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Effects of intermittent hypoxia exposures and interval hypoxic training on exercise tolerance (narrative review)

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ABSTRACT

The ability to perform steady-state submaximal exercise at a certain intensity (exercise tolerance) predicts endurance performance in athletes, but also the quality of life and the capability to perform daily living activities in older people and patients suffering from chronic diseases. Improvements in exercise tolerance following exercise training are well established but may also occur or be enhanced as a consequence of adaptations to other stimuli, e.g., repeated exposures to real or simulated altitude. Adaptive responses (i.e., beneficially impacting exercise tolerance) depend on the type and extent of hypoxia stimuli, in particular, whether they are applied during exercise (intermittent hypoxia training, IHT) or at rest (intermittent hypoxia exposure, IHE).

This brief review summarizes the evidence showing that IHT seems to elicit more pronounced effects on exercise tolerance than IHE. The most relevant adaptations to IHT are primarily provoked within the working skeletal muscles, whereas the rather small effects of IHE may include improved autonomic regulatory processes, endothelial function, cardioprotection, and increasing antioxidant capacity, all of which can probably be enhanced by combination with exercise (IHT). While IHE seems particularly suited for sedentary and elderly people or those suffering from chronic diseases, IHT will be more appropriate for young and already trained people. Thus, IHE is recommended for those with low exercise tolerance and can be followed up with exercise training in normoxia and finally with IHT.

Keywords: interval hypoxic training, interval hypoxic exposures, adaptation, hypoxic stimuli, physical performance

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Эффекты интервальных гипоксических экспозиций и интервальных гипоксических тренировок на переносимость физических нагрузок (нарративный обзор)

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РЕЗЮМЕ

Способность успешно выполнять повторяющиеся субмаксимальные физические нагрузки/упражнения с определенной интенсивностью (переносимость физических нагрузок) позволяет прогнозировать выносливость спортсменов, а также качество жизни и способность выполнять повседневные действия у пожилых людей и пациентов, страдающих хроническими заболеваниями. Повышение переносимости физических нагрузок после серии спортивных тренировок хорошо известно, однако эти эффекты могут потенцироваться при параллельной адаптации к другим стимулам, например повторным воздействиям реального или моделируемого среднегорья. Адаптивные реакции (т. е. благотворно влияющие на переносимость физических нагрузок) зависят от типа и степени гипоксических стимулов, в частности, применяются они во время физических нагрузок (интервальная гипоксическая тренировка, ИГТ) или в состоянии покоя (интервальные гипоксические экспозиции, ИГЭ).

В кратком обзоре обобщены доказательства, показывающие, что ИГТ, по-видимому, вызывает более выраженные эффекты на переносимость физических нагрузок, чем ИГЭ. Наиболее значимые эффекты адаптации к ИГТ в первую очередь провоцируются в рабочих скелетных мышцах, кроме того, небольшие эффекты ИГЭ могут включать улучшение автономных регуляторных процессов, эндотелиальной функции, кардиопротекцию и повышение мощности антиоксидантных механизмов, большинство из которых, вероятно, могут быть потенцированы применением гипоксических экспозиций в сочетании с физическими нагрузками (ИГТ). В то время как ИГЭ, по-видимому, особенно подходит для малоподвижных и пожилых людей или тех, кто страдает хроническими неинфекционными заболеваниями. Курсы ИГТ являются доказанно более эффективными для молодых тренированных людей, квалифицированных атлетов. Таким образом, процедуры ИГЭ рекомендуются для начала или вовлечения в занятия физическими упражнениями для людей с низкой переносимостью физических нагрузок. В дальнейшем их тренировочный режим может дополняться тренировками в нормоксии и, наконец, собственно процедурами ИГТ.

