Lessons from a 20-Year Investigation of Intermittent Hypoxia: Principles and Practices

Chapter · July 2014

DOI: 10.1007/978-81-322-1928-6_22

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Metadata of the chapter that will be visualized online

Chapter Title	Lessons from a 20-Year Investigation of Intermittent Hypoxia: Principles and Practices	
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Abstract	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 and the development of different medical equipment – hypoxicators – for its implementation in sport practice and 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 the most effective and safe regimen for the introduction in human practice.	

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Abstract

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 and the development of different medical equipment – hypoxicators – for its implementation in sport practice and 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 the 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 the 30th year of the twentieth century in Soviet Union due to military needs, the most fundamental investigations were made during the last two decades. The number of publications indexed in PubMed under the keyword "intermittent hypoxia" increased from 49 in 1993 to 520 during

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S.B. Singh et al. (eds.), *Translational Research in Environmental and Occupational Stress*,
DOI 10.1007/978-81-322-1928-6_22, © Springer India 2014

the first half-year of 2013. Several monographs have been published [1–4].

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. Principles of IHT application for cell cultures and 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 have 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'?" [5]. All papers using this term should be divided into 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), and (4) obstructive sleep apnea syndrome (OSAS) and other diseases associated with brainstem disorders.

The 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 apneic patients [6, 7 and many others]. Meanwhile, such comparison seems to be rather mechanistic because it 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-disordered breathing, during the 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.), and (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 [8, 9].

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 does not substantially influence hypercapnic ventilatory sensitivity (HCVR) [10]. Later on John Weil and his co-workers [11] described variations in the HVR in human subjects. There are many reviews that reflected further investigations in this field [12–14 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 [15]. The 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 [16].

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 catecholamine level in the brainstem and adrenal medulla [9]. In our lab, it was shown that a 2-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 [17].

However, different IH paradigms produce remarkably divergent effects on systemic arterial pressure in the posthypoxic steady state [18]. The hypertensive effects of OSA versus 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 hypoxic periods, hypercapnia and acidemia versus hypocapnia and alkalemia, hypoxic episodes occurring at day- or nighttime, 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 the parasympathetic system and dampens other factors.

Another IH effects on the cardiorespiratory system should be only mentioned here. There are increased alveolar ventilation and lung diffusion capacity, increased hematopoiesis, increased capillary density and tissue perfusion, suppressed function of mitochondrial enzyme complex I (MEC I), and the alternative activation of MEC II (see reviews [8, 13, 19–22]). Some authors [23] 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 the last decade it was shown that short-term hypoxic exposures can mobilize hematopoietic stem cells (HSC) and increase their presence in peripheral circulation [24–27]. 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 [28]. The effect of a 2-week program of cyclic 5 min exposures to 10 % O_2 were (1) decrease in circulating hematopoietic stem cells, (2) complement activation, and (3) phagocytic and bactericidal activities of neutrophil stimulation while suppressing proinflammatory 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 posthypoxic 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 [29]. On the other hand, ROS function as signaling molecules in a variety of physiological systems [30, 31]. Several attempts were undertaken to analyze this question [20, 32, 33]. 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 [8, 34]. Recent studies have shown that HIF-1 and HIF-2- regulate the expression of gene products with opposing functions that regulate the redox state [16]. For instance, HIF-1 regulates the expression of prooxidant enzymes, including NADPH oxidases, whereas HIF-2 regulates the expression of antioxidant enzymes.

In our lab, Drevytska et al. [35] 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 changed after a 5-week IHT. Inhibition of HIF-3α expression led to an increase in physical endurance. Thus, every 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 [16, 36, 37]. 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 the abovementioned fundamental studies provided important insights into mechanisms of HIF activation by hypoxia, they cannot answer as yet practical question on 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 deficiency anemia, postradiation 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.), postradiation disorders of the immune system and male reproductive system, and many others. In this mini-review we cannot mention all spectrum of papers devoted to this problem. The interested reader is referred to several reviews and monographs [3, 4, 37–39 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 [40]. Among others, he described beneficial results of IHT application for treatment of bronchial asthma, chronic obstructive pulmonary disease, and 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 [41]. Intermittent hypoxia protocols may be developed for treatment and prevention of osteopenia and osteoporosis [42, 43].

Recently, a new mode of adaptive training was explored, which combines periods of hypoxia and hyperoxia [44–46]. A novel principle of short-term periodic adaptive training by varying the oxygen level from hypoxia to hyperoxia is substantiated both theoretically and experimentally. Studies support the viewpoint that moderate periodic generation of free radical signal during hypoxic/hyperoxic bouts causes better induction of antioxidant enzyme protein synthesis than hypoxic/normoxic exposures that may be an important trigger for specific adaptations.

Another new direction in IHT application is developing during the last years: hypoxic postconditioning [47–51]. While preconditioning is induced before stroke onset, experiments on animals have shown that ischemic postconditioning performed after reperfusion attenuates brain injury. Clinical investigations testify on cardioprotective impact of postconditioning in patients with acute myocardial infarction and cardiac surgery patients.

Some works are devoted to the application of hypoxic-hypercapnic or intermittent hypercapnic treatment to clinical practice. This question is elucidated in the review of Pokorski and Serebrovskaya [52]. 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 brainstem 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 Research 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. One of the attempts to solve this problem was made by applying a new mathematical method – "Method of Expert Assessing Scales" (MEAS) – for the estimation of IHT application safety in human practice [53]. 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 AU2 values of causal factors, (c) influences of separate factors on the origin of basic events, and (d) joint influence of factors on basic event 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 cardiorespiratory reactivity, and development of proper IHT regimen for every class of reactivity.

But this 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, while 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 to 12 short hypoxic sessions (2–10 min) with 2–20 min normoxic breaks during 7–30 days to hypoxic influences lasting from 1 to 12 h during 2–90 days. In our lab, we compared the effects of the five most spread modes of IHT on rat gastrocnemius muscle PO_2 and heart and liver mitochondrial respiration [54]. Minutes of hypoxia, % O_2, and recovery minutes on air in each mode were (1) 5, 12 %, 5; (2) 15, 12 %, 15; (3) 5, 12 %, 15; (4) 5, 7 %, 5; and (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 2 or 3 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. A 2-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 [55], 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 and the development of different medical equipment – hypoxicators – for its implementation in sport practice and military operations and also for clinical application [56].

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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Author Queries

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