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Fitness and therapeutic potential of intermittent hypoxia training: a matter of dose

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The introduction of different methods of intermittent hypoxic training (IHT) into fitness, sports, military and medical practice has raised a lot of questions about the most beneficial regimens of such treatment and their optimal instrumental implementation. Low doses of hypoxia might not be sufficient stimuli to mobilize adaptive mechanisms, while severe or prolonged hypoxia may provoke dangerous pathological processes. In this review, we pay attention to narrow practical question of the most effective and convenient technology of IHT implementation, notably the inhalation of hypoxic gas mixtures. Data strongly suggest that in humans the training with 15-13% inhaled oxygen (FiO_2) at various time characteristics does not provide marked positive changes. Short-term daily sessions consisting 3-4 bouts of 5-7 min exposures to 12-10% FiO_2 alternating with equal durations of normoxia for 2-3 weeks have been shown as a most beneficial without maladaptive consequences for fitness and treatment of some diseases. More severe or longer intermittent hypoxia protocols must be accompanied by strict monitoring of blood oxygen saturation (SpO_2), electrocardiogram, breathing pattern and arterial blood pressure in order to avoid unexpected undesirable individual reactions. For sports purposes, the reduction of oxygen content to individually tolerable level for some minutes is justified as far as it maximizes benefits. However, such regimen requires preliminary diagnostics of individual hypoxic tolerance and cardio-respiratory reactivity as well as rigorous monitoring of vital functions during IHT and good feedback device. The use of oxygen concentrations below 12% for treatment of diseases, especially in children and the elderly, are required substantial additional research. Recently, a new mode of adaptive training was explored, which combines periods of hypoxia (12-10% FiO_2) and hyperoxia (30-35% FiO_2). Limited evidences suggest that such regime can reduce the time of recovery periods, that is shorten the duration of sessions. However, there is still no strong comparative evidence for humans that this method is much more efficient than hypoxic-normoxic mode. We appeal to all scientists working in the field of IHT not to hide their negative results but publish all observations in the open press. It will make a significant contribution in developing of common guidelines for IHT implementation to improve public health of our Planet.

Key words: intermittent hypoxia training; mode of IHT; hypoxic-hyperoxic training; hemoglobin oxygen saturation; adaptation to hypoxia

INTRODUCTION

The proliferation of intermittent hypoxic training/treatment (IHT) methods in fitness, sports, military and medical practice during recent decades has caused debate about the most beneficial regimens of hypoxic training and methods of their instrumental implementation. Intermittent hypoxia (periodic, interval, cyclic hypoxia, hypoxic preconditioning – diff. terminology) is drug-free method that has been routinely used by about 2 million patients in the last 30 years and revealed good and satisfactory results in 75 – 95% of cases [1, 2]. Beneficial results of IHT application were obtained for enhancement of physical and mental operability, the prevention of premature aging, the achievement of high results in sports, increased tolerance to adverse environmental factors, for altitude pre-acclimatization, as well as for the treatment and prevention of various diseases.

The mechanisms underlying the effects of hypoxic training at all levels - from systemic physiological reactions to the genome - are widely debated. This topic is the subject of many articles, reviews and monographs. To avoid repetition we refer readers to the most recent reviews [3-10].

The biological responses to intermittent hypoxia may be adaptive or maladaptive, depending on the severity of the hypoxemia, its frequency of occurrence, its duration, and, importantly, the "pattern" and timing of each of the HbO_2 desaturation/ resaturation cycles [7, 11]. Many types of protocol with different numbers of hypoxia episodes, severity, and total exposure duration have been used by investigators, and these combinations may have resulted in various physiological responses. Mode of hypoxic influence (depth, duration, and intermittence) is critical for the determination of beneficial or detrimental effects of IHT. Low doses of hypoxia might not be sufficient stimuli to mobilize adaptive mechanisms, while severe or prolonged hypoxia may provoke dangerous pathological processes.

The question arises: what is the concentration of inhaled oxygen and temporal characteristics of hypoxic pattern that may be relatively safe and useful, and what level of hypoxia requires unconditional monitoring of functional parameters and clear alarm-service. In this review, we will pay attention to narrow practical question of IHT application in human practice and provide unbiased analysis of hypoxia training protocols that use the most effective and convenient technology - the inhalation of hypoxic gas mixtures.

