population appear to range from not effective to beneficial.
- There is some evidence that severe PHE can be harmful at the cellular level (even in the absence of physical performance change) and so, researchers should carefully consider their population when designing their interventions.
- Based on the current literature, 1 hour of IHE to an F_IO_2 of 0.12 for at least 2 weeks is likely to be most worthwhile for health adaptation, with little risk of harm to health. Intervention response seems to decline following 3 months of treatment. More research is needed on the frequency of IHE per week for beneficial adaptation.
- Further research is needed regarding the effects of simulated altitude on autonomic function, vascular health, blood lipid profile, and the optimal hypoxic dosage for the improvement of these measures.

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References

Astorino TA, Harness ET, and White AC. (2015). Efficacy of acute intermittent hypoxia on physical function and health status in humans with spinal cord injury: A brief review. Neural Plast 2015, Article ID 409625

Balykin MV, Gening TP, and Vinogradov SN. (2004). Morphological and functional changes in overweight persons under combined normobaric hypoxia and physical training. Hum Physiol 30:184–191.

Bärtsch P, Dehnert C, Friedmann-Bette B, and Tadibi V. (2008). Intermittent hypoxia at rest for improvement of athletic performance. Scand J Med Sci Sports 18:50–56.

Bernardi L, Passino C, Serebrovskaya Z, Serebrovskaya T, and Appenzeller O. (2001). Respiratory and cardiovascular adaptations to progressive hypoxia. Eur Heart J 22:879–886.

Burtscher M, Gatterer H, Szubski C, Pierantozzi E, and Faulgaber M. (2010). Effects of interval hypoxia on exercise tolerance: Special focus on patients with CAD or COPD. Sleep Breath 14:209–220.

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

Burtsher M, Pachinger O, Ehrenbourg I, Mitterbauer G, Faulhaber M, Puhringer R, and Thatchouk E. (2004). Intermittent hypoxia increases exercise tolerance in elderly men with and without coronary artery disease. Int J Cardiol 96:247–254.

Ciuha U, Eiken O, and Mekjavic IB. (2015). Effects of normobaric hypoxic bed rest on the thermal comfort zone. J Therm Biol 49–50:39–46.

Clark SA, Quod MJ, Clark MA, Martin DT, Saunders PU, and Gore CJ. (2009). Time course of haemoglobin mass during 21 days live high:train low simulated altitude. Eur J Appl Physiol 106:399–406.

Debevec T, Simpson EJ, Mekjavic IB, Eiken O, and Macdonald IA. (2016). Effects of prolonged hypoxia and bed rest on appetite and appetite-related hormones. Appetite 107:28–37.

del Pilar Valle M, García-Godos F, Woolcott OO, Marticorena JM, Rodríguez V, Gutiérrez I, Fernández-Dávila L, Contreras A, Valdivia L, and Robles J. (2006). Improvement of myocardial perfusion in coronary patients after intermittent hypobaric hypoxia. J Nucl Cardiol 13:69–74.

Emonson D, Aminuddin A, Wight R, Scroop GC, and Gore CJ. (1997). Training-induced increases in sea level VO2max and endurance are not enhanced by acute hypobaric exposure. Eur J Appl Physiol Occup Physiol 76:8–12.

Engfred K, Kjær M, Secher NH, Friedman DB, Hanel B, Nielsen OJ, Bach FW, Galbo H, and Levine BD. (1994). Hypoxia and training-induced adaptation of hormonal responses to exercise in humans. Eur J Appl Physiol Occup Physiol 68:303–309.

Foster GE, McKenzie DC, Milsom WK, and Sheel AW. (2005). Effects of two protocols of intermittent hypoxia on human ventilatory, cardiovascular and cerebral responses to hypoxia. J Physiol 567:689–699.

Friedmann B, Kinscherf R, Borisch S, Richter G, Bärtsch P, and Billeter R. (2003). Effects of low-resistance/high-repetition strength training in hypoxia on muscle structure and gene expression. Pflügers Arch 446:742–751.

Fulco C, Muza S, Ditzler D, Lammi E, Lewis S, and Cymerman A. (2006). Effect of acetazolamide on leg endurance exercise at sea level and simulated altitude. Clin Sci 110:683–692.

