Intermittent Hypoxia in Treatment of Bronchial Asthma in Childhood

Article · May 2014

DOI: 10.1007/978-1-4471-2906-6_11

4 authors, including:

T. V. Serebrovskaya
Bogomolets Institute of Physiology NASU
104 PUBLICATIONS **991** CITATIONS
SEE PROFILE

Alexander N. Bakunovsky
Bogomolets Institute of Physiology NASU
3 PUBLICATIONS **6** CITATIONS
SEE PROFILE

Iryna Mikitivna Mankovska
Bogomolets Institute of Physiology NASU
31 PUBLICATIONS **130** CITATIONS
SEE PROFILE

Metadata of the chapter that will be visualized online

Series Title		
Chapter Title	Intermittent Hypoxia in Treatment of Bronchial Asthma in Childhood	
Chapter SubTitle		
Copyright Year	2012	
Copyright Holder	Springer-Verlag London	
Corresponding Author	Family Name	Serebrovskaya
	Particle	
	Given Name	**Tatiana V.**
	Suffix	
	Division	Department of Hypoxia
	Organization	Bogomoletz Institute of Physiology, National Academy of Sciences of Ukraine
	Address	Kiev, Ukraine
	Email	
Author	Family Name	Bakunovsky
	Particle	
	Given Name	**Alexander N.**
	Suffix	
	Division	Department of Hypoxia
	Organization	Bogomoletz Institute of Physiology, National Academy of Sciences of Ukraine
	Address	Kiev, Ukraine
	Email	
Author	Family Name	Nesvitailova
	Particle	
	Given Name	**Klaudia V.**
	Suffix	
	Division	Department of Hypoxia
	Organization	Bogomoletz Institute of Physiology, National Academy of Sciences of Ukraine
	Address	Kiev, Ukraine
	Email	
Author	Family Name	Mankovska
	Particle	
	Given Name	**Iryna N.**
	Suffix	
	Division	Department of Hypoxia
	Organization	Bogomoletz Institute of Physiology, National Academy of Sciences of Ukraine
	Address	Kiev, Ukraine
	Email	

Abstract

According to the World Health Organization, bronchial asthma (BA) is a serious public health problem with over 300 million sufferers of all ages. In this chapter, we demonstrate the possibility to treat BA in childhood with intermittent hypoxia treatment/training (IHT) programs and provide clinical evidence, adverse effects, and latest experience in IHT implementation. Particularly, it was shown that 2-week IHT resulted in a significant decline in breath shortness and feelings of chest congestion in BA children (aged 9–13 years). The cough was diminished or disappeared, and the amount of sputum was reduced and passed more easily. The attacks of asphyxia disappeared or became more occasional. Considerable augmentation of ventilatory response to hypoxic stimuli was observed as well as a diminution of heart rate (HR) reactions to increased hypoxia and an attenuated fall of SaO_2 under hypoxic conditions. Mitochondrial enzymes activity of immune cells such as succinate dehydrogenase (SDG) and alpha-glycerophosphate dehydrogenase (GPDG) increased significantly under IHT. Strong correlation between individual hypoxic sensitivity and enzymes activities was found. In conclusion, 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 must be titrated for each patient in order to avoid negative effects of hypoxia and to augment the favorable ones.

11 Intermittent Hypoxia in Treatment of Bronchial Asthma in Childhood

Tatiana V. Serebrovskaya, Alexander N. Bakunovsky, Klaudia V. Nesvitailova, and Iryna N. Mankovska

Abstract

According to the World Health Organization, bronchial asthma (BA) is a serious public health problem with over 300 million sufferers of all ages. In this chapter, we demonstrate the possibility to treat BA in childhood with intermittent hypoxia treatment/training (IHT) programs and provide clinical evidence, adverse effects, and latest experience in IHT implementation. Particularly, it was shown that 2-week IHT resulted in a significant decline in breath shortness and feelings of chest congestion in BA children (aged 9–13 years). The cough was diminished or disappeared, and the amount of sputum was reduced and passed more easily. The attacks of asphyxia disappeared or became more occasional. Considerable augmentation of ventilatory response to hypoxic stimuli was observed as well as a diminution of heart rate (HR) reactions to increased hypoxia and an attenuated fall of SaO_2 under hypoxic conditions. Mitochondrial enzymes activity of immune cells such as succinate dehydrogenase (SDG) and alpha-glycerophosphate dehydrogenase (GPDG) increased significantly under IHT. Strong correlation between individual hypoxic sensitivity and enzymes activities was found. In conclusion, 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 must be titrated for each patient in order to avoid negative effects of hypoxia and to augment the favorable ones.

Abbreviations

BA	Bronchial asthma
CAT	Catalase
COPD	Chronic obstructive pulmonary disease
EPO	Erythropoietin
GPDG	Alpha-glycerophosphate dehydrogenase
GST	Glutathione-s-transferase
HIF	Hypoxia-inducible factor
HR	Heart rate
HVR	Hypoxic ventilatory response
IH	Intermittent hypoxia
IHT	Intermittent hypoxia training/treatment
MEAS	Method of expert assessing scales
NO	Nitric oxide
NOS	Nitric oxide synthase
OSAS	Obstructive sleep apnea syndrome
ROS	Reactive oxygen species
SaO_2	Arterial oxygen saturation
SDG	Succinate dehydrogenase
Cu,Zn – SOD	Cu,Zn-superoxide dismutase
V_E	Minute ventilation

[AU1] T.V. Serebrovskaya (✉) • A.N. Bakunovsky •
[AU2] K.V. Nesvitailova • I.N. Mankovska
Department of Hypoxia,
Bogomoletz Institute of Physiology,
National Academy of Sciences of Ukraine,
Kiev, Ukraine

11.1 Introduction

All body cells and tissues are able to alter their functions according to changes in actual blood oxygen content. Oxygen, as two-faced Janus, is necessary for life, but this very aggressive molecule has to get into an organism in strictly dosed quantity. Intermittent hypoxia (IH) is the most frequent form

L. Xi, T.V. Serebrovskaya (eds.), *Intermittent Hypoxia and Human Diseases*,
DOI 10.1007/978-1-4471-2906-6_11, © Springer-Verlag London 2012

of hypoxia, occurring in the developing mammals. It has been widely accepted that for the majority of a population, recurrent episodes of hypoxia are more often encountered during lifetime than sustained hypoxia. During the last decades, the IH has been investigated as a procedure with notable preventative, curative, and rehabilitative potential. It has been referred as an effective stimulus evoking various respiratory, cardiovascular, metabolic, and cellular responses.

