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Lessons from twenty years' investigations of intermittent hypoxia: principles and practices

Widespread use of the intermittent hypoxic training/treatment (IHT) methods in sports, military and medical practice during recent decades has provoked a discussion: What is 'intermittent hypoxia'? In contrast to studies from the former Soviet Union countries, that emphasized mainly the beneficial effects of IHT on an organism, intermittent hypoxia research in Western Europe and North America was primarily focused on the detrimental effects associated with sleep apnea. However, during the past decade, such a gap of division between East and West is progressively shrinking, and mutual understanding on what "intermittent hypoxia" means, becomes clearer. Potential mechanisms underlying both beneficial and adverse effects of IHT have been described. Basic investigations led to the proliferation of various methods of IHT exposure, the development of different medical equipment – hypoxicators – for its implementation in sport practice, military operations and also for clinical application. However, wide array of different protocols and measurements makes the results difficult to harmonize. Meanwhile, the mode of hypoxic influence (depth, duration, and intermittence) appeared to be critical for the determination of healing or harmful result. Therefore, special purposeful investigations are needed to elucidate basic mechanisms of different IHT effects depending on the modality of hypoxic stimuli and elaborate most effective and safe regimen for the introduction in human practice.

INTRODUCTION

Intermittent hypoxia (periodic hypoxia, interval hypoxia, hypoxic preconditioning etc) became today "the talk of the town" among physiologists and clinicians who deal with hypoxic problems. Although the roots of this topic go deep into Middle Ages, sharply intensifying in 30th years of XX century in Soviet Union due to military needs, most fundamental investigations were made during last two decades. The number of publications indexed in PUBMED under the key-word "Intermittent Hypoxia" increased from 49 in 1993 to 520 during the first half-year of 2013. Several monographs have been published [Kolb, 2004; Gozal et al., 2011; Xi & Serebrovskaya, 2009; 2012].

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. Principals of IHT application for cell cultures, animal experiments (mice, dogs, cats, rabbits, pigs, horses and even insects) have been elaborated. A variety of technical implementations for treatment of animals and humans has been tested.

Widespread use of the intermittent hypoxic training/treatment (IHT) methods in sports, military and medical practice during recent decades has provoked a discussion: "What is 'intermittent hypoxia'?" [Semenza, 2012]. All papers using this term should be divided into the four main classes: (1) hypoxic hypoxia (intermittent hypoxic training using gas mixtures or barochambers, recurrent sojourn at high altitudes, hypoxic preconditioning in stem cell transplantation therapy); (2) ischemic preconditioning (cardiac, cerebral etc); (3) hypoxia induced by breath holding (divers, yogic technique Pranayama, training with extra dead space); (4) obstructive sleep apnea syndrome (OSAS) and other diseases associated with brainstem disorders.

Three first classes are generally considered as beneficially influencing on an organism, whereas the fourth one (which is characterized by the similar pattern of hypoxic and normoxic episodes) is an example of the pathological process. Rats exposed to chronic intermittent hypoxia (CIH) simulating recurrent apnea in OSAS patients demonstrate autonomic morbidities and hypertension similar to those described in recurrent apnea patients [Fletcher, 2001; Prabhakar et all., 2005, and many others]. Meanwhile, such comparison seems to be rather mechanistic because does not take into account several significant differences between other factors accompanying hypoxia in these four paradigms.

For example, most researchers do not take into account that IHT methods in the vast majority of cases use eucapnic hypoxia which results in hyperventilation and hence hypocapnia. At the same time, ischemic preconditioning which was proved to activate endogenous defense mechanisms and shows marked protective effects is accompanied by hypercapnia, acidosis and the accumulation of metabolites absent during IHT. In experiments on rats, only hypoxic component is modulated, whereas inspired CO_2 is maintained at normal level. Meanwhile, pCO_2 and pH play one of the main regulative roles in respiration and metabolism and could affect the organism very differently from hypoxia per se. Intracellular acidosis due to hypercapnia raises concerns about potential harmful effects. In contrast to intermittent hypoxia, the effects of intermittent hypercapnia and its cohabitation with hypoxia are the areas of research that remain to be explored. Therefore, a direct comparison of IHT, ischemia and sleep apnea effects seems inconsistent.

Although intermittent hypoxia research in Western Europe and North America was primarily focused on the detrimental effects of chronic intermittent hypoxia associated with sleep-disorder breathing, during last decade such a gap of division is progressively shrinking, and mutual understanding on what “intermittent hypoxia” means, becomes clearer.

In this mini-review we will just outline the main recent achievements in the field of intermittent hypoxia focusing on recent advances in the mechanisms of IH investigation.