Ключевые слова: интервальные гипоксические тренировки, интервальные гипоксические экспозиции, адаптация, гипоксические стимулы, физическая работоспособность

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1. Introduction

The ability to perform sustained exercise at a certain submaximal intensity is an indicator of the individual tolerance of exercise. This measure not only predicts endurance performance in athletes but also the quality of life and the capability to perform daily living activities in older people and patients [1]. Exercise tolerance is related to maximal aerobic capacity (maximal oxygen consumption, VO_2max) and exercise efficiency, the amount of O_2 needed to perform exercise at certain intensity. It decreases with detraining (e. g., bedrest) and increases with exercise training [2, 3]. Changes in exercise tolerance resulting from exercise training or any other appropriate intervention, e. g., exposures to different environmental conditions like terrestrial or simulated altitude, can be assessed by monitoring physiological steady-state responses (e. g., respiratory, cardiovascular, or metabolic) to a certain submaximal workload before and after the intervention. It is well-established that ventilatory demands (i. e., minute ventilation, VE) [4], heart rate (HR) [5], and blood lactate concentration [6] at a certain workload can all be reduced, e. g., by a 2–3-week period of exercise training [5]. While steady-state oxygen uptake (VO_2) during submaximal exercise remains unchanged or slightly decreases (due to improved exercise efficiency), ventilatory changes consistently observed aside from VE are carbon dioxide output (VCO_2), the respiratory exchange ratio (VCO_2/VO_2), and VE/VO_2 [4]. Depending on the type of training, training adaptations are primarily attributed to central (e. g., increased cardiac output associated with elevations in left ventricular mass, stroke volume, and circulating blood volume) [7–9] and peripheral (e. g., increases of oxidative enzyme capacity and capillary density of skeletal muscles) [9–11] factors. The question arises, whether and how adding a hypoxic stimulus to exercise, i.e., training at real or simulated altitude, may provide additional training effects, and if true, whether a hypoxic stimulus could be effective even without exercise.

Generally, when acutely exposed to submaximal exercise in hypoxia, VO_2 and stroke volume seem to be rather unaffected at the same workload, but peripheral oxygen saturation (SpO_2) decreases, and VE, HR, and cardiac output increase to compensate for the lower oxygen availability, associated with increased sympathetic nervous system activity, a more pronounced increase of lactate concentration in blood and rating of perceived exertion [12–15]. Thus, stress responses due to hypoxic stimuli may induce a variety of adaptations (e.g., involving skeletal muscle, cardiovascular, respiratory, and autonomic nervous systems) that could beneficially impact exercise tolerance. The adaptive responses depend on the type and extent of the hypoxia stimuli, and, in particular, whether repeated hypoxia stimuli are applied during exercise (intermittent hypoxia training, IHT); or at rest (intermittent hypoxia exposure, IHE). This review focuses on the existing evidence of IHT and IHE effects on exercise tolerance (primarily the ability to perform submaximal exercise in normoxia).

2. Intermittent hypoxia training (IHT)

Terrados and colleagues have conducted one of the first well designed experiments convincingly demonstrating beneficial effects elicited by IHT [16]. These researchers compared normobaric and hypobaric (simulated 2300 m) training effects by applying one-legged training (cycle ergometer), on submaximal exercise performance. Each leg was trained in normobaric or hypobaric conditions for 30 minutes 3–4 times per week over a 4-week period at an intensity corresponding to 65% of the one-legged maximal pre-training work capacity (Wmax). Submaximal exercise testing was performed before and after training at 80% of the pre-training Wmax in normoxia. Submaximal exercise performance increased considerably in both legs from 28.3 (± 10.4) min (pre-training) to 96.8 (± 27.0) min (post-training) in the normobarically and to 116.8 (± 40.4) min (post-training) in the hypobarically trained leg (significant changes between groups), which was associated with a lower HR response after training in hypobaria. The authors demonstrated that additional benefits from hypoxia stimulus were accompanied by elevated citrate synthase activity, a flux-generating enzyme in the carboxylic acid cycle (considered a marker of aerobic capacity) [16]. This finding has been confirmed in later studies [17]. Consequently, IHT seems to promote the aerobic capacity of the working muscles and is associated with an improved ability to perform a prolonged submaximal exercise at lower cardiac stress (indicated by lower heart rates -HRs). In the following three decades, several hypoxia training paradigms have been introduced and developed. Their superior performance-enhancing efficacy compared to normoxic training has been summarized in a recent meta-analysis [18]. The authors report varying benefits (standardized mean differences (SMDs) ranging from 1.45 to 7.10) of all 7 hypoxic training paradigms (different combinations of exercise and hypoxia/normoxia exposures) (42 studies including 1246 individuals), whereby IHT (corresponding to "live low-train high") was most promising among non-elite athletes.