Regimes of IHT with hypoxic gas mixtures inhalation: recommended doses and potential adverse effects

Traditional treatment protocols for IHT comprises repeated exposures to low oxygen atmosphere breathing, altered with breathing ambient air. However, hypoxic regimens which are used for IHT implementation in human practice vary broadly in terms of severity of hypoxia (from 2% to 18% inspired oxygen), duration of hypoxic and normoxic episodes (from 15–30 s to 12 h), the number of cycles per day (from 3 to 25 sessions), the duration of IHT course (2-90 days), etc. Such diversity is largely dependent on a contingent designed for this training: for athletes of varying skill, mountain hikers, soldiers of alpine troops, pregnant women, elderly people who want to extend their active life, or patients for the prevention or treatment of various diseases.

Some characteristics of different regimes are described in recent reviews [4, 5, 7, 8, 12, 13]. Historically, first methodical recommendations for IHT implementation in human practice were published by the Russian Health Ministry in 1988 which recommended the inhalation of 10-12% O_2 during 5- min periods with 5 min rest, 1 h per session, 1-4 weeks per course for the treatment of various diseases. The evidence base was represented by the investigations of R.Strelkov, A. Chizhov, H.Gurvich, A.Kolchinskaya, N. Geppe and many others (look the review [14]). Most achievements in IHT practical implementation were based on a thorough study of the mechanisms of both positive and negative IHT actions in sport practice and clinical pilot studies. Unfortunately, serious research on the use of IHT in rejuvenation practice and fitness is still not presented in the medical literature.

In the Table we presented the most typical literature data concerning the use of IHT in human practice during last 2 years, as well as some classical works of the past. Data are ranked in order of decreasing oxygen concentration in the inspired gas. Human investigations strongly suggest that the training with 15-13% inhaled oxygen (FiO_2) at various time characteristics do not provide any positive changes [15-24]. 12-10% FiO_2 is the most common concentration caused a positive effect [25-39, 48, 49]. None of the articles that use such concentrations describe adverse effects. There are few papers which documented adverse effects, but starting with 8-9% FiO_2 [40-47]. All study results cited in the Table as well as other known papers

Regimens of IHT that use the inhalation of gas mixtures for humans
(The papers presented in order of decreasing inspired oxygen concentration that used for research)

Authors	Subjects	Regimen of IHT	Results
[15]	12 healthy participan	18-15 % FiO_2 , 10 min, ergometer at 20% peak VO_2	Hypoxia has no effects on cognitive function
[16]	9 male games players	17 % FiO_2 at 40 min cycling intermittent 5 s sprint protocol	Peak and mean power output and total work done reduced, Heart rate was higher and SaO2 lower during HYP. The results suggest athletes will be at a disadvantage when performing intermittent sprinting at moderate altitude
[17]	22 subjects age 17-25 yr	16.4-14.5 % FiO_2, exercises at 6-h hypoxia weekly, 4 weeks	Weight loss, improvement of blood pressure, no effect on brachial-ankle pulse wave velocity
[18]	10 untrained men	15% FiO_2, five sets of 15 repetitions of squat exercise	No significant differences in blood lactate, growth hormone, total testosterone and cortisol under normixia and hypoxia, i.e. low-intensity resistance exercise performed under mild hypoxia does not induce greater anabolic hormonal responses
[19]	18 male trained triathletes	14.5 - 15% FiO2, two 60-min sessions per week during 7 weeks	Hemoglobin and erythrocytes values increased, aerobic performance and physiological variables did not increase
[20]	9 physically active men	14,5% FiO_2, 25 min training sessions, 3 wk	No effect on time-to-exhaustion during incremental exercise and muscle metabolite concentrations,i.e. IHT does not alter muscle metabolic responses
[21]	10 trained male team sport athletes	14.5% FiO2, repeat-sprint training session comprised 3 sets of 9 × 5 s maximal sprints commencing every 25s	No post-exercise inflammation, little effect on oxidative stress
[22]	16 highly trained footballers	14.3% FiO_2, 60 min per sprint training, 2 d·wk, 5 weeks	Maximal aerobic speed, lower-limb explosive power and sprint decrement remained unchanged; repeated-sprint times and repeated-agility improved
[23]	16 heathy subjects	13.8% FiO2, three 10-hour exposures	SOD, GPX and catalase activities, advanced oxidation protein products increased
[24]	18 male cyclists	~13-14% FiO2, 5 training sessions (75 min hypoxic period) per week during 3 weeks.	Peak power output increased but VO2max did not; no differences in monocarboxylate lactate transporter protein content. There are no additional benefits of IHT compared to normoxic training
[25]	55 children 6 to 17 yr with symptoms of bronchospasm	12 % FiO_2, three 15-min sessions per day with 10-min breaks during 7-14 days	Lung vital capacity and breath-holding time increased, bronchial obstruction and heart rate decreased
[26]	8 healthy male subjects	12% O2 for 5 min followed by 5 min of normoxia for 1 h/d during 10 days	Ventilatory response to hypoxia increased, cerebrovascular sensitivity to CO_2 remained unchanged