MECHANISMS

An impressive amount of scientific information has been gathered with regard to the responses to hypoxia, from the integrative systems level to the molecular and genomic level, such as: (1) regulation of respiration and circulation; (2) free radical production; (3) mitochondrial respiration; (4) role of genetic factors (HIF, MTF-1, NF-βκ, c-Fos, c-Jun, etc); (5) epigenetic mechanisms of adaptation to IH. Repeated exposures to hypoxia have been examined for both their beneficial and adverse effects. The following questions arise: what are the key mechanisms determining the adaptive versus maladaptive nature of different paradigms of intermittent hypoxia, and, what molecular pathways are mediating the observed pathological or physiological response? Until now there is no exact evidence about the precise mechanism for switching adaptive or maladaptive responses to hypoxic impact. The most important arguments are presented in recent papers [Prabhakar & Semenza, 2012; Raghuraman et al., 2013].

Many discoveries demonstrated that intermittent hypoxia leads to remodeling of the carotid body function manifested by augmented sensory response to hypoxia and induction of sensory long-term facilitation (LTF). More than 20 years ago we have shown that intermittent normobaric hypoxia augments hypoxic ventilatory response (HVR) and do not substantially influence hypercapnic ventilatory sensitivity (HCVR) [Serebrovskaya, 1992]. Later on John Weil and his co-workers [2003] described variations in the HVR in human subjects. There are many reviews reflected further investigations in this field [Prabhakar & Kline, 2002; Serebrovskaya, 2002; Teppema & Dahan, 2010; and oth.]. Recent studies strongly indicate that endothelin-1 takes part in this process resulting from reactive oxygen species-dependent activation of endothelin converting enzyme [Peng et al., 2013]. Role of such gasotransmitters as nitric oxide, carbon dioxide and hydrogen sulfide (H2S) in the regulation of respiration under intermittent hypoxia was excellently described by N. Prabhakar [2013].

It is widely known that during acute episodes of hypoxia, chemoreceptor-mediated sympathetic activity increases heart rate, cardiac output, peripheral resistance and systemic arterial pressure. Tyrosine hydroxylase (TH) is the rate-limiting enzyme for catecholamine synthesis. Several mechanisms contribute to the short- and long-term regulation of TH which are well-established. IH-mediated activation of TH leads to the increase in catecholamines level in the brainstem and adrenal medulla [Raghuraman et al., 2013]. In our lab, it was shown that two-week IHT course increased dopamine synthesis in adult and old rats and the animals with experimental Parkinson's disease (PD), especially in the right striatum, restoring partially the skewness of DA distribution between brain hemispheres which has been lost during aging [Belikova et al., 2012].

However, different IH paradigms produce remarkably divergent effects on systemic arterial pressure in the posthypoxic steady state [Serebrovskaya et al., 2008]. The hypertensive effects of OSA vs. the depressor effects of therapeutic hypoxia exemplify this divergence. Why do OSA and IHT produce such disparate effects on blood pressure? It is useful to consider the fundamental differences between the two phenomena: duration of hypoxia periods; hypercapnea and acidemia versus hypocapnea and alkalemia; hypoxic episodes occur at day- or night-time, etc. As a result, OSA ignites a crescendo of factors which activate the sympathetic nervous system and systemic inflammation, culminating in maladaptive, persistent hypertension. In contrast, therapeutic IHT activates parasympathetic system and dampens other factors.

Another IH effects on cardio-respiratory system should be only mentioned here. There are increased alveolar ventilation and lung diffusion capacity; increased haematopoiesis, increased capillary density and tissue perfusion, suppressed function of mitochondrial enzyme respiratory complex I (MEC I) and the alternative activation of MEC II and many others (see reviews Schmidt, 2002; Serebrovskaya, 2002; Mankovska et al., 2005; Lukyanova et al., 2009; Faiss et al., 2013; Prabhakar & Semenza, 2012). Some authors [Prokopov, 2012] consider intermittent hypoxia as a multifunctional tool of a natural mitochondria-rejuvenative strategy.

Besides, hypoxic exposure significantly increases the tolerance and regenerative properties of stem cells and progenitor cells. During last decade it was shown that short-term hypoxic exposures can mobilize hematopoietic stem cells (HSC) and increase their presence in peripheral circulation [Tang et al., 2009; Viscor et al., 2009; Serebrovskaya et al., 2011; Ranera et al., 2012]. Different intensities and durations of hypoxia could have important and diverse effects on stem cell development. Special study was designed to compare the effects of intermittent versus acute hypoxia on human HSCs and some immune parameters [Serebrovska et al., 2010]. The effect of two-week program of cyclic 5 min exposures to 10% O_2 were: (1) decrease in circulating hematopoietic stem cells; (2) complement activation; (3) phagocytic and bactericidal activities of neutrophils stimulation while suppressing pro-inflammatory cytokines. In contrast to the 14d program, a single IHT session provoked appreciable yet transitory increase in circulating HSC which quickly subsided after hypoxic exposures. Results raise the possibility that IH induces HSC emigration from niches into the circulation, followed by homing and sequestration in target tissues during post-hypoxic recovery. The IH-induced decrease in blood TNF-α content with simultaneous increase in IFN-γ could contribute to the moderation of infectious-inflammatory processes.