Asthma is a global health problem affecting around 300 million individuals of all ages, ethnic groups, and countries. It is a chronic inflammatory disorder of the airways characterized by an obstruction of airflow, which may be completely or partially reversed with or without specific therapy [11]. Airflow obstruction is the main criterion of distinction between bronchial asthma (BA) and chronic obstructive pulmonary diseases (COPD) when airflow limitation is irreversible [26]. Moreover, bronchial asthma is associated with subepithelial fibroblast activation, myofibroblast hyperplasia, and hypoxia [81].

The prevalence of asthma among adults has been increasing over the last 20 years in three times. But asthma in childhood is much more serious problem for today. It is the most frequent cause of children's disability (about 90% of total number of children with disability because of COPD). According to the recent health statistics for US children [9], 14% of children aged 3–17 had ever been diagnosed with asthma. BA affects at least 12% of Canadian children, whereas in Germany, more than 10% of children suffer from this chronic disorder, which ranged 8–12% in Russia. Among them, about 20% falls in severe and moderately severe bronchial asthma and about 60% in mild forms. Severe bronchial asthma is the reason of considerable limitation of vital functions and drop in social activity of sick children, i.e., decline of their quality of life. Regular absence from classes and limitation of social and physical activity negatively influence the children's physical and intellectual growth and development.

In spite of considerable progress in understanding of BA essence and pharmaceutical success, statistical data indicate an increase of morbidity and death rate from this illness. Current drug therapy does not often achieve the target because of mass distribution of allergic reactions and common decline of body resistance to negative factors. This situation requires the development of new nonpharmacological methods for prophylaxis, medical treatment, and rehabilitation of BA. In this respect, intermittent hypoxia training/treatment (IHT) has emerged as a procedure revealing its notable preventative, curative, and rehabilitative potential. The majority of clinical investigations devoted to the use of IHT for disease treatment have been conducted by clinicians and researches from the prominent Ukrainian and Russian academic centers, who presented mostly positive clinical effects. Several thousand patients were treated during more than 30 years in different clinics.

11.2 Historical Sketch

People noticed healing properties of mountain air since olden times. Hippocrates recommended people with sick lungs and after serious illness to go to mountains for some period. Marco Polo, the famous Venetian traveler of thirteenth to fourteenth century, traveling through Asia, marked that dales men suffering from different ailments being lodged in the mountains to convalesce for a few days. There was a legend from Carpathian Mountains (Ukraine) that in an ancient village, children who suffered from asthmatic bronchitis were ranged on foot during 7 days successively on a high sacred mountain, where they were submitted to the influence of special ceremonies and drank high-altitude herbal tea. The children had recovered. One of the folk medicine recipes for patients with pant was: "When you feel the approach of asthmatic fit, close that nostril through which it is easier to breath at this moment for 15 minutes."

One of the first applications of "artificial mountain air" (i.e., hypoxic gas mixture) was carried out in Kiev Institute of Tuberculosis and Thoracic Surgery (Ukraine) in 1969 during the preparation of a patient for lung resection [5]. Numerous publications concerning the use of IHT for treatment of BA in children and adults have appeared in the Soviet Union and the CIS in the 1990s [1, 5, 18, 20, 21, 46, 54, 62, 69, 79]; ~~Ragozin et al. (2000)~~. More detailed historical review of the papers devoted to use of IHT for treatment of BA and COPD can be found in Chap. 9 by Mikhail Levashov.

11.3 Proposed Mechanisms

The detailed mechanisms of IH impact on human organism are under intensive investigation today at different levels – from molecular to systemic physiology. One of the main players is hypoxia-inducible factor (HIF), which initiates a gene transcription program of adaptation. It triggers a complex signaling cascade and thereby activates the expression of a variety of genes linked to such processes as angiogenesis, glycolysis, extracellular matrix remodelling, differentiation, and apoptosis [27]. Many studies in cultured cells suggest that IHT is more potent in activating HIF-1 than sustained hypoxia [12, 17, 57, 65].

Recently, Vogtel and Michels [80] denote the following basic mechanisms of beneficial effects of IHT on patients with BA: (1) HIF-1α induces the expression of erythropoietin (EPO), a glycoprotein hormone that controls erythropoiesis, plays an important role in the brain's response to neuronal injury and is also involved in the wound healing process; (2) HIF-1α provokes expression of the adaptive gene product VEGF, potent mediator of angiogenesis which produces multiple effects in lung development and physiology. Via the target

of VEGF pathway – cytokine IL-4, proangiogenic effects in the lung exist under hypoxic conditions; (3) nitric oxide synthase (NOS) and heme oxygenase (HO) are two HIF-1 target genes, both triggering vasodilatation; (4) glucose uptake (glucose transporters) and glycolysis (glycolytic enzymes) are upregulated by HIF-1; (5) various HIFs influence tyrosine hydroxylase, the rate-limiting enzyme for the biosynthesis of dopamine; and (6) HIF transcription factors regulate iron metabolism. Iron is an essential cofactor for oxygen-binding proteins. The links between the cited functions and oxygen homoeostasis show that additional experimental studies are needed to determine the impact of various HIFs upon therapeutic effects of IHT on BA patients.

Numerous studies collectively show that IH (1) increases exercise tolerance, hypoxic ventilatory response, hematocrit, and blood hemoglobin content; (2) stimulates endothelial nitric oxide (NO) production provoking vasodilation, opening of reserve capillaries, and preventing Ca^{2+} overload; (3) stimulates angiogenic growth factor synthesis by endotheliocytes and monocytes; (4) augments the activity of parasympathetic nervous system; (5) enhances antioxidant defense system and increases the resistance of Na^{+}-K^{+} ATPase to oxidative stress; (6) induces changes within mitochondria that increase the O_2 utilization efficiency of ATP production; and (7) mobilizes hematopoietic progenitors and augments cellular and humoral elements of innate immunity, etc. These data served as the basis for IHT in treatment of various diseases including BA.

As previously summarized [38, 69, 75, 76], other basic mechanisms underlying the beneficial effects of IHT were elaborated mainly in three areas: regulation of respiration, free radical production, and mitochondrial respiration. Findings showed that IHT induces increased ventilatory sensitivity to hypoxia and other hypoxia-related physiological changes [32, 72]. A great deal of evidence indicates that the respiratory control system is "plastic," which means that acute hypoxia can trigger a long-term augmentation of respiratory motor output [2, 47]. Following IHT, cellular membranes become more stable and improvement of O_2 transport in tissues is evident. IHT also induces changes in mitochondria, involving NAD-dependent metabolism, which in turn increases the efficiency of oxygen utilization in ATP production [41, 43, 49]. These effects are partly mediated by NO-dependent reactions [40, 51, 52]; Kurhalyuk et al. (2001), which are especially important for BA pathogenesis because exhaled NO is related to actual levels of airway inflammation in asthmatic patients [29, 82]. There are pieces of evidence that IHT may actually decrease the pronouncement of tissue hypoxia and intracellular acidosis under acute hypoxic exposure, improve O_2 transport in tissues, increase oxidative metabolism enzyme synthesis and ion-transport systems in cell membranes, and rearrange the cell membrane phospholipid composition. IHT also seems to increase tissue capillary growth. IHT also mobilizes hematopoietic progenitors and augments cellular and humoral elements of innate immunity [74].