[27]	48 children 6 -17 yr from radioactive territories	12 % FiO_2, three 15-min sessions per day with 10-min breaks during 7-14 days	Latent period of complex visual-motor response to one of three colors reduced, personal anxiety decreased
[28]	14 healthy, 60- to 74-yr-old men	12 % FiO_2 , 3-5 min , with 5 min breaks, 4/day during 10 days	No changes in hemodynamic indices and work capacity in routinely daily exercised subjects and increased submaximal work and anaerobic threshold in untrained men
[29]	45 elderly patients with stable angina	12 % FiO_2 , 5-7 min , with 5 min breaks, 4/day, 10-12 days	Reduction in clinical symptoms of angina and duration of daily myocardial ischemia, normalization of lipid metabolism and increase exercise tolerance, normalization of microcirculation
[30]	16 children aged 9–13 yr with bronchial asthma	12 % FiO_2 , 3-5 min , with 5 min breaks, 3/day during 2 weeks	Decline in breath shortness and feelings of chest congestion, diminishing of cough and sputum, attacks of asphyxia disappeared or became less frequent, increased HVR, no changes in airway conductance
[31]	20 endurance-trained men	11% FiO_2 on days 1-7 and 10% O2 on days 8-15; 10 bouts during 15 days	No effect on aerobic or anaerobic performance
[32]	15 athletes with overtraining syndrome	10 % FiO_2 with hyperoxic breaks (30% O_2), 6-8 cycles, three times a week over 4 weeks	Exercise performance and sympatho-parasympathetic index improved, hematological parameters were unchanged
[33]	8 young non-smokers	10 % FiO_2, five to ten 5-6-min sessions per day with 4-min breaks during 14 days	IH exposures significantly diminish variations of cerebral perfusion in response to hypercapnia and hypocapnia without compromising cerebral tissue oxygenation. No adverse effects
[34]	patients with stage 1 arterial hypertension	10 % FiO_2, four to ten 3-min sessions per day with 3-min breaks during 14 days	Increased nitric oxide synthesis and decreased blood pressure
[35]	42 patients with BA and 14 patients with COB	10 % FiO_2, 5 min , with 5 min breaks, 20-25 sessions	Positive effect is obtained in 76% of patients with BA and 92.8% of patients with COB1
[36]	8 young non-smokers	10 % FiO_2, five to ten 5-6-min sessions per day with 4-min breaks during 14 days	A rightward shift in the oxyhemoglobin equilibrium response, attenuated tachycardiac response to hypoxia while significantly enhancing normoxic R-R interval variability in low-frequency and high-frequency spectra without changes in arterial blood pressure at rest or during hypoxia, i.e. the enhancement of arterial O2 delivery and improvement of vagal control of HR.