One of the key mechanisms of cell damage during hypoxia and reoxygenation is an excessive production of reactive oxygen and nitrogen species (ROS and RNS) in mitochondria. ROS and RNS generation leads to mitochondrial protein, lipid and DNA oxidation which impedes normal mitochondrial physiology and initiates cellular death pathways [Thompson et al., 2013]. On the other hand, ROS function as signaling molecules in a variety of physiological systems [Prabhakar, 2011; Wang et al., 2011). Several attempts were undertaken to analyze this question [Sazontova & Arkhipenko, 2009; Lukyanova et al, 2009, 2012]. It was shown, that low levels of ROS production are protective and may serve as a trigger for hypoxic adaptations. At the cellular level, intermittent hypoxia leads to reprogramming of mitochondrial metabolism that ensures adequate ATP generation and prevents adverse consequences of excess mitochondrial ROS generation. These metabolic adaptations are due to hypoxia-inducible factors 1 and 2 (HIF-1 and HIF-2) transcriptional regulation of glycolytic enzymes, mitochondrial electron transport chain components, and other metabolic enzymes [Semenza & Prabhakar, 2007; Prabhakar & Semenza, 2012]. Recent studies have shown that HIF-1 and HIF-2 regulate the expression of gene products with opposing functions that regulate the redox state (Prabhakar, 2013). For instance, HIF-1 regulates the expression of pro-oxidant enzymes, including NADPH oxidases, whereas HIF-2 regulates the expression of antioxidant enzymes.

In our lab, Drevytska et al [2012] investigated the role of another subunit - HIF-3α – in adaptation to IH and physical load. It was shown that this subunit plays a negative role in the adaptation to hypoxia. HIF-3α mRNA expression increased sharply under acute hypoxia in the heart, lung, and kidney but did not change after 5-week IHT. Inhibition of HIF-3α expression led to an increase in physical endurance. Thus, every of HIF-subunits plays different role in response to hypoxic load. It seems that the investigation of their ensemble functioning under different IH modes (depth, duration, and intermittence) could explain the mechanism for switching adaptive or maladaptive cellular and systemic responses to hypoxic impact.

One of the new directions in the investigation of hypoxic adaptations is epigenetics – heritable modifications of DNA that do not involve changes in the DNA primary sequence [Gluckman, 2011; Nanduri et al., 2011; Prabhakar, 2013]. Epigenetic mechanisms can determine whether a gene is activated or silenced. These studies seem to be very promising in this rapidly emerging area.

While all above mentioned fundamental studies provided important insights into mechanisms of HIF activation by hypoxia, they can not answer as yet practical question what dose and regimen of hypoxic impact could be mostly beneficial for animals and humans.

Use in clinical practice

To the present days, intermittent hypoxic training (IHT) has been used extensively for altitude pre-acclimatization, for treatment of a variety of clinical disorders and in sports. Wide spectrum of protocols for IHT is represented now in literature showing both beneficial and detrimental effects. Beneficial results were shown for treatment and prophylaxis of numerous disorders in pulmonology (chronic obstructive diseases, bronchial asthma, chronic rhinitis etc), cardiology (ischemic heart disease, hypertension, cardiosclerosis, etc), hematology (hypoplastic and iron-deficient anemia, post-radiation hematological disturbances, etc), neurology (functional neurological disorders, Parkinson's and Alzheimer's diseases, neurosis, syndrome of autonomic dystonia, diabetic neuropathy, psychosomatic disorders), diabetes mellitus, obstetrics and gynecology (juvenile bleedings, toxicosis of expectant mothers, pathology of climacteric period etc), gastrointestinal diseases (gastroduodenitis, peptic ulcer), professional diseases (pneumoconiosis, vibration- and dust-induced pathology, acute and chronic intoxication etc), post radiation disorders of immune system and male reproductive system, and many others. In this mini-review we can not mention all spectrum of papers devoted to this problem. The interested reader is referred to several reviews and monographs [Karash et al., 1988; Berezovskii and Levashov, 1992; Fesenko and Lisyana, 1992; Xi & Serebrovskaya, 2009; 2012; and many others]. Much literature may be found on the websites *www.go2altitude.com* and *www.bionova.ru.* Here we mention just some last publications.

IHT clinical applications are clearly presented by S.Basovich in his last review [2013]. Among others, he described beneficial results of IHT application for treatment of bronchial asthma and chronic obstructive pulmonary disease, hypertension, to correct abnormalities during pregnancy, in epilepsy treatment, for preparation of patients to surgery to increase nonspecific resistance, etc.