The influence of IHT on free radical processes seems of key significance, as these processes are implicated in the pathogenesis of BA. Alveolar macrophages, blood neutrophils, and eosinophils from asthmatic patients have been shown to release more oxygen radicals than healthy subjects do. The mitochondrial damage in asthmatic lung due to reactive oxygen species (ROS) was also described in mice [36]. ROS induce airway hyperreactivity, destruction of lung epithelial cells, mucus hypersecretion, platelet-activating factor synthesis, and other reactions typical for BA in humans and animals [15, 58, 64]. These unwanted changes are often caused by tissue hypoxia and consequent reduction of electron transfer in the respiratory chain, an increase of functional activity of inflammatory cells, and impaired antioxidant defense system. The cyclic hypoxia-reoxygenation episodes in IH also generate ROS. Although high concentrations of these substances are cytotoxic, at physiological concentrations, ROS function as signaling molecules to elicit gene expression and synthesis of cytoprotective proteins. In this manner, ROS may have mediated the induction of cardioprotection [48]. In addition, IHT acts positively on an organism by eliminating tissue hypoxia, normalizing the number and phagocytic activity of white blood cells, and enhancing antioxidant enzymes activity [66]. Interestingly, if the hypoxic periods are much briefer than normoxia, and if this exposure sequence is repeated over a number of days, the antioxidant defenses could be enhanced much more effectively than under sustained hypoxia [50, 53, 72]. Taken together, these data serve as the prerequisite to the use of IHT for treating and correcting various diseases during which the ROS outbreaks are anticipated, in particular, BA.

11.4 Clinical Evidence

All above-mentioned mechanisms may explain positive clinical effects of IHT on BA patients. Many studies showed significant decline in breath shortness and feelings of chest congestion. The cough was diminished or disappeared, and the amount of sputum was reduced and passed more easily. The attacks of asphyxia disappeared or became more occasional. Rebalance of early autonomic dysfunction was also observed [5, 10, 18, 30, 39, 54, 62]. IHT positively affected the psychoemotional state of patients. Most evident positive results were obtained in children (from 4 years) [4, 21, 69, 79].

Anokhin and coauthors [1] performed 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 4–14 years who suffered from BA. The results were

compared with the sham group. A positive effect was seen in 85% of subjects in the group with IH and in 25% of the sham group. In children with mild BA, complete discontinuance of attacks was observed. In patients with middle-severe forms, a significant improvement was registered, namely, the attacks became rare and stopped without medicines. In patients with the severe form, small improvement was noted. As Ehrenburg and Kordykinskaya [20] reported, the lowest efficacy was noted in children with an infection-dependent form of BA. Half of the patients with a severe steroid-dependent form of BA displayed a worsening of the clinical course of the disease. A positive clinical effect in patients with mild and middle atopic BA lasted for an average of 4 months posthypoxic therapy. Hypoxic treatment in children with BA of mild and middle severity can be performed only in between, and not during, the arrest periods. In the hormone-dependent form of BA, IHT was unsatisfactory [30]. These observations have been subsequently confirmed [14, 59, 69].

On the average, a good effect of IHT was noted in 85–95% of BA patients, satisfactory effect in 40–50%, and no effect in only 4–8% of patients who had mostly the hormone-dependent form of BA. The best effect was achieved for atopic form of BA and less pronounced effect was found in the infection-allergic and mixed forms of BA. About 40% of adult patients decreased the dose of constantly taken drugs and almost 90% of children were able to quit the drug treatment. Improvement of the clinical state was retained for 1 year in 40–50% of patients, for 6 months in 20–30%, and for 3–4 months in 15–20%.

Individual differences in respiratory reactions to hypoxia, ranging from ventilatory hypersensitivity to complete absence of reaction, have been described with special approaches suggested for individual dosage of IHT regimen [6, 7, 20, 37, 46, 68, 78].

11.5 Adverse Effects

Meanwhile, a reduction in the partial pressure of inspired oxygen may be a potential risk factor for severe impairment of pulmonary function and even sudden death. It has been postulated that IH-induced oxidative stress may contribute to several chronic diseases associated with obstructive sleep apnea syndrome (OSAS), which has increased predisposition for metabolic dysfunction by impairing insulin sensitivity, glucose effectiveness, etc. [42]. A large number of clinical studies, cell culture and animal models utilizing IH, have demonstrated the central role of oxidative stress in OSAS. Besides, there are some evidences concerning the adverse effect of chronic or intermittent hypoxia on cognition in childhood, more specifically on development, behavior, and academic achievement [3]. Failure to adapt to hypoxia may be a common pathophysiological mediator for a number of other conditions of childhood with cognitive deficit [34]. This should be taken into account in any situation that may expose children to hypoxia. Ability of adaptation to intermittent or sustained hypoxia may determine the type of neurological complications for which patients are at risk when exposed to acute hypoxia [34]. For example, persistently low levels of tissue oxygen in anemia may lead to neuroprotective erythropoietin production, but release of the younger, more adhesive red cells and any associated hemolysis [63] may adversely affect endothelial function [24], eventually leading to irreversible vascular disease. Because the adverse effects have been noted at even mild levels of oxygen desaturation, future research should include precisely defined data on the safety of exposure to all levels of hypoxia.

During the past few years, there are debates about the ethical evaluation of diagnostic and therapeutic use of hypoxia in humans. Although the papers devoted to this problem obtained the approval from the Human Investigation Ethics Committees, there is a lack of evidences about strong evaluation of risk/benefit ratio. The analysis of such ratio and the creation of standardized guidelines for IHT application are complicated due to the differences in criteria for individual dosage and utilized methods. As Vogtel and Michels [80] pointed out, future research examining the potential risks and benefits of IHT could pave the way for the development of new therapeutic approaches for patients suffering from BA. Thereupon, a new mathematical method – "Method of Expert Assessing Scales" (MEAS) – was proposed for estimation of IH application safety in human practice [77]. MEAS expands capabilities of traditional probabilistic safety assessment and allows determining the danger degree at the earliest stage of its development and fulfilling well-timed actions for risk 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, and (d) joint influence of factors on basic events probability. This methodology provides the forming of a system of indexes characterizing the risk of IHT negative effects and determination of legitimate value scopes for basic physiological parameters; creation of a classification system, allowing to set individual cardiorespiratory reactivity; and development of proper IHT regimen for every class of reactivity in humans.