As an example of IHT, Park and colleagues compared the effects of a 6-week normobaric and hypobaric training program on submaximal exercise responses in moderately trained swimmers. Participants performed 120-min training sessions (consisting of warm-up, continuous training on a treadmill, and interval training on a cycle ergometer, and cool down) 3 days per week in normoxia or hypobaric hypoxia (simulated altitude of 3000 m) [19]. The authors found improved 400-m trial performance only in the IHT group. Submaximal exercise testing (at the same intensity in normoxia) revealed reduced HRs and cardiac output independent of training in normoxia or hypoxia, but a decrease in VO_2 was only observed after IHT [19]. Accordingly, a lesser arterio-venous oxygen difference during submaximal exercise and a larger reserve of oxygen extraction during maximal exercise (as indicated by the improved VO_2max after hypoxic training)[19] seems reasonable. The lower submaximal VO_2 (during submaximal cycling) after IHT indicates improved exercise efficiency. This improvement may partially be explained by a higher amount of mitochondria in the working skeletal muscles and a faster ability to regenerate adenosine triphosphate (ATP) [20], induced by IHT [16, 21, 22].

Although both animal [21] and human studies [23] found that this kind of hypoxic training (IHT or "Live lower, train higher") regimen may presumably promote mitochondrial biogenesis and angiogenesis in skeletal muscles, as well as associated performance benefits in normoxia, others did not [24, 25]. These discrepancies may be due to many reasons, e.g., differences in the training status of the study participants, the severity of hypoxia, type and intensity of exercise, training duration, regeneration, diet, etc. Training in hypoxia (e. g., between 2500 and 4500 m) at higher exercise intensities (i .e., > 75 % of the individual VO_2max or peak power output) may be the most promising approach [23, 26], possessing the potential to promote mitochondrial biogenesis, angiogenesis, and more efficient oxygen utilization due to a tighter coupling between energy utilization and production sites [17]. This approach seems reasonable, as the molecular mediators of high-intensity exercise and hypoxic responses overlap. The shared mediators are for example involved in mitochondrial biogenesis and angiogenesis and include peroxisome proliferator-activated receptor gamma co-activator 1α, hypoxia inducible factor 1-α (HIF1-α), and vascular endothelial growth factor [27, 28]. However, the optimal dosing of both stimuli on an individual basis needs further investigation. In addition, several other mechanisms accompanied by the exercise and hypoxia intervention, including autonomic regulatory processes, and hematological, endothelial, myocardial, and metabolic adaptations may all play a role [28, 29].

Generally, sympathetic nervous system activity is increased during exercise (arising from central command, muscle metabo- and mechanoreceptors, and the involvement of baro- and chemoreceptors), which supports blood flow redistribution to working skeletal muscles [29]. Those mechanisms may be dysfunctional in sedentary and particularly in diseased individuals, where both IHT and IHE could restore proper functioning and improve exercise tolerance [30]. In addition, elevated hemoglobin levels contributing to improved oxygen transport capacity and exercise tolerance have been repeatedly found after IHT, and were associated with hypoxia-mediated stimulation of renal erythropoietin secretion, resulting in reduced plasma volume by osmosis, improved oxygen utilization of skeletal muscle, and maintained acid-base balance [31].