The efficacy of IHT was demonstrated for improving male subfertility and other andrological disorders [Swanson & Serebrovska, 2012]. Intermittent hypoxia protocols may be developed for treatment and prevention of osteopenia and osteoporosis [Berezovskii et al., 2004; Guner, 2013].

Recently, a new mode of adaptive training was explored, which combines periods of hypoxia and hyperoxia [Arkhipenko et al., 2005; Glazachev et al., 2010; Sazontova et al., 2012; Gonchar & Mankovska, 2012]. 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.

Another new direction in IHT application is developing during last years: hypoxic postconditioning [Leconte et al., 2009; Maslov et al., 2012; Joo et al., 2013; Xie et al., 2013]. While pre-conditioning is induced before stroke onset, experiments on animals have shown that ischemic post-conditioning performed after reperfusion attenuates brain injury. Clinical investigations testify on cardioprotective impact of postconditioning in patients with acute myocardial infarction and cardiosurgery patients.

Some works are devoted to the application of hypoxic-hypercapnic or intermittent hypercapnic treatment to clinical practice. This question is elucidated in review of Pokorski & Serebrovskaya [2009]. The effects of hypercapnia are somewhat surprising. CO_2 is a recognized vasodilator of myocardial blood vessels, it is capable to substantially increase cerebral blood flow leading to increased tissue oxygenation. Hypercapnic acidosis may have a beneficial effect in its own right in severe respiratory conditions and may, paradoxically, be helpful in patients with organ failure due to ischemia-reperfusion-related cellular injury. That brings us to the use of "therapeutic hypercapnia", a purposefully increased inspired CO_2 concentration to achieve some beneficial health effects. Hypoxia and hypercapnia, used in tandem, may strengthen the curative effects of either. So, intermittent hypercapnia seems an obvious area of future research focusing not only on the mechanisms of long-term potentiation and synaptic plasticity in the brain stem respiratory network, but also on the health-related applicability of this kind of respiratory strategy. The controversies that surround the use of therapeutic hypercapnia uphold research interest. The potential of intermittent hypercapnia is just starting to be realized and hopefully will be further explored.

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 guide-lines for hypoxic treatment/training application are complicated due to the differences in criteria for individual dosage and utilized methods. One of the attempts to solve this problem was made by applying a new mathematician method - "Method of Expert Assessing Scales" (MEAS) - for the estimation of IHT application safety in human practice [Serebrovsky & Serebrovska, 2009]. MEAS dilates capabilities of traditional probabilistic safety assessment and allows determining the danger degree at the most early stage of its development and fulfilling well-timed actions for danger prevention. It includes the description of: a) hazard causal factors; b) situations as a set of values of causal factors; c) influences of separate factors on the origin of basic events; d) joint influence of factors on basic events probability. The methodology provides the forming of the system of indexes characterizing the risk of IHT negative effects and determination of legitimate value scopes for basic physiological parameters; creation of the classification system allowing to set human individual cardio-respiratory reactivity; development of proper IHT regimen for every class of reactivity.

But there is just one of the first steps which is far from the elaboration of concrete methodic recommendations. Mode of hypoxic influence (depth, duration, and intermittence) appeared to be critical for the determination of beneficial or detrimental effects of IHT. Low doses of hypoxia might not be sufficient stimuli to mobilize adaptive mechanisms, whilst severe or prolonged hypoxia may provoke dangerous pathological processes.

Meanwhile, in practice hypoxic regimens which are used for the study of hypoxic adaptations vary broadly from 3-12 short hypoxic sessions (2-10 min) with 2-20 min normoxic breaks during 7-30 days to hypoxic influences lasting from 1 - 12 hours during 2-90 days. In our lab, V.Nosar compared the effects of five most spread modes of IHT on rat gastrocnemius muscle PO_2 and heart and liver mitochondrial respiration [Serebrovskaya et al., 2013]. Min of hypoxia, % O_2 and recovery min on air in each mode were: 1) 5, 12%, 5; 2) 15, 12%, 15; 3) 5, 12%, 15; 4) 5, 7%, 5; 5) 5, 7%, 15. Our experimental data indicated that among 5 tested modes of IHT, optimal hypoxic dose for muscle oxygen supply is 5-min breathing with 12 % O_2 gas mixture and 5-min breaks (Mode 1), 5-6 times a day during two or three weeks. Under such mode, PmO_2 dropped minimally to the end of every hypoxic period and recovered quickly after every hypoxic set to initial level or even exceeded it. Two-week training with this mode raised basal tissue oxygenation during normoxia and provided higher PmO_2 level during acute hypoxia. Such mode caused the substrate dependent reorganization of liver and heart mitochondrial energy metabolism favoring NADH-dependent oxidation and improving the efficiency of oxidative phosphorylation.