In brief, contraindications to IHT application include acute infectious diseases, exacerbation of chronic inflammatory processes, fever, acute somatic diseases, respiratory insufficiency of II–III stage, pulmonary tuberculosis in active phase, etc. [6, 7, 37, 46, 62, 79].

11.6 Latest Experience in IHT Implementation

After all, we would like to share with readers our latest experience in IHT implementation for treatment of children with BA. Two groups of children aged 9–13 years participated in

the study: experimental group (Gr. I) – 16 children (13 boys and 3 girls) who underwent IHT alone with traditional medical treatment – and control group (Gr. II) – 8 children (4 boys and 4 girls) who got received the same medical treatment, but not IHT. All patients had a similar diagnosis: persistent atopic bronchial asthma, moderate form of disease without the signs of respiratory insufficiency.

Before and next day after the 2-week IHT, individual cardiorespiratory reactions to hypoxia were investigated in the morning, 2 h after a light breakfast. With the subject seated, normobaric hypoxia was administered with device "Hypoxotron – Complex," a modified closed spirometer with CO_2 absorption [73]. Initial inspired gas contained atmospheric O_2 (20.9%). The inspired O_2 fell to 12% during the first 60–90 s of rebreathing, and then O_2 was added gradually to the Hypoxotron to maintain inspired O_2 at 12% during the remaining 3.5–4 min. The final arterial O_2 saturation (SaO_2) during first investigation was typically 89–92%. All children easily tolerated the hypoxia periods without any untoward effects. Standard spirometry was performed before and after hypoxic test in accordance with the American Thoracic Society criteria. Between first and second examinations, IHT was conducted bedside using portable device "Hypoxotron-Simplex" [67] during 14 consecutive mornings, after a light breakfast. Every session consisted of four 5–7 min periods, with 5 min interval periods of room air inspiration.

As a result of IHT, a significant decline in breath shortness and feelings of chest congestion were noted in patients of Gr. I. The cough was diminished or disappeared, and the amount of sputum was reduced and passed more easily. The attacks of asphyxia disappeared or became less frequent. Children liked the procedure, and in cases of relapse, they wanted another treatment with IHT. We did not find significant changes in airway conductance before (I) and after (II) IHT (Table 11.1). Significant differences in hypoxic ventilatory sensitivity were found as a result of hypoxic training. Gr. I (in contrast to Gr. II) showed increased hypoxic ventilatory response, which was analyzed by relative minute ventilation (V_E) with respect to $P_{ET}O_2$ and estimated using piecewise linear approximation technique [72]: slope I (S_I) increased by 104% ($p<0.01$); slope II (S_{II}) by 79% ($p<0.05$), maximal lung ventilation by 24% ($p<0.05$; Fig. 11.1). These data suggest that adaptation to IH caused considerable augmentation of ventilatory response to hypoxic stimuli. Several mechanisms are involved in this process, embracing events happening on both central and peripheral levels [31, 71]. At the same time, reaction of heart rate (HR) to increasing hypoxia became less pronounced (Fig. 11.2) and SaO_2 fell less at 12% O_2 (Fig. 11.3). Thus, after IHT, cardiovascular system became more effective to support oxygen supply during hypoxia.

Table 11.1 Lung function parameters before and after IHT

	Before IHT	After IHT
FVC pred (%)	85.51 ± 6.58	91.47 ± 6.97
FEV_1 pred (%)	59.7 ± 4.7	64.6 ± 4.5
FEV1/FVC (%)	67.58 ± 3.47	64.18 ± 2.12
PEF pred (%)	61.32 ± 5.25	60.94 ± 5.34

Data are Mean ± SD

Abbreviations: *FVC* forced vital capacity, FEV_1 forced expiratory volume in 1 s, *PEF* peak expiratory flow

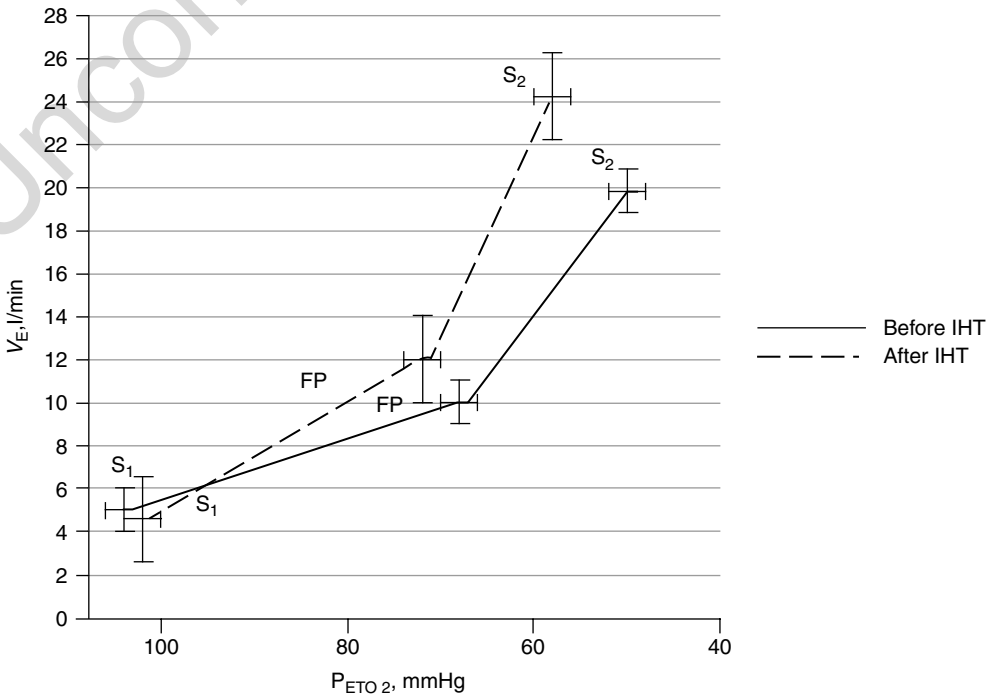

Fig. 11.1 Data plot of hypoxic ventilatory response before and after IHT (Gr. I, Mean ± SD). S_1 slope during the first phase of sharply increasing ventilation, S_2 slope during the second phase of sharply increasing ventilation, *FP* fracture point co-ordinate

[AU5]