[37]	123 patients with hypertension stage I and II.	10% FiO_2, 2-6 min + 3-8 min normoxia, 5-12 cycles/d, 15-30 d	Reduction of the arterial pressure, rise of physical performance A pronounced depressor effect persisted for – 6 months in 63 patients
[38]	41 patients with hypertonic disease	10% FiO_2, 13-25 sessions	Arterial pressure and emotional tension decreased, oxygen consumption and transport normalized.
[39]	10 healthy subjects	10% FiO_2, four 5-min bouts/day during 2 wk	Enhancement of innate immunity by mobilizing circulating hematopoietic stem and progenitor cells, activating neutrophils, and increasing circulating complement and immunoglobulins.
[40]	19 subjects with chronic incomplete spinal cord injury	9 % FiO2, 90-sec with 60-sec normoxic breaks, 15 exposures during 5 days	Improved walking speed and distance.
[41, 42]	13 individuals with chronic, incomplete spinal cord injury	9 % FiO2, 15 exposures with 1-min intervals	Plantar flexion torque and ankle plantar flexor electromyogram activity increased, i.e. elicits sustained increases in volitional somatic motor output. IHT was not accompanied by increases in blood pressure or changes in heart rate variability
[43]	26 participants with OSA	8-9% FiO2, twelve 4-min episodes followed by a single breath of 100% O_2	Chemoreflex sensitivity to hypoxia increased promoting apneic events and ultimately exacerbating breathing instability
[44]	12 healthy males	8-12% FiO_2 (PETO2=45Torr), 6 h on three ocasions	Increased resting ventilation and the HVR, TNF-α was decreased with only selective COX-2 inhibition, i.e. inflammation does not contribute to human intermittent hypoxia-induced respiratory plasticity
[45]	One 55-year-old female with a C4 chronic, incomplete spinal cord injury	8% O2, eight 2 min exposures with 2 min normoxia during 10 days	Significant improvements in airflow generated in response to applied inspiratory resistive load. No significant changes in the respiratory perceptual sensitivity to inspiratory resistive loads.
[46]	8 individuals with incomplete spinal cord injury	8% O2, eight 2 min exposures with 2 min normoxia during 10 days	Minute ventilation increased, FVC and FEV-1 improved, but the magnitude of ventilatory long-term facilitation was not enhanced
[47]	8 healthy adult men	5% FiO_2 until SaO_2 dropped to 85% (25 hypoxic events/h),five hours	Two fold up-regulation of the pro-inflammatory gene toll receptor 2 that may lead to systemic inflammation, insulin resistance and atherosclerosis
		Rebreathing technique:	
[48]	29 residents of Chernobyl	A decrease from 20,9 to 9 % FiO_2 during 5 min, three daily sessions with 15 min breaks, 10 days	normalizing effect on free radical processes; a decrease in spontaneous and initiated blood chemiluminescence and MDA
[49]	18 patients with idiopathic parkinsonism	A decrease from 20,9 to 9 % FiO_2 during 5 min, three daily sessions with 10 min breaks, 14 days	Increase in hypoxic ventilatory response, no changes in hypercapnic ventilatory response, decrease in DOPA blood concentration, improvement of respiratory system functioning

show that there have been no reported adverse physiological effects when users have followed the recommendations [12]: “a few minutes of targeted SpO_2 75–88% at rest, alternated with reoxygenation”.

In a recent review [5], it was also suggested that modest levels of hypoxia (9–16% O_2) and a relatively low number of exposures (3–15 episodes per day) seem to elicit beneficial effects without pathology, whereas severe hypoxia (2–8% O_2) characterized by an extensive amount of episodes (48–2,400 exposures per day) elicits progressively greater pathology. In the latest review Astorino [8] analyzing the efficacy of acute intermittent hypoxia on physical function and health status in humans with spinal cord injury comes to the conclusion that 2min exposures to intermittent hypoxia equivalent to 8-9 % O_2 interspersed with 2min normoxic exposures during 10 days can be successfully used to treat such patients.

Thus, according to numerous data, short exposures to 12-10% O_2 are harmless in most cases.

One could see the correspondence between such data distribution and the critical points of oxyhemoglobin dissociation curve. It is known [50-52] that during the decline of oxygen partial pressure in arterial blood from ~ 95 mm Hg (corresponding to 20,9 % FiO_2) to 80 mmHg, hemoglobin oxygen saturation decreases insignificantly, only by 5%. Then, from 80 to 50 mm Hg (corresponding to ~10-12 % FiO_2), oxygen saturation falls by 15%. After 50 mm Hg the concentration of oxyhemoglobin in arterial blood falls rapidly. In this part of the curve the gradient of a few mm Hg in the inhaled air can cause significant changes in oxygen supply slowing down ATP synthesis that is a direct destructive effect. As Dempsey and Morgan [6] have written in their last review, the sigmoid shape of the HbO_2 disassociation curve permits substantial (up to one-third) reductions from the normal arterial PO_2 before serious reductions occur in arterial O_2 saturation and content and therefore in O_2 transport. In the range of 80 to 50 mm Hg, there is such a degree of hypoxia when the supply of reduced coenzymes in the electron transport chain of mitochondria slows down. This in no way affects the rate of ATP synthesis, but increases the concentration of superoxide anion which activates numerous intracellular adaptation mechanisms [53, 54]. Thus, the data obtained by various authors about IHT therapeutic effects under the inhalation of 12% O_2 and less fits into this picture.