However, we must take into account that all these beneficial results were obtained on rat models. Are we ready to propose this as a clinical therapeutic method? More rigorous studies need to be provided in the near future on patients with several diseases. Besides, in actual human practice including sports and military applications of hypoxic training [Musa, 2007], the IHT regimen (the degree of hypoxia, exposure duration and number of sessions) could be also titrated to the mission requirements, such as the operational target altitude, risk of developing acute mountain sickness, or anticipated physical activity levels.

Basic investigations led to the proliferation of various methods of IHT exposure, the development of different medical equipment – hypoxicators – for its implementation in sport practice, military operations and also for clinical application [Lopata & Serebrovskaya, 2012].

In conclusion, intermittent hypoxic treatment/training represents a promising field of study in prevention and treatment of many diseases. The proper choice of the hypoxic dosage depending on individual's reactivity must be titrated for each patient to avoid negative effects of hypoxia and to augment the favorable properties. We can envisage a bright future for individualized IHT, which may play a significant role in the fast developing field of personalized preventive medicine against various human diseases.

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УРОКИ ДВАДЦЯТИРІЧНОГО ВИВЧЕННЯ ІНТЕРВАЛЬНОЇ ГІПОКСІЇ: ПРИНЦИПИ І ПРАКТИКА

Широке застосування методів інтервального гіпоксичного тренування (ІГТ) в спорті, військовій та медичній практиці протягом останніх десятиліть викликало широку

дискусію: що таке «інтервальна гіпоксія»? На відміну від досліджень, проведених у країнах колишнього Радянського Союзу, в яких підкреслювалися в основному позитивні ефекти ІГТ на організм, дослідження інтервальної гіпоксії в Західній Європі і Північній Америці були зосереджені головним чином на негативних наслідках, пов'язаних з сонним апное. Тим не менш, протягом останнього десятиліття такий розрив у поглядах між Сходом і Заходом поступово скорочується, і взаємне розуміння того, що означає цей термін, стає ясніше. Були описані потенційні механізми, що лежать в основі як позитивних, так і негативних наслідків ІГТ, розроблені різні методи застосування ІГТ та обладнання для їх реалізації в спортивній практиці, військових операціях, а також для клінічного застосування. Тим не менш, широкий спектр різних протоколів і вимірювань робить результати важко узгодженими. Проте, саме режим гіпоксичного впливу (сила, тривалість і уривчастість) є критичним для отримання позитивного або негативного результату. Тому мають бути проведені спеціальні цілеспрямовані дослідження для з'ясування основних механізмів різних ефектів ІГТ залежно від модальності гіпоксичного стимулу і розробки найбільш ефективних і безпечних режимів впливу для впровадження в практичну медицину.

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УРОКИ ДВАДЦАТИЛЕТНЕГО ИЗУЧЕНИЯ ИНТЕРВАЛЬНОЙ ГИПОКСИИ: ПРИНЦИПЫ И ПРАКТИКА

Широкое применение методов интервальной гипоксической тренировки (ИГТ) в спорте, военной и медицинской практике в течение последних десятилетий вызвало широкую дискуссию: Что такое «интервальная гипоксия»? В отличие от исследований, проведенных в странах бывшего Советского Союза, в которых подчеркивались в основном положительные эффекты ИГТ на организм, исследования интервальной гипоксии в Западной Европе и Северной Америке были сосредоточены главным образом на негативных последствиях, связанных с сонным апноэ. Тем не менее, в течение последнего десятилетия такой разрыв во взглядах между Востоком и Западом постепенно сокращается, и взаимное понимание того, что означает этот термин, становится яснее. Были описаны потенциальные механизмы, лежащие в основе как положительных, так и негативных последствий ИГТ, разработаны различные методы применения ИГТ и оборудование - гипоксикаторы- для их реализации в спортивной практике, военных операциях, а также для клинического применения. Тем не менее, широкий спектр различных протоколов и измерений делает результаты трудно согласуемыми. Между тем, именно режим гипоксического воздействия (сила, длительность и прерывистость) являются критическим для получения положительного или отрицательного результата. Поэтому должны быть проведены специальные целенаправленные исследования для выяснения основных механизмов различных эффектов ИГТ в зависимости от модальности гипоксического стимула и разработки наиболее эффективных и безопасных режимов воздействия для внедрения в практическую медицину.