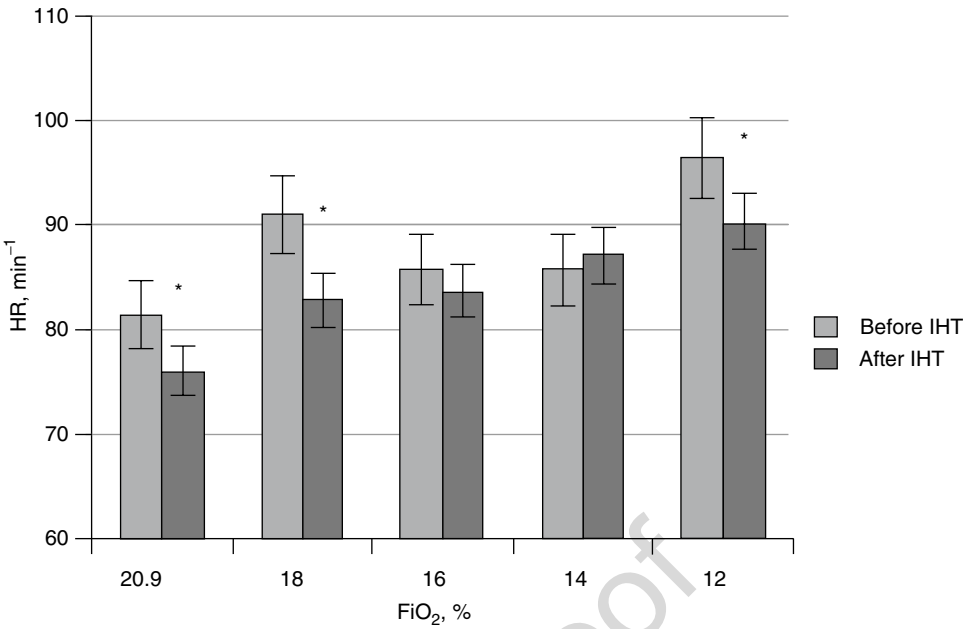

Fig. 11.2 Heart rate during increasing hypoxia test before and after IHT (Gr. I, Mean ± SD)

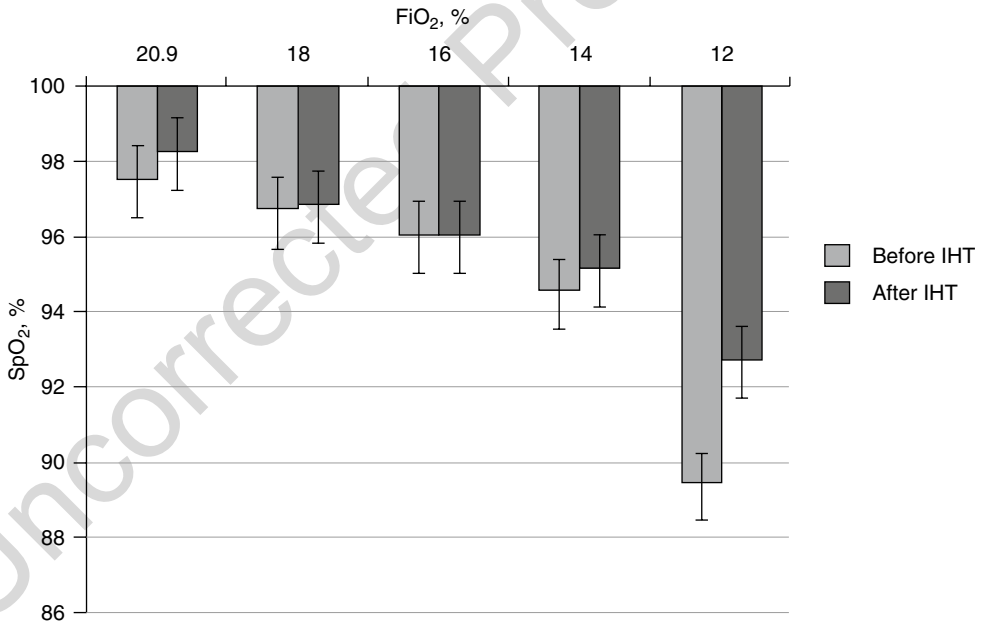

Fig. 11.3 SaO_2 during incremental hypoxia test before and after IHT (Gr. I, Mean ± SD)

Furthermore, IHT influenced mitochondrial enzymes activity of immune cells in asthmatic children, particularly succinate dehydrogenase (SDG) and alpha-glycerophosphate dehydrogenase (GPDG). These enzymes reflect cell energy potential and its reserve mechanisms. Investigation of mitochondrial respiratory chain enzymes is an important step for establishing a diagnosis of mitochondrial dysfunction – one of pathogenetic links of the BA development. Low activity levels of these enzymes suggest cellular metabolic dysfunction that is usually associated with unfavorable clinical signs [22, 33, 36, 55, 61]. Kinetic parameters for mitochondrial enzymes in the substrate region of the respiratory chain correlate with hypoxic resistance [44].

In this investigation, the measurements of SDG and GPDG activities in peripheral lymphocytes were carried out on blood slides cytophotometrically. Both SDG and GPDG activities increased significantly under IHT (by 78% and 42%, respectively, Fig. 11.4). Similar results were obtained in the previous animal investigations [41]. A strong correlation between the individual hypoxic sensitivity and mitochondrial enzymes activities was found by linear regression analysis, mostly expressed according to GPDG: in children

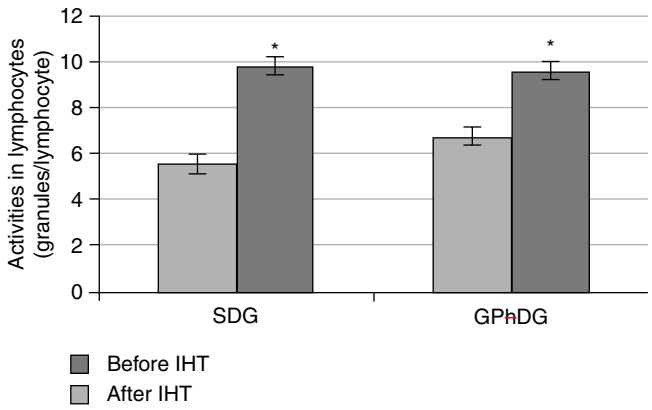

Fig. 11.4 SDG and GPDG activities in lymphocytes under IHT (Gr. I, Mean ± SD)

with decreased hypoxic ventilatory response (HVR), heightened initial SDG and GPDG activities was observed (for GPDG, $r=-0.64$, $p<0.05$; for SDG, $r=-0.36$, $p<0.1$) and greater increase under IHT (for GPDG, $r=-0.58$, $p<0.05$; for SDG, $r=-0.41$, $p<0.1$). This reaction was accompanied by more expressed positive clinical effect in children with low hypoxic sensitivity. Reciprocal relationships between hypoxic sensitiveness and enzymatic activity of dehydrogenases indicate an important role of the mitochondrial enzymes in the compensatory reactions of an organism to hypoxia. In addition to their crucial role in energy homeostasis, mitochondria are the main site of ROS generation. When moderately produced, they function as physiological signaling molecules. Thus, mitochondrial ROS trigger hypoxia-dependent gene expression.