Garvican L, Pottgiesser T, Martin D, Schumacher Y, Barras M, and Gore C. (2011). The contribution of haemoglobin mass to

increases in cycling performance induced by simulated LHTL. Eur J Appl Physiol 111:1089–1101.

Gatterer H, Haacke S, Burtscher M, Faulhaber M, Melmer A, Ebenbichler C, Strohl KP, Hogel J, and Netzer NC. (2015). Normobaric intermittent hypoxia over 8 months does not reduce body weight and metabolic risk factors-a randomized, single blind, placebo-controlled study in normobaric hypoxia and normobaric sham hypoxia. Obes Facts 8:200–209.

Geiser J, Vogt M, Billeter R, Zuleger C, Belforti F, and Hoppeler H. (2001). Training high-living low: Changes of aerobic performance and muscle structure with training at simulated altitude. Int J Sport Med 22:579–585.

Girard O, Koehle MS, MacInnis MJ, Guenette JA, Koehle MS, Verges S, Rupp T, Jubeau M, Perrey S, Millet GY, et al. (2012). Comments on Point:Counterpoint: Hypobaric hypoxia induces/does not induce different responses from normobaric hypoxia. J Appl Physiol 112:1788–1794.

Gore CJ, Clark SA, and Saunders PU. (2007). Nonhematological mechanisms of improved sea-level performance after exposure. Med Sci Sports Exerc 39:1600–1609.

Haider T, Casucci G, Linser T, Faulhaber M, Gatterer H, Ott G, Linser A, Ehrenbourg I, Tkatchouk E, Burtscher M, and Bernardi L. (2009). Interval hypoxic training improves autonomic cardiovascular and respiratory control in patients with mild chronic obstructive pulmonary disease. J Hypertens 27:1648–1654.

Katayama K, Ishida K, Iwasaki K-I, and Miyamura M. (2009). Effect of two durations of short-term intermittent hypoxia on ventilatory chemosensitivity in humans. Eur J Appl Physiol 105: 815–821.

Katayama K, Sato K, Hotta N, Ishida K, Iwasaki K, and Miyamura M. (2007). Intermittent hypoxia does not increase exercise ventilation at simulated moderate altitude. Int J Sport Med 28:480–487.

Katayama K, Sato K, Matsuo H, Hotta N, Sun Z, Ishida K, Iwasaki K-I, and Miyamura M. (2005). Changes in ventilatory responses to hypercapnia and hypoxia after intermittent hypoxia in humans. Respir Physiol Neurobiol 146:55–65.

Katayama K, Sato Y, Ishida K, Mori S, and Miyamura M. (1998). The effects of intermittent exposure to hypoxia during endurance exercise training on the ventilatory responses to hypoxia and hypercapnia in humans. Eur J Appl Physiol Occup Physiol 78:189–194.

Koehle MS, Sheel AW, Milsom WK, and McKenzie DC. (2007). Two patterns of daily hypoxic exposure and their effects on measures of chemosensitivity in humans. J Appl Physiol 103:1973–1978.

Koves TR, Noland RC, Bates AL, Henes ST, Muoio DM, and Cortright RN. (2005). Subsarcolemmal and intermyofibrillar mitochondria play distinct roles in regulating skeletal muscle fatty acid metabolism. Am J Physiol Cell Physiol 288:C1074–C1082.

Levine BD, Kubo K, Kobayashi T, Fukushima M, Shibamoto T, and Ueda G. (1988). Role of barometric pressure in pulmonary fluid balance and oxygen transport. J Appl Physiol 64: 419–428.

Levine BD, and Stray-Gundersen J. (2005). Point: Positive effects of intermittent hypoxia (live high:train low) on exercise performance are mediated primarily by augmented red cell volume. J Appl Physiol 99:2053–2055.

Lizamore CA, Kathiravel Y, Elliott J, Hellemans J, and Hamlin MJ. (2016). The effect of short-term intermittent hypoxic exposure on heart rate variability in a sedentary population. Acta Physiol Hung 103:75–85.

Manimmanakorn N, Hamlin MJ, Ross JJ, and Manimmanakorn A. (2014). Long-term effect of whole body vibration training on jump height: Meta-analysis. J Strength Cond Res 28:1739–1750.

Mao T-Y, Fu L-L, and Wang J-S. (2011). Hypoxic exercise training causes erythrocyte senescence and rheological dysfunction by depressed Gardos channel activity. J Appl Physiol 111:382–391.