REFERENCES

1. Arkhipenko YV, Sazontova TG, Zhukova AG. Adaptation to periodic hypoxia and hyperoxia improves resistance of membrane structures in heart, liver, and brain. Bull Exp Biol Med. 2005;**140**(3):278-281.
2. Basovich SN. Trends in the use of preconditioning to hypoxia for early prevention of future life diseases. Biosci Trends. 2013, **7**(1):23-32.
3. Belikova MV, Kolesnikova EE, and Serebrovskaya TV. Intermittent Hypoxia and Experimental Parkinson's Disease. In: Lei Xi & Tatiana V. Serebrovskaya (Eds). Intermittent Hypoxia and Human Diseases / Springer, UK, 2012, Chapter 12, p. 147-153.
4. Berezovskii V.A. and Levashov M.I. [Physiological premises and mechanisms of normalizing effect of normobaric hypoxia and inhalation therapy]. Fiziol Zh; 1992, **38**(5):3-12.
5. Berezovskii VA, Litovka IG, Kostyuchenko AS. Low oxygen tension may defence the bone tissue from unloading simulated osteopenia. J Gravit Physiol. 2004 Jul;**11**(2):P153-154.
6. Drevytska T, Gavenauskas B, Drozdovska S, Nosar V, Dosenko V, Mankovska I. HIF-3α mRNA expression changes in different tissues and their role in adaptation to intermittent hypoxia and physical exercise. Pathophysiology. 2012 Jun;**19**(3):205-214.
7. Faiss R, Léger B, Vesin JM, Fournier PE, Eggel Y, Dériaz O, Millet GP. Significant molecular and systemic adaptations after repeated sprint training in hypoxia. PLoS One. 2013; **8**(2):e56522.
8. Fesenko M.E. and Lisyana T.O. [Approach to employment of hypoxic stimulation for treatment of lingering and relapsing bronchitis in children of early age]. Fiziol. Zh. 1992; **38**(5):31-33.
9. Fletcher E.C. Invited review: Physiological consequences of intermittent hypoxia: systemic blood preassure. J.Appl. Physiol 2001; **90** (4): 1600-1605.
10. Glazachev OS, Zvenigorodskaia LA, Dudnik EN, Iartseva LA, Mishchenkova TV, Platonenko AV, Spirina GK. Interval hypoxic-hyperoxic training in the treatment of the metabolic syndrome. Eksp Klin Gastroenterol. 2010; 7:51-56.
11. Gluckman PD. Epigenetics and metabolism in 2011: Epigenetics, the life-course and metabolic disease. Nat Rev Endocrinol. 2011; 20;**8**(2):74-76.
12. Gonchar O, Mankovska I. Moderate hypoxia/hyperoxia attenuates acute hypoxia-induced oxidative damage and improves antioxidant defense in lung mitochondria. Acta Physiol Hung. 2012 Dec;**99**(4):436-446.
13. Gozal D, Kheirandish-Gozal L, Yang Wang , and Zhang