On the other hand, the development of inflammatory process in lungs is usually associated with activation of free radical oxidation and decline of antioxidant enzymes activity and intensification of glycolysis in both humans and animals [14, 16, 36]. To elucidate the role of antioxidant enzymes in adaptation to IHT, another investigation was carried out using the same protocol [56]. The effect of 10-day IHT on the mRNA expression and protein content of antioxidant enzymes – Cu,Zn-superoxide dismutase (Cu,Zn-SOD), catalase (CAT), and glutathione-S-transferase (GST) in blood leukocytes of asthmatic children was studied. Level of protein expression of antioxidant enzymes was determined by Western blot analysis [28]. We found that Cu,Zn-SOD protein content did not change significantly, but Cu,Zn-SOD mRNA expression increased by 32.5% ($p<0.05$). Conversely, GST protein synthesis increased by 90% ($p<0.05$), but its mRNA gene expression was invariable. CAT protein content and its mRNA gene expression both increased by 37% and 13%, respectively ($p<0.05$). A previous investigation in animals have also shown a negative correlation between Mn-SOD mRNA expression and its protein content in mitochondria from hypoxic myocardium [25]. It is possible that during hypoxia, the strengthening of translation processes could take place with accelerated protein synthesis without evident activation of mRNA expression at this stage. Nevertheless, analysis of the mRNA expression dynamics may provide additional information of the antioxidant enzymes as the markers of the IHT effectiveness in children with BA.

Conclusion

IHT represents a promising approach in prevention and treatment of BA 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. Further studies on individual approaches to dosage selection must be performed. The absence of negative side effects, typically observed during drug therapy, and the stimulation of an organism's general resistance to pathological factors of BA would make IHT a beneficial treatment with a bright future.

References

1. Anokhin MI, Geppe NA, Dairova RA. Effects of hypoxic stimulation observed in the animal experiments and in children with bronchial asthma. Fiziol Zh. 1992;38:33–9 [In Russian].
2. Baker TL, Fuller DD, Zabka AGGS, et al. Respiratory plasticity: differential actions of continuous and episodic hypoxia and hypercapnia. Respir Physiol. 2001;129:25–35.
3. Bass JL, Corwin M, Gozal D, et al. The effect of chronic or intermittent hypoxia on cognition in childhood: a review of the evidence. Pediatrics. 2004;114:805–16.
4. Belikova VV. Correlation between clinical and cytochemical changes in bronchial asthma in children. Pediatriia. 1976;11:30–3 [In Russian].
5. Berezovskiĭ VA, Levashov MI. Physiological premises and mechanisms of normalizing effect of normobaric hypoxia and inhalation therapy. Fiziol Zh. 1992;38:3–12 [In Russian].
6. Berezovskii VA, Levashov MI. Introduction in orotherapy. Kiev: Academy of Hypoxia Problems of Russian Federation; 2000. p. 75 [In Russian].
7. Berezovskii VA, Levashov MI. The build-up of human reserve potential by exposure to intermittent normobaric hypoxia. Aviakosm Ekolog Med. 2000;34:39–43 [In Russian].
8. Berezovskii VA, Serebrovskaia TV, Lipskii PI. Respiratory function in twins under different gas mixtures. Fiziol Zh. 1981;27:20–5 [In Russian].
9. Bloom B, Cohen RA, Freeman G. Summary health statistics for U.S. children: National Health Interview Survey 2009. Vital Health Stat 10. 2010;1–82.
10. Borukaeva IK. Intermittent hypoxic training in the sanatorium and spa treatment for patients with chronic obstructive pulmonary disease. Vopr Kurortol Fizioter Lech Fiz Kult. 2007;5:21–4 [In Russian].
11. Bousquet J, Mantzouranis E, Cruz AA. Uniform definition of asthma severity, control, and exacerbations: document presented for the World Health Organization Consultation on Severe Asthma. J Allergy Clin Immunol. 2010;126:926–38.