Moreover, hypoxia exposure effects on endothelial function, antioxidant defense, and cardio-protection [32–35] (see IHE effects below) may contribute to improvements in exercise tolerance as well. However, skeletal muscle adaptations seem to be the most important consequences of IHT, but may be more or less negligible in IHE.

One psychological aspect could be the influence of expectations or effort justification. As significantly more effort is required for IHT (as compared to exercising with comparable workloads in normoxia), it is possible that the performance-related output expectation of this intervention leads to better results. This is suggested by studies demonstrating increased therapeutic effectiveness, if greater effort was required [36]. With regard to IHT, we are not aware of any studies that have investigated the potential effects of expectation or effort justification. However, the greater and longer-lasting physical improvement of a 12-week long IHT (interval trainings in 17% oxygen conditions, as compared to the same training in normoxia) in untrained but healthy adult women may be explained by mental health effects [37]. These women reported increased self-perceived general health and vitality only after IHT [37], possibly reflecting greater satisfaction with their training due to the higher required effort in IHT.

3. Intermittent hypoxia exposure at rest (IHE)

As outlined above, it is well-established, that exercise training can improve exercise tolerance and some evidence suggests greater benefits when exercise is performed in hypoxic environmental conditions (natural or simulated, artificial). However, it is much less clear how IHE could increase exercise tolerance [38].

3.1. IHE in healthy individuals

In an early study, 28 healthy young men (n = 16) and women (n = 12) were randomly assigned to IHE (11 to 9 % oxygen) or normoxic (21 % oxygen) air breathing at rest (5 sessions per week over 4 weeks). Each session consisted of 3 to 7 cycles of 3–6 min hypoxic periods interspersed by 3–5 min lasting normoxic intervals [39]. Submaximal cardiopulmonary exercise tests, performed in normoxia before and after the breathing program, revealed significantly reduced heart rate responses to exercise after IHE and associated reduction in the rate-pressure product (HR x systolic blood pressure), an indirect measure of myocardial oxygen consumption. Reduced sympatho-adrenergic responses to exercise have been suggested to be responsible for the observed changes/adaptations. However, the exact underlying mechanisms of adaptation remain elusive.

Katayama and colleagues performed a controlled trial comparing IHE effects (simulated altitude of 4500 m for 90 min, 3 times a week for 3 weeks) on submaximal exercise performance compared to controls (40). The authors demonstrated improved 3000 m running times after hypoxia and reduced submaximal VO_2, indicating improved exercise efficiency [40]. However, it remains unclear whether this is a true improvement in exercise efficiency or only related to decreased cardiorespiratory costs and greater reliance on carbohydrates in resting conditions [41].

In a controlled experiment, including 18 healthy subjects, Mekjavic and colleagues added IHE (1 hour per day) to usual training in normoxia (1 hour per day, 5 days per week over 4 weeks) [42]. Both groups showed improved submaximal performance (constant power test) but intermittent hypoxia did not yield additional significant benefits on exercise tolerance. These findings indicate that the rather small effects of IHE are masked by those of exercise training and cannot be readily discerned. This assumption has been confirmed by a study comparing the effects of IHE between regularly exercising and sedentary groups of elderly men [35]. Improved exercise tolerance was associated with greater positive effects on hemodynamics and microvascular endothelial function only in blood lactate concentration, and rating of perceived exertion after IHE are usually not accompanied by ventilatory responses, which seem to remain unchanged or can even increase due to an elevated chemoreflex sensitivity induced by IHE [42]. However, IHE-induced chemoreflex sensitivity may be reduced when combined with endurance training [43]. Similar or even greater benefits outlined above, might be expected when IHE is applied in sedentary patients suffering from chronic diseases like coronary artery disease or chronic obstructive pulmonary disease.