However, further reduction of inspired oxygen concentration in weak individuals and patients with different pathology may result in adverse changes. Besides oxyhemoglobin dissociation curve, there are other factors affecting the tissue oxygenation. For example, during blood acidification that can occur at different pathologies, critical points at oxyhemoglobin dissociation curve shift toward higher oxygen concentrations (not 50 but 60 mmHg). During anemia blood oxygen capacity is reduced, thus tissue hypoxia develops faster. Intoxication alters the zeta potential of red blood cells and decreases their functionality. This also reduces the degree of tissue oxygenation. The data presented in the table suggest that for healthy subjects the short-term inhalation of 10% O_2 is not dangerous, and such training does not require constant medical supervision. As for the patients and older people, the use of 12-10% FiO_2 can be considered effective and safe just only if the monitoring of the most important physiological functions takes place. The biological costs of many types of hypoxic adaptations can sometimes outweigh their benefits [12].

Regarding the optimization of the duration of hypoxic exposures and the length of IHT course, it worth to mention the results of earlier work of Foster et al. [55]. Authors provided the comparison of two protocols of normobaric, isocapnic, intermittent hypoxia: short-duration intermittent hypoxia with 12% O_2 separated by 5 min of normoxia for 1 h, or long-duration intermittent hypoxia 30 min of 12% O_2. Both groups had 10 exposures over a 12 day period. Measuring hypoxic ventilatory response (HVR), blood pressure, heart rate, arterial oxyhemoglobin saturation and cerebral tissue oxygen saturation, authors concluded that both short- and long-duration intermittent hypoxia had similar effects on the ventilatory and cardiovascular responses, thus the long-term hypoxic exposures can be successfully replaced by short-term impacts with the same result. These investigations also show that the break in training for one or two days do not significantly affect the outcome of the IHT course. These conclusions were also expressed by Katayama et al. [56, 57], Koehle et al. [58] and others. Later on, Katayama et al. [59] conducted a study using the hypoxic tent, which was supported by 12.3% O_2, one and 3 hours during the week. HVR growth in the group which trained 1 hour was no less than in the group that trained 3 hours. Thus, short-term regime impacts may have the same result as longer regime.

Experiments on animals also confirm that short cycles of hypoxic exposures alternating with normoxic periods are more effective than longer bouts or continuous daily hypoxic exposures [13, 60-61]. Powerful hypoxic-induced gene transcription factors (HIF-1/HIF-2 alpha) are activated very early upon hypoxic exposure, guaranteeing time-dependent up-regulation of cardiorespiratory and hematological responses aimed at limiting deficits in O_2 transport [62]. As Dempsey and Morgan [6] have written, on the adaptive side, short-term exposures (via manipulation of FiO_2) to a few weeks of daily sessions consisting of 10–15 1- to 2-min bouts of moderate isocapnic hypoxemia (SpO_2 75–80%) alternating with equal durations of normoxia have been shown to yield several benefits without maladaptive consequence.

The use of IHT in pediatrics requires special attention. Major achievements in this direction were made by scientists from the former Soviet Union [9]. Here we just briefly mention some papers to illustrate the mode of IHT for children.

A study of Anokhin and co-authors [63] applied IHT with a normobaric hypoxic stimulation with four sessions of 5 min 12-15% O_2, followed by 5 min normoxic interval, for 10 days in 200 children aged 4 to 14 years who suffered from bronchial asthma. Researchers from Brazil studied 48 adolescents (12-14 years of age) under three conditions: mild intermittent asthma; mild persistent asthma; and control [64]. They concluded that adolescents with mild persistent asthma have a greater capacity to adapt to hypoxia than do those with other types of asthma. In addition, Serebrovskaya et al. [30] used IHT for treatment of children (aged 9-13 years) with persistent atopic bronchial asthma in moderate form without the signs of respiratory insufficiency. Normobaric hypoxia was administered with a portable device “Hypoxytron”, a modified closed spirometer with CO_2 absorption [65]. The initial inspired gas had 20.9% O_2 that fell to 12% during first 60-90 seconds of rebreathing, and then O_2 was added gradually to the device to maintain inspired O_2 at 12% for the remaining 3.5-4 min with a final arterial O_2 saturation typically 89-92%. All children easily tolerated the hypoxia periods without any untoward effects. Each IHT session consisted of four 5-7 min hypoxic periods, followed by 5 min interval with room air inspiration. Heart rate response to hypoxia became less pronounced and SpO_2 fell less at 12% O_2 after the course, indicating IHT improved efficiency of cardiovascular system in supporting oxygen supply during hypoxia.