12. Brzecka A. Brain preconditioning and obstructive sleep apnea syndrome. Acta Neurobiol Exp (Wars). 2005;65:213–20.
13. Chizhov AI. Physiologic bases of the method to increase nonspecific resistance of the organism by adaptation to intermittent normobaric hypoxia. Fiziol Zh. 1992;38:13–7 [In Russian].
14. Chizhov AI, Bludov AA. Efficiency of intermittent and resonance intermittent normobaric hypoxia therapy in patients with infection-dependent bronchial asthma. Vestn Ross Akad Med Nauk. 2000;9:48–50 [In Russian].
15. Damon M, Cluzel M, Chanez P, et al. Phagocytosis induction of chemiluminescence and chemoattractant increased superoxide anion release from activated human alveolar macrophages in asthma. J Biolumin Chemilumin. 1989;4:279–86.
16. Daniliak IG, Kogan AK, Bolevich S. The generation of active forms of oxygen by the blood leukocytes, lipid peroxidation and antiperoxide protection in bronchial asthma patients. Ter Arkh. 1992;64:54–7 [In Russian].
17. Dewhirst MW. Intermittent hypoxia furthers the rationale for hypoxia-inducible factor-1 targeting. Cancer Res. 2007;67:854–5.
18. Donenko YI. Comparison of intermittent normobaric hypoxic therapy and hypobaric therapy in treatment of chronic nonspecific lung diseases. In: Intermittent hypoxic training – effectiveness and mechanisms of action. Kiev: Institute of Physical Culture; 1992. p. 65–8 [In Russian].
19. Eckes L. Altitude adaptation. Part III. Altitude acclimatization as a problem of human biology. Gegenbaurs Morphol Jahrb. 1976;122:535–69 [In German].
20. Ehrenburg IV, Kordykinskaya II. Effectiveness of the use of intermittent normobaric hypoxia in treatment of chronic obstructive lung diseases. In: Intemittent hypoxic training – effectiveness, mechanisms of action. Kiev: Institute of Physical Culture; 1992. p. 96–8 [In Russian].
21. Fesenko ME, Lisyana TO. Approach to employment of hypoxic stimulation for treatment of lingering and relapsing bronchitis in children of early age. Fiziol Zh. 1992;38:31–3 [In Russian].
22. Fursova ZK, Balika IuD, Abubakirova AM. Dynamics of the activity of redox enzymes in peripheral blood lymphocytes of the newborn with a history of chronic intrauterine hypoxia. Akush Ginekol (Mosk). 1995;4:29–31 [In Russian].
23. Gerasimov SV. Lipid peroxidation and antioxidant defense in patients with bronchial asthma. Ukr Med Chasopys. 2000;1:86–94 [In Ukrainian].
24. Gladwin MT, Kato GJ. Cardiopulmonary complications of sickle cell disease: role of nitric oxide and haemolytic anemia. Hematology Am Soc Hematol Educ Program. 2005;51–7.
25. Gonchar OO, Steshenko MM, Mankovska IM, et al. Correction of mitochondrial dysfunction in rat myocardium under hypoxia. Zagalna Patoligia ta Patologichna Phyziologia. 2010;3:44–8 [In Ukrainian].
26. Gordon E, Lazarus SC. Management of chronic obstructive pulmonary disease: moving beyond the asthma algorithm. J Allergy Clin Immunol. 2009;124:873–80.
27. Gordan JD, Simon MC. Hypoxia-inducible factors: central regulators of the tumor phenotype. Curr Opin Genet Dev. 2007;17:71–7.
28. Hanta I, Kocabas A, Canacankatan N, et al. Oxidant–antioxidant balance in patients with COPD. Lung. 2006;184:51–5.
29. Jones SL, Herbison P, Cowan JO, et al. Exhaled NO and assessment of anti-inflammatory effects of inhaled steroid: dose–response relationship. Eur Respir J. 2002;20:601–8.
30. Karash YM, Strelkov RB, Chizhov AY. Normobaric hypoxia in treatment, prophylaxis and rehabilitation. Moscow: Meditsina; 1988 [In Russian].
31. Katayama K. Effect of intermittent hypoxia on hypoxic ventilatory response. In: Xi L, Serebrovskaya TV, editors. Intermittent hypoxia: from molecular mechanisms to clinical applications. New York: Nova; 2009. p. 245–59.
32. Katayama K, Sato Y, Morotome Y, et al. Intermittent hypoxia increases ventilation and SaO_2 during hypoxic exercise and hypoxic chemosensitivity. J Appl Physiol. 2001;90:1431–40.
33. Kiernan MC, Bullpitt P, Chan JH. Mitochondrial dysfunction and rod-like lesions associated with administration of beta2 adrenoceptor agonist formoterol. Neuromuscul Disord. 2004;14:375–7.
34. Kirkham FJ, Datta AK. Hypoxic adaptation during development: relation to pattern of neurological presentation and cognitive disability. Dev Sci. 2006;9:411–27.
35. Kolchinskaya AZ, Hatsukov BH, Zakusilo MP. Oxygen insufficiency: destructive and constructive actions. Nalchik: Kabardino-Balkaria Scientific Center; 1999 [In Russian].
36. Konga DB, Kim Y, Hong SC, et al. Oxidative stress and antioxidant defenses in asthmatic murine model exposed to printer emissions and environmental tobacco smoke. J Environ Pathol Toxicol Oncol. 2009;28:325–40.
37. Korkushko OV, Serebrovskaya TV, Shatilo VB, et al. Selection of the optimal modes for intermittent hypoxia training in medical practice and sports medicine. Methodical recommendations. Kiev; 2010 [In Ukrainian].
38. Kowalski J, Gutkowski P, Serebrovskaya T. Beneficial either detrimental consequences for respiration and hemodynamics. Vestn Hyg Epidemiol. 2007;11:9–13.
39. Kulberg AY. Regulation of the immune response. Moscow; 1997. p. 148–57 [In Russian].
40. Kurhalyuk NM, Serebrovskaya TV. Intermittent hypoxic training influences on antioxidant enzymes activity, processes of lipid peroxidation under acute hypoxia and nitric oxide donor treatment. Med Chem. 2001;3:69–71.
41. Kurhalyuk NM, Serebrovskaya TV, Kolesnikova EE, et al. Exogenous L-arginine modulates the effects of acute and intermittent hypoxia on liver mitochondrial and microsomal oxidation. Fiziol Zh. 2002;48:67–73.
42. Louis M, Punjabi NM. Effects of acute intermittent hypoxia on glucose metabolism in awake healthy volunteers. J Appl Physiol. 2009;106:1538–44.
43. Lukyanova LD. Molecular, metabolic and functional mechanisms of individual resistance to hypoxia. In: Sharma BK, Takeda N, Ganguly NK, et al., editors. Adaptation biology and medicine. New Delhi: Narosa Publishing House; 1997. p. 236–50.
44. Lukyanova LD, Dudchenko AM, Tsybina TA, et al. Effect of intermittent normobaric hypoxia on kinetic properties of mitochondrial enzymes. Bull Exp Biol Med. 2007;144:795–801.
45. Lukyanova LD, Germanova EL, Kopaladze RA. Development of resistance of an organism under various conditions of hypoxic preconditioning: role of the hypoxic period and reoxygenation. Bull Exp Biol Med. 2009;147:400–4.
46. Lysenko GI, Serebrovskaya TV, Karaban IN, et al. Use of gradually increasing normobaric hypoxia in medical practice. Methodical recommendations. Kiev: Ukrainian Ministry of Health Care; 1998 [In Russian].
47. Mahamed S, Mitchell G. Is there a link between intermittent hypoxia-induced respiratory plasticity and obstructive sleep apnoea? Exp Physiol. 2007;92:27–37.
48. Mallet RT, Ryou M-G, Manukhina EB, et al. β-Adrenergic signaling and ROS: pivotal roles in intermittent, normobaric hypoxia-induced cardioprotection. In: Xi L, Serebrovskaya TV, editors. Intermittent hypoxia: from molecular mechanisms to clinical applications. New York: Nova; 2009. p. 151–74.
49. Man'kovskaia IN, Vavilova GL, Kharlamova ON, et al. Activity of the cell membrane marker enzymes in rats under adaptation to hypoxia. Ukr Biochem J. 1997;69:79–87 [In Russian].
50. Mankovskaya IN. Peculiarities of lipid peroxidation realization mechanisms in intermittent hypoxic hypoxia. Hypoxia Med J. 1993;4:8–11 [In Russian].