X L. Sleep Apnea: Pathogenesis, Diagnosis and Treatment. eBook ISBN 9781420020885, 2011, 570 pp.
14. Guner I, Uzun DD, Yaman MO, Genc H, Gelisgen R, Korkmaz GG, Hallac M, Yelmen N, Sahin G, Karter Y, Simsek G. The effect of chronic long-term intermittent hypobaric hypoxia on bone mineral density in rats: role of nitric oxide. Biol Trace Elem Res. 2013 Aug;**154**(2):262-267.
15. Joo SP, Xie W, Xiong X, Xu B, Zhao H. Ischemic postconditioning protects against focal cerebral ischemia by inhibiting brain inflammation while attenuating peripheral lymphopenia in mice. Neuroscience. 2013; 23;243:149-157.
16. Karash Yu.M., Strelkov R.B., and Chizhov A.Yu. (1988). [Normobaric hypoxia in treatment, prophylaxis and rehabilitation]. Moscow: Meditsina, 352 p.
17. Kolb JC. Physiological responses to intermittent hypoxia in humans. Boca Raton, Florida (USA), 2004, 196 pp.
18. Leconte C, Tixier E, Freret T, Toutain J, Saulnier R, Boulouard M, Roussel S, Schumann-Bard P, Bernaudin M. Delayed hypoxic postconditioning protects against cerebral ischemia in the mouse. Stroke. 2009 Oct;**40**(10):3349-3355.
19. Lopata VA and Serebrovskaya TV. Hypoxicators: Review of the Operating Principles and Constructions. In: Lei Xi & Tatiana V. Serebrovskaya (Eds). Intermittent Hypoxia and Human Diseases / Springer, UK, 2012, Chapter 24, p. 291-302.
20. Lukyanova L.D., Germanova E.L., Kopaladze R.A. Development of resistance of an organism under various conditions of hypoxic preconditioning: role of the hypoxic period and reoxygenation. Bull. Exp. Biol. Med., 2009, **147**(4):400-404 [In Russian].
21. Lukyanova L.D., Kirova Yu. I., and Germanova E.L. Energotropic Effects of Intermittent Hypoxia: Role of Succinate-Dependent Signaling. In: Lei Xi & Tatiana V. Serebrovskaya (Eds). Intermittent Hypoxia and Human Diseases. Springer, UK, 2012; Chapter 20, pp. 239-252.
22. Mankovska IM, Gavenauskas BL, Hosar VI, Nazarenko AI, Rozova KV, and Bratus LV. Mechanisms of muscular tissue adaptation to intermittent hypoxia. Sport Medicine (Ukr), 2009; 1:3-11 [In Ukrainian].
23. Maslov LN, Mrochek AG, Hanus L, Pei J-, Zhang Y, Wang H, Naryzhnaia NV. [Phenomenon of heart ischemic postconditioning]. Ross Fiziol Zh Im I M Sechenova. 2012 Aug;**98**(8):943-961. Review. Russian.
24. Muza S.R.. Military applications of hypoxic training for high-altitude operations. Med. Sci. Sports. Exerc. 2007; **39**(9):1625-1631.
25. Nanduri J, Makarenko V, Reddy VD, Yuan G, Pawar A, Wang N, Khan SA, Zhang X, Kinsman B, Peng YJ, Kumar GK, Fox AP, Godley LA, Semenza GL, Prabhakar NR. Epigenetic regulation of hypoxic sensing disrupts cardiorespiratory homeostasis. Proc Natl Acad Sci U S A. 2012;**109**(7):2515-2520.
26. Peng YJ, Nanduri J, Raghuraman G, Wang N, Kumar GK, Prabhakar NR. Role of Oxidative Stress Induced Endothelin Converting Enzyme Activity in the Alteration of Carotid Body Function by Chronic Intermittent Hypoxia. Exp Physiol. 2013 Aug 2. [Epub ahead of print].
27. Pokorski M. & Serebrovskaya T. Intermittent Hypercapnia. In: Intermittent Hypoxia: From Molecular Mechanisms to Clinical Applications/. Editors: Lei Xi & Tatiana V. Serebrovskaya/ Nova Science Publishers, 2009, p. 297-310.
28. Prabhakar NR. Sensing hypoxia: physiology, genetics and epigenetics. J Physiol. 2013, **591**(Pt 9):2245-2257.
29. Prabhakar NR. Sensory plasticity of the carotid body: role of reactive oxygen species and physiological significance. Respir Physiol Neurobiol. 2011; 178(3):375-380.
30. Prabhakar N.R., Fields R.D. , Baker T., and Fletcher E. C. Intermittent hypoxia: cell to system. Am J. Physiol 2001; **281** (3): L524-L528.
31. Prabhakar NR, Kline DD. Ventilatory changes during intermittent hypoxia: importance of pattern and duration. High Alt Med Biol. 2002; **3**(2):195-204.
32. Prabhakar NR, Peng YJ, Jacono FJ, Kumar GK, Dick TE. Cardiovascular alterations by chronic intermittent hypoxia: Importance of carotid body chemoreflexes. Clin Exp Pharmacol Physiol 2005; **32**:447-449.
33. Prabhakar N.R., Semenza G.L. Adaptive and maladaptive cardiorespiratory responses to continuous and intermittent hypoxia mediated by hypoxia-inducible factors 1 and 2. Physiol. Rev., 2012, **92**: 967–1003.
34. Prokopov AF. Intermittent Hypoxia and Health: From Evolutionary Aspects to Mitochondria Rejuvenation. In: Lei Xi & Tatiana V. Serebrovskaya (Eds). Intermittent Hypoxia and Human Diseases / Springer, UK, 2012, Chapter 21, p. 253-269.
35. Raghuraman G, Prabhakar NR, Kumar GK. Differential regulation of tyrosine hydroxylase by continuous and intermittent hypoxia. Adv Exp Med Biol. 2012;758:381-385.
36. Ranera B, Remacha AR, Álvarez-Arguedas S, Romero A, Vázquez FJ, Zaragoza P, Martín-Burriel I, Rodellar C. Effect of hypoxia on equine mesenchymal stem cells derived from bone marrow and adipose tissue. BMC Vet Res. 2012 Aug 22;8:142.
37. Sazontova TG & Arkhipenko YuV. Intermittent hypoxia in resistance of cardiac membrane structures: role of reactive oxygen species and redox signaling. In: Intermittent Hypoxia: From Molecular Mechanisms to Clinical Applications/. Editors: Lei Xi & Tatiana V. Serebrovskaya/ Nova Science Publishers, 2009, Chapter 5, p. 113-150.
38. Sazontova TG, Bolotova AV, Bedareva IV, Kostina NV, and Arkhipenko YuV. Adaptation to intermittent hypoxia/hyperoxia enhances efficiency of exercise training. In: Lei Xi & Tatiana V. Serebrovskaya (Eds). Intermittent Hypoxia and Human Diseases / Springer, UK, 2012, Chapter 16, p. 191-205.
39. Schmidt W. Effects of intermittent exposure to high altitude on blood volume and erythropoietic activity. High Alt Med Biol. 2002; **3**(2):167-176.
40. Semenza GL, Prabhakar NR. HIF-1-dependent respiratory, cardiovascular, and redox responses to chronic intermittent hypoxia. Antioxid Redox Signal. 2007 Sep;**9**(9):1391-1396.
41. Semenza GL. Foreword. In: Lei Xi & Tatiana V. Serebrovskaya (Eds). Intermittent Hypoxia and Human Diseases. Springer, UK, 2012; p.V.