Thus, IHT represents a promising approach in prevention and treatment of bronchial asthma in childhood. The proper choice of the hypoxic dosage depending on individual’s reactivity to hypoxia must be titrated for each patient to avoid negative effects of hypoxia and to augment the favorable ones.

Hypoxic-hyperoxic exposures

Recently, a new mode of adaptive training was explored, which combines periods of hypoxia and hyperoxia [66-69]. A novel principle of short-term periodic adaptive training by varying the oxygen level from hypo- to hyperoxia is substantiated both theoretically and experimentally. Studies supports the viewpoint that moderate periodic generation of free radical signal during hypoxic/hyperoxic bouts causes better induction of antioxidant enzyme protein synthesis then hypoxic/normoxic exposures, that may be an important trigger for specific adaptations.

Currently, this method is just beginning to enter the practice, so at this moment there are only a few papers in medical literature describing the results of such training in humans. Traditional protocols include alternating of breathing hypoxic gas mixtures (10-12% FiO_2) and periods of breathing hyperoxic mixture (about 30-35 % O_2).

Combined hypoxic-hyperoxic training was used in the treatment of the metabolic syndrome [70]. The use of hypo-hyperoxic exposures leads to a significant reduction in body weight. It was achieved mainly by reducing fat mass accompanied by a reduction of total cholesterol, low-density lipoproteins, fasting plasma glucose, optimization of blood pressure, increased hypoxic stability, physical endurance, improved mental status.

In more recent publication, Glazachev & Dudnik [67] provided the hypoxic test (10 min breathing with 10% FiO_2 followed by 30% FiO_2) in 30 healthy young men and described two different types of microcirculatory reactions: among the subjects sensitive to hypoxia such test led to a significant reduction in SpO_2 in the absence of changes in the microcirculation regulation; among the subjects resistant to hypoxia the test leads to the nutritive blood flow activation by increasing the initially lower endothelium-dependent and neurogenic sympathetic components in regulation of microhaemodynamics activity, reduction of blood shunting.

Susta et al [32] investigated sportsmen with overtraining syndrome with application a conditioning program consisting of repeated exposures to hypoxia (10% FiO_2) and hyperoxia (30% FiO_2) , 6-8 cycles (total time 45 min -1 h), three times a week, delivered 1·5-2 h after a low-intensity exercise session over 4 weeks. This pilot study showed that such training can facilitate functional recovery among athletes with overtraining syndrome in a relatively short time.

Potential Side Effects

The maladaptive side of intermittent hypoxia of pathological origin is mainly considered in the context of obstructive sleep apnea (OSA). Mechanisms of maladaptive responses are very good described in recent reviews [6, 54, 62, 71, 72, and many others]. Studies in this field have led to the view that intermittent hypoxia is the principal, if not the only, risk factor for the development of a number of detrimental cardiovascular, respiratory, metabolic, and cognitive outcomes [7]. The authors having analyzed a large number of studies concluded that protocols that were employed to establish the link between intermittent hypoxia and detrimental outcomes were typically severe in regards to intensity, duration, or both. The role of pattern, intensity, and duration of hypoxic application were largely ignored and the beneficial effects linked to milder forms of intermittent hypoxia were generally overlooked.

The balance between benefits and injury appears to primarily depend on the ability of the organism to activate adaptive mechanisms to IHT. In this context, the adaptive or maladaptive responses can be generally predicted by the frequency, severity, and duration of intermittent hypoxia [11]. However, the presence of underlying conditions such as hypertension or obesity, as well as age, sex, or genotypic variance, may be important factors tilting the balance between an appropriate homeostatic response and decompensation. Thus, careful monitoring for major functional performance during hypoxic sessions required when using the oxygen concentrations below 10% for fitness and sports, but for patients with various diseases as well as older people such medical monitoring must be carried out starting with 12% O2. The duration and number of hypoxic episodes must be individually selected.

Individual prescription of hypoxic regimes

Individual variability to breathing the same hypoxia air is remarkable. Although all individuals respond and their respiration and heart rate increase according to the drop in arterial oxygen saturation, the pattern and magnitude of the response significantly varies from person to person which was mentioned in early works [74 - 76]. To determine individual sensitivity to hypoxic exposure investigators use different hypoxic stress-tests (spiroergometer test, breathing with hypoxic mixture with certain oxygen concentration, rebreathing test, breathing through an additional dead space, breath-holding tests).