Millet GP, Faiss R, and Pialoux V. (2012a). Last Word on Point: Counterpoint: Hypobaric hypoxia induces different responses from normobaric hypoxia. J Appl Physiol 112:1795.

Millet GP, Faiss R, and Pialoux V. (2012b). Point: Counterpoint: Hypobaric hypoxia induces/does not induce different responses from normobaric hypoxia. J Appl Physiol 112:1783–1784.

Mounier R, and Brugniaux JV. (2012a). Counterpoint: Hypobaric hypoxia does not induce different responses from normobaric hypoxia. J Appl Physiol 112:1784–1786.

Mounier R, and Brugniaux JV. (2012b). Last Word on Counterpoint: Hypobaric hypoxia does not induce different physiological responses from normobaric hypoxia. J Appl Physiol 112:1796.

Muza SR. (2007). Military applications of hypoxic training for high-altitude operations. Med Sci Sports Exerc 39:1625–1631.

New Zealand Guidelines Group. (2003). Evidence-Based Best Practice Guideline: The Assessment and Management of Cardiovascular Risk. NZGG, Wellington, New Zealand.

Nishiwaki M, Kawakami R, Saito K, Tamaki H, Takekura H, and Ogita F. (2011). Vascular adaptations to hypobaric hypoxic training in postmenopausal women. J Physiol Sci 61:83–91.

Ockene IS, Chiriboga DE, Stanek IE, Harmatz MG, Nicolosci R, Saperia G, Well AD, Freedson P, Merriam PA, Reed G, Ma Y, Matthews CE, and Hebert JR. (2004). Seasonal variation in serum cholesterol levels: Treatment implications and possible mechanisms. Arch Intern Med 164:863–870.

Pesta D, Hoppel F, Macek C, Messner H, Faulhaber M, Kobel C, Parson W, Burtscher M, Schocke M, and Gnaiger E. (2011). Similar qualitative and quantitative changes of mitochondrial respiration following strength and endurance training in normoxia and hypoxia in sedentary humans. Am J Physiol Regul Integr Comp Physiol 301:R1078–R1087.

Rehn B, Lidström J, Skoglund J, and Lindström B. (2007). Effects on leg muscular performance from whole-body vibration exercise: A systematic review. Scand J Med Sci Sports 17:2–11.

Ricart A, Casas H, Casas M, Pagés T, Palacios L, Rama R, Rodríguez FA, Viscor G, and Ventura JL. (2000). Acclimatization near home? Early respiratory changes after short-term intermittent exposure to simulated altitude. Wilderness Environ Med 11:84–88.

Rittweger J, Debevec T, Frings-Meuthen P, Lau P, Mittag U, Ganse B, Ferstl PG, Simpson EJ, Macdonald IA, Eiken O, and Mekjavic, IB. (2016). On the combined effects of normobaric hypoxia and bed rest upon bone and mineral metabolism: Results from the PlanHab study. Bone 91:130–138.

Roach RC, Loeppky JA, and Icenogle MV. (1996). Acute mountain sickness: Increased severity during simulated altitude compared with normobaric hypoxia. J Appl Physiol 81:1908–1910.

Rodway GW, Sethi JM, Hoffman LA, Conley YP, Choi AM, Sereika SM, Zullo TG, Ryter SW, and Sanders MH. (2007). Hemodynamic and molecular response to intermittent hypoxia (IH) versus continuous hypoxia (CH) in normal humans. Transl Res 149:76–84.

Saeed O, Bhatia V, Formica P, Browne A, Aldrich TK, Shin J, and Maybaum S. (2012). Improved exercise performance and

skeletal muscle strength after simulated altitude exposure: A novel approach for patients with chronic heart failure. J Card Fail 18:387–391.

Saunders PU, Telford RD, Pyne DB, Hahn AG, and Gore CJ. (2009). Improved running economy and increased hemoglobin mass in elite runners after extended moderate altitude exposure. J Sci Med Sport 12:67–72.

Sausen KP, Bower EA, Stiney ME, Feigl C, Wartman R, and Clark JB. (2003). A closed-loop reduced oxygen breathing device for inducing hypoxia in humans. Aviat Space Environ Med 74:1190–1197.