51. Manukhina EB, Downey HF, Mallet RT. Role of nitric oxide in cardiovascular adaptation to intermittent hypoxia. Exp Biol Med. 2006;231:343–65.
52. Manukhina EB, Mashina SY, Smirin BV, et al. Role of nitric oxide in adaptation to hypoxia and adaptive defense. Physiol Res. 2000;49:89–97.
53. Meerson FZ. Adaptation to intermittent hypoxia: mechanisms of protective effects. Hypoxia Med J. 1993;3:2–8 [In Russian].
54. Meerson FZ, Frolov BA, Volianik MN, et al. The effect of adaptation to the periodic action of hypoxia on the indices of the immunity system and on the course of allergic diseases. Patol Fiziol Eksp Ter. 1990;3:16–21 [In Russian].
55. Moroz LA, Sukhorukov VV, Kravchenko LF, et al. Significance of a complex of laboratory methods of study in the differential diagnosis of various forms of bronchial asthma. Med Tr Prom Ekol. 1994;2:32–4 [In Russian].
56. Nesvitalova KV, Gonchar OA, Drevitskaya TI, et al. Changes in mRNA and protein expression of antioxidant enzymes as markers of the interval hypoxic training effectiveness in children with bronchial asthma. Fiziol Zh. 2011 ~~(in press)~~ [In Ukrainian].
57. Prabhakar NR, Fields RD, Baker T, et al. Intermittent hypoxia: cell to system. Am J Physiol. 2001;281:L524–8.
58. Prasad K, Gupta JB. Relaxant effect of oxygen free radicals on rabbit tracheal smooth muscle. Pulm Pharmacol Ther. 2002;15:375–84.
59. Ragozin ON. Effectiveness of intermittent normobaric hypoxia in patients with bronchial asthma in various modes of chronotherapy. Vopr Kurortol Fizioter Lech Fiz Kult. 2002;2:8–10 [In Russian].
60. Ragozin ON, Balykin MV, Charikova EI, et al. The analysis of rhythm spectrum of respiratory and cardiovascular parameters in bronchial asthma patients under normobaric hypoxitherapy. Fiziol Zh. 2001;47:36–9 [In Russian].
61. Razumovskiĭ AE, Komissarova IA, Shatalov NN, et al. Effect of atmospheric pressure on leukocyte enzyme activity in bronchial asthma. Sov Med. 1980;12:19–22 [In Russian].
62. Redzhebova OK, Chizhov AI. Results of utilization of intermittent normobaric hypoxia in patients with bronchial asthma and chronic obstructive bronchitis. Fiziol Zh. 1992;38:39–42 [In Russian].
63. Rice L, Alfrey CP. The negative regulation of red cell mass by neocytolysis: physiologic and pathophysiologic manifestations. Cell Physiol Biochem. 2005;15:245–50.
64. Safronova OS, Serebrovskaya TV, Hordiĭ SK. Pro- and antioxidant system during the adaptation to intermittent hypoxia in healthy subjects and patients with bronchial asthma. Exper Clin Physiol Biochem. 1999;4:61–6 [In Russian].
65. Semenza GL. HIF-1: mediator of physiological and pathophysiological responses to hypoxia. J Appl Physiol. 2000;88:1474–80.
66. Serebrovs'ka TV, Safronova OS, Hordiĭ SK. Free-radical processes under different conditions of body oxygen allowance. Fiziol Zh. 1999;45:92–103 [In Ukrainian].
67. Serebrovska TV, Lopata VA, Roy VV, et al. Device for breathing with hypoxic mixtures "Hypoxytron". 2009. Patent 44179, МПК A61M 16/00; Ukraine, 25 Sept 2009, bulletin № 18 [In Ukrainian].
68. Serebrovskaia TV. Hereditary defect of sensitivity to hypoxia in normal sensitivity to hypercapnia. Patol Fiziol Eksp Ter. 1982;4:80–3.
69. Serebrovskaia TV, Man'kovskaia IN, Lysenko GI, et al. A method for intermittent hypoxic exposures in the combined treatment of bronchial asthma patients. Lik Sprava. 1998;6:104–8 [In Ukrainian].
70. Serebrovskaia ZA, Serebrovskaia TV, Afonina GB. Chemiluminescence, blood lipid peroxidation and neutrophil activity during the hypoxic training of persons subjected to ionizing radiation exposure. Radiats Biol Radioecol. 1996;36:394–9.
71. 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 Alt Med Biol. 2002;3:205–21.
72. Serebrovskaya TV, Karaban IN, Kolesnikova EE, et al. Human hypoxic ventilatory response with blood dopamine content under intermittent hypoxic training. Can J Physiol Pharmacol. 1999;77:967–73.
73. Serebrovskaya TV, Lopata VA. Apparatus for breathing with hypoxic gaseous mixtures. 2010. Patent International Application to all countries of PCT # PCT/UA 2010/000071, 7 Oct 2010.
74. Serebrovskaya TV, Nikolsky IS, Nikolska VV, et al. Intermittent hypoxia mobilizes hematopoietic progenitors and augments cellular and humoral elements of innate immunity in adult men. High Alt Med Biol. 2011;12:243–52.
75. Serebrovskaya TV, Serebrovskaya ZA, Afonina G. Effect of intermittent hypoxic training on human respiration, free radical processes and immune system. In: Ueda G et al., editors. High altitude medicine. Matsumoto: Shinshu University Press; 1992. p. 77–82.
76. Serebrovskaya TV, Swanson RJ, Kolesnikova EE. Intermittent hypoxia: mechanisms of action and some applications to bronchial asthma treatment. J Physiol Pharmacol. 2003;54:35–41.
77. 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. 2009. Book of abstracts, Session II, abstract #25, New York, 12–14 Mar 2009.
78. Tsvetkova AM, Tkatchouk EN. "Hypoxia user" – the opportunity of individual programming of interval hypoxic training. In: Hypoxia, mechanisms, adaptation, correction. BEBIM, Moscow; 1999. p. 83–4 [In Russian].
79. Vinnitskaya RS, Davidov EG, Ctruchkov PV. Hypoxic and hypercapnic gas mixtures in complex treatment and rehabilitation of patients with chronic obstructive diseases. In: Intermittent hypoxic training, effectiveness, and mechanisms of action. Kiev: Institute of Physical Culture; 1992. p. 62–4 [In Russian].
80. Vogtel M, Michels A. Role of intermittent hypoxia in the treatment of bronchial asthma and chronic obstructive pulmonary disease. Curr Opin Allergy Clin Immunol. 2010;10:206–13.
81. Zhong H, Belardinelli L, Maa T, et al. Synergy between A2B adenosine receptors and hypoxia in activating human lung fibroblasts. Am J Respir Cell Mol Biol. 2005;32:2–8.
82. Zietkowski Z, Bodzenta-Lukaszyk A. Nitric oxide in bronchial asthma. Pol Merkur Lekarski. 2002;12:519–21 [In Polish].

[AQ9]

Author Queries

Chapter No.: 11 0001518546

Queries	Details Required	Author's Response
AU1	Please confirm the affiliation details for author Tatiana V. Serebrovskaya, Alexander N. Bakunovsky, Klaudia V. Nesvitailova, and Iryna N. Mankovska.	
AU2	Pleas confirm corresponding author and also provide the e–mail ID.	
AU3	Ragozin et al. (2000) and Kurhalyuk et al. (2001) are cited in text but not given in the reference list. Please check.	
AU4	Citation Berezovskii and Levashov (2000) has been changed to Refs. [6, 7], so please fix whether [6] or [7] here and also in the following occurrences.	
AU5	Please specify the significance of "asterisk" provided in the artwork of Figs. 11.2 and 11.4.	
AU6	Please provide citation for Refs. [8, 13, 19, 23, 35, 45, 60, 70].	
AU7	Please provide volume number for Refs. [9, 24].	
AU8	Please provide publisher name for Refs. [37, 39].	
AU9	Please provide complete details for Ref. [56].	