42. Serebrovskaya T.V. Comparison of respiratory and circulatory human responses to progressive hypoxia and hypercapnia. Respiration, 1992; **59**(1), 35-41.
43. Serebrovskaya TV. Intermittent Hypoxia Research in the Former Soviet Union and the Commonwealth of Independent States (CIS): History and Review of the Concept and Selected Applications. High Altitude Medicine &Biology, 2002, **3**(2): 205-221.
44. Serebrovskaya TV, Manukhina EB, Smith ML, Downey HF, Mallet RT. Intermittent Hypoxia: Cause of or Therapy for Systemic Hypertension? Exp Biol Med (Maywood). 2008 Jun; **233**(6):627-50.
45. Serebrovska TV, Nikolsky I, Ishchuk V. Human adaptation to intermittent hypoxia: effects on hematopoietic stem cells and immune function. In: Adaptation Biology and Medicine, Volume 6: Cell Adaptations and Challenges, Eds: P.Wang, C.-H. Kuo, N.Takeda and P.K.Singal, Narosa Publisher, Canada, 2010, p. 181-191.
46. Serebrovskaya TV, Nikolsky IS, Nikolska VV, Mallet RT, Ishchuk VA . Intermittent hypoxia mobilizes hematopoietic progenitors and augments cellular and humoral elements of innate immunity in adult men. High Alt Med Biol. 2011; **12**(3):243-52.
47. Serebrovskaya TV, Nosar VI, Bratus LV, Gavenauskas BL, Mankovska IM. Tissue oxygenation and mitochondrial respiration under different modes of intermittent hypoxia. High Altitude Medicine & Biology, 2013, vol. 14 (in press).
48. Serebrovsky A. & Serebrovska T. Models and algorithms for the assessment of intermittent hypoxia application safety and efficacy in medical practice. In: Hypoxia and Consequences: From Molecule to Malady. New York, March 12-14, 2009, Book of Abstracts, Session II, abstract # 25.
49. Swanson RJ & Serebrovska ZA. Intermittent hypoxia remedies male subfertility. In: Lei Xi & Tatiana V. Serebrovskaya (Eds). Intermittent Hypoxia and Human Diseases / Springer, UK, 2012, Chapter 18, p. 221-227.
50. Tang YL, Zhu W, Cheng M, Chen L, Zhang J, Sun T, Kishore R, Phillips MI, Losordo DW, Qin G. Hypoxic preconditioning enhances the benefit of cardiac progenitor cell therapy for treatment of myocardial infarction by inducing CXCR4 expression. Circ Res. 2009 May 22;**104**(10):1209-1216.
51. Teppema LJ, Dahan A. The ventilatory response to hypoxia in mammals: mechanisms, measurement, and analysis. Physiol Rev. 2010; **90**(2):675-754.
52. Thompson JW, Dave KR, Young JI, Perez-Pinzon MA. Ischemic Preconditioning Alters the Epigenetic Profile of the Brain from Ischemic Intolerance to Ischemic Tolerance. Neurotherapeutics. 2013 Jul 19. [Epub ahead of print]
53. Viscor G, Javierre C, Pagès T, Ventura JL, Ricart A, Martin-Henao G, Azqueta C, Segura R. Combined intermittent hypoxia and surface muscle electrostimulation as a method to increase peripheral blood progenitor cell concentration. J Transl Med. 2009; **29**:7-91.
54. Wang ZH, Chen YX, Zhang CM, Wu L, Yu Z, Cai XL, Guan Y, Zhou ZN, Yang HT. Intermittent hypobaric hypoxia improves postischemic recovery of myocardial contractile function via redox signaling during early reperfusion. Am J Physiol Heart Circ Physiol. 2011 Oct;**301**(4):H1695-705.
55. Weil JV. Variation in human ventilatory control—genetic influence on the hypoxic ventilatory response. Respir Physiol Neurobiol 2003; 135: 239–246.
56. Xi L & Serebrovskaya T (Editors). Intermittent Hypoxia: From Molecular Mechanisms to Clinical Applications / Nova Science Publishers, Inc., 400 Oser Avenue, Suite 1600, Hauppauge, NY 11788, 2009, 615 pp.
57. Xi L & Serebrovskaya T (Editors). Intermittent Hypoxia and Human Diseases / Springer, UK, 2012, 316 pp.
58. Xie R, Wang P, Ji X, Zhao H. Ischemic post-conditioning facilitates brain recovery after stroke by promoting Akt/mTOR activity in nude rats. J Neurochem. 2013 Jun 18.[Epub ahead of print].

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