Schmutz S, Daepp C, Wittwer M, Durieux A-C, Mueller M, Weinstein F, Vogt M, Hoppeler H, and Flueck M. (2010). A hypoxia complement differentiates the muscle response to endurance exercise. Exp Physiol 95:723–735.

Schoene RB, Bates PW, Larson EB, and Pierson DJ. (1983). Effect of acetazolamide on normoxic and hypoxic exercise in humans at sea level. J Appl Physiol 55:1772–1776.

Semenza GL. (2001). Hypoxia-inducible factor 1: Oxygen homeostasis and disease pathophysiology. Trends Mol Med 7: 345–350.

Semenza GL. (2009). Regulation of oxygen homeostasis by hypoxia-inducible factor 1. Physiology (Bethesda) 24:97–106.

Serebrovskaya TV, Swanson RJ, and Kolesnikova EE. (2003). Intermittent hypoxia: Mechanisms of action and some applications to bronchial asthma treatment. J Physiol Pharmacol 54:35–41.

Shatilo VB, Korkushko OV, Ischuk VA, Downey HF, and Serebrovskaya TV. (2008). Effects of intermittent hypoxic training on exercise performance, haemodynamics, and ventilation in healthy senior men. High Alt Med Biol 9:43–52.

Shi B, Watanabe T, Shin S, Yabumoto T, and Matsuoka T. (2013). Effect of normobaric hypoxia on cardiorespiratory and metabolic risk markers in healthy subjects. Adv Biosci Biotechnol 4:340–345.

Snyder EM, Beck KC, Hulsebus ML, Breen JF, Hoffman EA, and Johnson BD. (2006). Short-term hypoxic exposure at rest and during exercise reduces lung water in healthy humans. J Appl Physiol 101:1623–1632.

Stavrou NA, McDonnell AC, Eiken O, and Mekjavic IB. (2015). Psychological strain: Examining the effect of hypoxic bedrest and confinement. Physiol Behav 139:497–504.

Thayer JF, and Lane RD. (2007). The role of vagal function in the risk for cardiovascular disease and mortality. Biol Psychol 74:224–242.

Tin'kov AN, and Aksenov VA. (2002). Effects of intermittent hypobaric hypoxia on blood lipid concentrations in male coronary heart disease in patients. High Alt Med Biol 3:277–282.

Tomanek RJ. (2013). In Coronary Vasculature: Development, Structure-Function, and Adaptations. Springer, New York.

van Tulder MW, Assendelft WJ, Koes BW, and Bouter LM. (1997). Method guidelines for systematic reviews in the Cochrane Collaboration Back Review Group for Spinal Disorders. Spine (Phila Pa 1976) 22:2323–2330.

Vogt M, Puntschart A, Geiser J, Zuleger C, Billeter R, and Hoppeler H. (2001). Molecular adaptations in human skeletal muscle to endurance training under simulated hypoxic conditions. J Appl Physiol 91:173–182.

Wang J-S, Chen L-Y, Fu L-L, Chen M-L, and Wong M-K. (2007a). Effects of moderate and severe intermittent hypoxia on vascular endothelial function and haemodynamic control in sedentary men. Eur J Appl Physiol 100:127–135.

Wang J-S, Lin H-Y, Cheng M-L, and Wong M-K. (2007b). Chronic intermittent hypoxia modulates eosinophil- and neutrophil-platelet aggregation and inflammatory cytokine secretion caused by strenuous exercise in men. J Appl Physiol 103:305–314.

Wang J-S, Wu M-H, Mao T-Y, Fu T-c, and Hsu C-C. (2010). Effects of normoxic and hypoxic exercise regimens on cardiac, muscular, and cerebral hemodynamics suppressed by severe hypoxia in humans. J Appl Physiol 109:219–229.

Wenger RH, and Gassmann M. (1997). Oxygen(es) and the hypoxia-inducible factor-1. Biol Chem 378:609–616.

Wilber RL. (2001). Current trends in altitude training. Sports Med 31:249–265.

Wilber RL. (2007). Application of altitude/hypoxic training by elite athletes. Med Sci Sports Exerc 39:1610–1624.

Zhao L, Mason NA, Morrell NW, Kojonazarov B, Sadykov A, Maripov A, Mirrakhimov MM, Aldashev A, and Wilkins MR. (2001). Sildenafil inhibits hypoxia-induced pulmonary hypertension. Circulation 104:424–428.

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