The suggested impacts of IHT and/or IHE are depicted **in figure.**

3.2. IHE in patients suffering from chronic diseases

Several studies have tested the effects of a course of hypoxic exposures at rest on exercise tolerance in patients with various chronic pathologies. Improved exercise tolerance was demonstrated in 16 males (50–70 years, with and without prior myocardial infarction) [44]. Subjects were randomly assigned to receive 15 sessions (within 3 weeks) of intermittent hypoxia or normoxia (sham breathing) at rest. Each session consisted of 3–5 hypoxic (14–10 % oxygen; normoxic air for controls) periods with 3-min normoxic intervals. Controls inhaled only normoxic air in the same way. Incremental cycle ergometry (in normoxia) was performed before and after the 3-week breathing intervention. After 3 weeks of IHE, VO_2 peak had increased and was closely related to the arterial oxygen content (increase in hemoglobin concentration and lesser reduction in SpO_2) (r = 0.9, p < 0.001) [44]. Submaximal exercise responses (cycling at 1 W/kg), i. e., HRs, systolic blood pressure, the rate-pressure product were all diminished after IHE (compared to controls, all p < 0.05) [44]. Elevated hemoglobin levels and benefits on exercise tolerance have been reported from IHT protocols (see above) [31], but may even occur following IHE in these patients.

A similar clinical trial has been performed including patients suffering from mild chronic obstructive pulmonary diseases, also demonstrating improved exercise tolerance following IHE (12–15 % O_2 for 3–5 min, interspersed by intervals of 3–5 min of normoxia, 5–9 episodes per day, for 15 days) [45]. Eighteen patients (randomized to IHE or sham breathing) performed incremental cycle spiro-ergometry (in normoxia) before and after the breathing program. After IHE, a 9.7 % increase in total exercise time and a 13 % increase in exercise time to the anaerobic threshold were observed (compared to 0 % and -7.8 % in the control group, p < 0.05) [45]. Noteworthy, increases in the total exercise time were positively correlated to the elevated total hemoglobin mass (r = 0.59, p < 0.05), and the time to the anaerobic threshold was correlated with improved lung diffusion capacity for carbon monoxide (r = 0.48, p < 0.05) post-IHE [45]. These findings suggest that increased oxygen delivery to exercising muscles contributed to improved maximal and submaximal exercise performance after intermittent hypoxic exposures. Additionally, cardiovascular autonomic abnormalities in these patients (present at baseline) had normalized after the hypoxia intervention, which may also have contributed to the improved exercise tolerance [30], e. g., by effects on blood flow distribution (vasoconstriction in inactive muscle and vasodilation in working muscles by functional sympatholysis) [46]. Again, an increase in total hemoglobin mass and improvements in lung function parameters may have impacted exercise tolerance in patients with chronic obstructive pulmonary diseases.

More recently, in multimodal training programs, normoxic periods during IHE (3–5 sessions per week over 3–6 weeks) have been replaced by hyperoxic (e. g., 30–40 % oxygen) periods (intermittent hypoxia-hyperoxia exposure, IHHE), showing similar or even superior effects on physical and cognitive performance, associated with reduced cardiometabolic risk factors in older patients suffering from cardiovascular and metabolic diseases [47–49].