In order to establish an individual's type of hypoxia reaction it is advisable to complete a test for each person before they start a course of IHT. The literature describes just a few practical approaches to solving this problem [77 - 79].

Russian authors proposed to use the hypoxic test consisting of short term (several minutes) breathing of hypoxic air of known oxygen concentration (conventionally FiO_2 = 11%), followed by a recovery period, when the person takes the mask off and reverts to normal (ambient) air breathing [80, 81]. But still now we could not find out how to use in practice the resulting test information for selecting a specific training mode.

Bassovitch & Serebrovskaya [78] offered to analyze the shape of the SpO_2 curve under breathing with 11% FiO_2 hypoxic mixture. When SpO_2 reaches the targeted baseline of 85%, the patient is instructed to take the mask off and revert to ambient air breathing. The person remains sitting until the arterial oxygen saturation recovers back to the normal level of 95%. The specific methodology to use the results of this test for individual IHT mode selection has been described. However, in the later works, data validation of this technique in clinical or sport practice has not been published. The situation with the specific description of the principles of biofeedback control during the training session is also highly deplorable.

We know the only one laboratory where the study of individual reactions to hypoxia is given serious consideration and the proposed method of IHT mode selection was good described for older people with accelerated aging and patients with cardiovascular disorders and widely used in practice. This is the laboratory headed by Prof. O.Korkushko in the Institute of Gerontology, Kiev, Ukraine [28, 29, 77, 79].

During the past few years numerous debates about the ethical evaluation of diagnostic and therapeutic use of hypoxia in humans are raised. Although the works devoted to this problem obtained the approval from the Human Investigation Ethics Committees, there is the lack of evidences about strong evaluation of risk/benefit ratio. The analysis of such ratio and the creation of standardized guidelines for hypoxic treatment/training application are complicated due to the differences in criteria for individual dosage and utilized methods.

CONCLUSION

Collectively, the results suggest that short episodes of normobaric intermittent hypoxia leads to a variety of physiological benefits with minimal risk. Three to 5 exposures to reduced inspired oxygen up to 12-10 %, 5-7 min each during 2 to 3 weeks can be used for fitness and treatment of various diseases. More severe or longer intermittent hypoxia protocols must be accompanied by strict monitoring of respiratory and cardiovascular functions in order to avoid side effects. The reduction of oxygen content to individually tolerable level is justified for sports training and fitness as far as it effectively includes adaptation mechanisms and maximizes benefits. However, such regimen requires preliminary diagnostics of individual hypoxic tolerance and cardio-respiratory reactivity as well as rigorous monitoring of vital functions and good feedback device. The use of oxygen concentrations below 12% for treatment of diseases, especially in children and the elderly, are required substantial additional research.

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We appeal to all scientists working in this field not to hide their negative results but publish all observations in the open press. It will help a lot in developing common guidelines for IHT implementation to improve public health of our Planet.

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ТРЕНИРОВОЧНЫЙ И ТЕРАПЕВТИЧЕСКИЙ ПОТЕНЦИАЛ ИНТЕРВАЛЬНОЙ ГИПОКСИИ: ВОПРОС ДОЗЫ