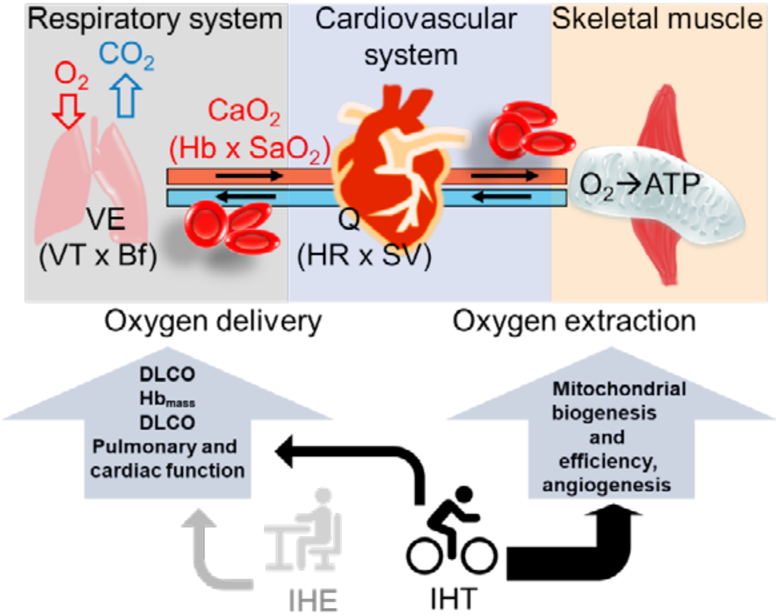

Fig. Suggested hypoxia effects of IHT and IHE on exercise tolerance by improving oxygen delivery and/or oxygen extraction in healthy individuals and patients suffering chronic diseases. IHT, intermittent hypoxic training; IHE, intermittent hypoxia exposure at rest; ATP, adenosine triphosphate; Bf, breathing frequency; CaO_2, arterial oxygen content; DLCO, lung diffusion capacity for carbon monoxide; Hb_{mass}, hemoglobin mass; HR, heart rate; Q, cardiac output; SV, stroke volume; VE, pulmonary minute ventilation; VT, tidal volume (the figure is original and composed by the authors).

Рис. Предполагаемые гипоксические эффекты ИГТ и ИГЭ относительно переносимости физических нагрузок за счет улучшения доставки и/или извлечения кислорода у здоровых людей и пациентов, страдающих хроническими заболеваниями. ИГТ, интервальная гипоксическая тренировка; ИГЭ, интервальные гипоксические экспозиции в состоянии покоя; АТФ, аденозинтрифосфат; Bf, частота дыхания; CaO_2, содержание кислорода в артериальной крови; DLCO, диффузионная способность легких для оксида углерода; Hbmass, масса гемоглобина; HR, частота сердечных сокращений; Q, сердечный выброс; SV, ударный объем; VE, минутная вентиляция легких; VT, дыхательный объем (рисунок оригинальный и составлен авторами).

However, it is necessary to reiterate the lack of convincing data on the positive effect of IHE on exercise tolerance and aerobic performance in professional athletes.

4. Conclusion

Taking all the arguments presented together, we can conclude that IHT elicits more pronounced effects on exercise tolerance than IHE. While sedentary and elderly people or those suffering from chronic diseases may already benefit from IHE, IHT is more appropriate for young and trained people, professional athletes. Thus, intermittent hypoxic exposures at rest are well suited for those with low exercise tolerance and decreased fitness level, which can be followed by exercise training in normoxia and finally by IHT.

Intermittent hypoxic exposures or intermittent hypoxic-hyperoxic exposures seems to induce specific small adaptations requiring only mild and well-tolerated hypoxic stress; it may improve autonomic regulatory processes, promote improvement of endothelial function and cardioprotection, increase antioxidant capacity, and provoke certain metabolic adaptations. Exercising in hypoxic environment (IHT) represents more pronounced metabolic and physical stress but accordingly also elicits more robust benefits at molecular, biochemical and systemic levels. The primary effects of IHT include adaptations within the skeletal muscle (such as the promotion of mitochondrial biogenesis and efficiency, and vascularization) as well as increasing the power of myocardial function and the stability of autonomic regulation, and require an exercise component in training modalities (see **Figure**).

Author contributions:

Burtscher Johannes — writing the manuscript.

Oleg S. Glazachev — manuscript editing, adding literature sources.

Kopp Martin — collection of the relevant literature sources, processing the data.

Burtscher Martin — review conceptualization, review the manuscript.

Вклад авторов:

Бурчер Йоханнес — подготовка текста обзора.

Глазачев Олег Станиславович — анализ литературных источников, редактирование рукописи.

Копп Мартин — сбор релевантных литературных источников, подготовка текста рукописи.

Бурчер Мартин — концепция обзорной работы, общение результатов анализа литературных источников.

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