Распространение в последнее десятилетие методов интервальной гипоксической тренировки (ИГТ) в фитнесе, спорте, военной и медицинской практике вызвало дискуссию о наиболее эффективных режимах гипоксической тренировки и методах ее инструментальной реализации. Низкие дозы гипоксии могут быть недостаточным стимулом для мобилизации адаптивных механизмов, в то время как глубокая или продолжительная гипоксия способна провоцировать опасные патологические процессы. В этом обзоре мы касаемся узкого практического вопроса о наиболее эффективной и удобной технологии реализации ИГТ, а именно методов, основанных на вдыхании человеком гипоксических газовых смесей. Данные, полученные при исследовании людей, убедительно свидетельствуют о том, что использование смесей с 15-13% кислорода во вдыхаемом воздухе (FiO_2) при различных временных характеристиках не вызывает выраженных положительных изменений. Кратковременные ежедневные сеансы, состоящие из 5-7-минутных вдыханий 12-10% O_2, чередующихся с равными интервалами нормоксии, в течение 2-3 нед, считаются наиболее эффективными и безвредными как для фитнеса, так и лечения некоторых заболеваний. Протоколы с более жесткой или более длительной гипоксией должны сопровождаться строгим мониторингом жизненно важных функций для избежания побочных эффектов. Снижение на несколько минут содержания кислорода до индивидуально переносимого предела оправдано в спортивной практике, поскольку это максимизирует положительный эффект. Тем не менее, такой режим требует предварительной диагностики индивидуальной переносимости гипоксии и реактивности респираторно-гемодинамической системы, а также строгого контроля жизненно важных функций и хорошей обратной связи пациента с прибором. Использование концентрации кислорода ниже 12% для лечения заболеваний, особенно у детей и пожилых людей, требует серьезных дополнительных исследований. Недавно был предложен новый режим гипоксическо-гипероксической тренировки, сочетающий в себе периоды дыхания гипоксической (12-10% FiO_2) и гипероксической (30-35% FiO_2) смесью. Немногочисленные данные свидетельствуют, что такой режим может сократить время реоксигенации, т.е. уменьшить продолжительность тренировочных сессий. Однако, до сих пор нет достаточной сравнительной базы для доказательства, что этот метод является более эффективным, чем гипоксически-нормоксические режимы. Мы обращаемся ко всем ученым, работающим в области ИГТ, не скрывать свои негативные результаты, а публиковать все наблюдения в открытой печати. Это внесет значительный вклад в разработку общих методических принципов осуществления ИГТ для улучшения здоровья населения нашей планеты.

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ТРЕНУВАЛЬНИЙ І ТЕРАПЕВТИЧНИЙ ПОТЕНЦІАЛ ІНТЕРВАЛЬНОЇ ГІПОКСІЇ: ПИТАННЯ ДОЗИ

Поширення в останнє десятиліття методів інтервального гіпоксичного тренування (ІГТ) у фітнесі, спорті, військовій та медичній практиці викликало дискусію про найбільш ефективні режими гіпоксичного тренування і методи їх інструментальної реалізації. Низькі дози гіпоксії можуть бути недостатнім стимулом для мобілізації адаптивних механізмів, у той час як глибока або тривала гіпоксія здатна провокувати небезпечні патологічні процеси. У цьому огляді ми торкаємося вузького практичного питання про найбільш ефективну і зручну технологію реалізації ІГТ, а саме методів, заснованих на вдиханні людиною гіпоксичних газових сумішей. Дані, отримані при дослідженні людей, переконливо свідчать про те, що використання сумішей з 15-13% кисню у вдихуваному повітрі (FiO2) при різних часових характеристиках не викликає виражених позитивних змін. Короткочасні щоденні сеанси, що складаються з 5-7-хвилинних вдихань 12-10% O_2, що чергуються з рівними інтервалами нормоксії, протягом 2-3 тиж, вважаються найбільш ефективними і нешкідливими як для фітнесу, так і лікування деяких захворювань. Протоколи з жорсткішою або більш тривалою гіпоксією повинні супроводжуватися суворим моніторингом життєво важливих функцій для уникнення побічних ефектів. Зниження на кілька хвилин вмісту кисню до межі, яка індивідуально переноситься, виправдано в спортивній практиці, оскільки це максимізує позитивний ефект. Тим не менше такий режим вимагає попередньої діагностики індивідуальної переносимості гіпоксії і реактивності респіраторно-гемодинамічної системи, а також суворого контролю життєво важливих функцій і хорошого зворотного зв'язку пацієнта з приладом. Використання концентрації кисню нижче за 12% для лікування захворювань, особливо у дітей і літніх людей, вимагає серйозних додаткових досліджень. Нещодавно був запропонований новий метод гіпоксично-гіпероксичного тренування, що

поєднує в собі періоди дихання гіпоксичною (12-10% FiO_2) і гіпероксичною (30-35% FiO_2) сумішшю. Обмежені дані свідчать, що такий режим може скоротити час реоксигенації, тобто зменшити тривалість тренувальних сесій. Проте, до цих пір немає достатньої порівняльної бази для доказу, що цей метод є більш ефективним, ніж гіпоксично-нормоксичні режими. Ми звертаємося до всіх вченим, які працюють в галузі ІГТ, не приховувати свої негативні результати, а публікувати всі спостереження у відкритій пресі. Це зробить значний внесок у розробку загальних методичних принципів здійснення ІГТ для поліпшення здоров'я населення нашої планети.

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