

Beneficial Effects of Intermittent Normobaric Hypoxic Training on Respiratory Function in Patients with Chronic Pulmonary Diseases

Mikhail I. Levashov

Abstract

In this chapter, we present the results of our studies regarding the INHT effects on respiratory functions in 103 high-risk chronic obstructive pulmonary disease (COPD) patients, 157 bronchial asthma (BA) patients, and 36 healthy individuals. Patients ranged in age from 21 to 59 years (women – 52.1%, men – 47.9%). INHT was carried out in “Orotron” chamber under such environmental parameters: PO_2 – 147–160 hPa, relative humidity – 60–70%, ambient temperature – 16–18°C, and content of light negative ions – up to 6,000/cm³. All patients received daily 90 min of INHT alone or INHT in combination with conventional therapy for 2–4 weeks. Total time of hypoxic gas mixture breathing for the whole INHT course ranged from 21 to 42 h. We performed pulmonary function tests in all patients before, during, and after INHT. Results of our studies indicated that INHT increased reserves of lung ventilation and restored the physiological level of alveolar ventilation in 78% of patients with COPD, optimized regional air distribution in lung, and decreased by 25–30% the lung ventilation unevenness. INHT reduced the bronchial resistivity by 31–37% in BA patients and changed the respiratory regulation in COPD patients and healthy individuals. It contributed to more complete restoration of the optimal structure of respiratory pattern. Further investigations will allow INHT to emerge as an important nonpharmacological therapy for care and rehabilitation of patients with pulmonary diseases.

Abbreviations

BA	Bronchial asthma
CIA	Central inspiratory activity
COPD	Chronic obstructive pulmonary diseases
f	Respiratory rate
ERV	Expiratory reserve volume
FEV_1	Volume at the end of the first second of forced expiration
FEF_{max}	Maximum instantaneous flow achieved during FVC maneuver

$FEF_{25\%}$	Average flow from the point were 25% of the FVC has been exhaled
$FEF_{50\%}$	Average flow from the point were 50% of the FVC has been exhaled
$FEF_{75\%}$	Average flow from the point were 75% of the FVC has been exhaled
FRC	Functional residual capacity
FVC	Forced vital capacity
G_{aw}	Airway conductance
INHT	Intermittent normobaric hypoxic training
IRV	Inspiratory reserve volume
MVV	Maximal voluntary ventilation
MVV/V_E	Ratio of respiratory reserve
PO_2	Partial pressure of oxygen
PI_{max}	Maximal inspiratory pressure
R_{aw}	Airway resistance
t_1	Inspiratory time of one respiratory cycle
t_E	Expiratory time of one respiratory cycle

M.I. Levashov
National Academy of Sciences of Ukraine,
A.A. Bogomoletz Institute of Physiology,
Kiev, Ukraine
e-mail: levashov@biph.kiev.ua

t_{tot}	Total duration of respiratory cycle
t_I/t_{tot}	Proportion of inspiration phase in total duration of respiratory cycle or “useful cycle” of breathing
t_E/t_I	Time respiratory quotient
V_A	Alveolar ventilation/min
VC	Vital capacity
V_E	Expired volume/min
V_T	Tidal volume
V_I/t_I	Mean rate of inspiratory flow of one breath
V_E/t_E	Mean rate of expiratory flow of one breath
$V_{I\text{max}}/t_I$	Maximum rate of inspiratory flow of one breath
$V_{E\text{max}}/t_E$	Maximum rate of expiratory flow of one breath

9.1 Historical Aspect of the Problem

Sanogenic and healing properties of mountain climate are known since ancient times. Alpine climate has been used for treating patients with pulmonary tuberculosis, chronic obstructive pulmonary diseases, and bronchial asthma for more than two centuries. Doctors recommended mountain climate for patients suffering from “bronchial catarrh with profuse expectoration” (Meyer-Arens 1867) and considered it the best remedy for “raw asthma” (Lombard 1885) [1]. However, intensive study of various aspects of mountain climate effects on healthy and sick people began only in the twentieth century. Mass survey of mountain populations in different countries showed that some diseases among natives are extremely rare and considerably milder than in plainsmen [2]. Academician NN Sirotinin and his collaborators and followers made a great contribution to study mountain climate sanogenic and healing properties in the former USSR [3]. They have developed a detailed method of stepwise acclimation to mountain climate and proved its effectiveness in patients with several diseases.

A lot of scientific information has been accumulated about various aspects of mountain climate treatment of patients with BA, COPD, and other pulmonary diseases not only in low and middle altitudes but also in high mountains [4–8]. It was found that cough, asthma attacks, and number of wheezing in lungs significantly decreased, especially in BA patients with the mild form of disease, from the first days of adaptation to altitude. Studies of respiratory and hemodynamic functions showed a decrease in bronchial obstruction, reduction of hypoxemia and myocardial hypoxia severity, diminution of pulmonary vascular spasm, increase in alveolar ventilation and circulating blood volume, etc. Significant changes in immune system have been demonstrated at high altitude, including reduction of the skin allergy tests, B- and T-helper cell activation, decrease of the total and site-specific immunoglobulin E antibodies, and other immunological

parameters. The positive effects of high-altitude treatment are most impressive in asthmatic children [9–11].

The well-defined therapeutic effect was obtained in COPD patients also [12, 13]. When these patients for some time remained at the middle altitudes, they experienced improvements in lung ventilation, respiratory tract aerodynamic properties, and ventilation-perfusion relationships in lungs. Gas exchange and pulmonary dust clearance were significantly better in patients with early-stage coal workers’ pneumoconiosis and COPD at altitude of 2,300 m above sea level. These changes sustained for up to 6 months after returning to plain [14]. Despite the fact that the sanogenic and healing effects of mountain climate are well established, the widespread use of it for medical purposes is limited by a number of objective factors. The rapid changes in climatic zone when moving residents of plains to mountains may negatively affect on the patients’ health status. That is why there exist a large number of medical contraindications for patients to stay in low barometric pressure and high-altitude hypoxia. It also should take into account the seasonal changes of meteorological, heliogeophysical, and other factors in mountains. As a result, the mountain climate therapy is unavailable for many healthy and sick people. That is why scientists and clinicians have attempted to simulate mountain climatic conditions on plains in order to use their sanogenic and healing properties in medical practice. Numerous studies have established that low partial pressure of oxygen (PO_2) is the most physiologically significant factor of mountain climate. Therefore, the main task for researchers was the creation of hypoxic conditions on plains. Hypobaric chamber was used for this purpose initially.

The first experience of treating BA patients in hypobaric chamber is associated with the name of academician NN Sirotinin. He attained encouraging results already in 1940–1941. Works done in the USSR in 1960s–1970s confirmed the high efficiency of this method in adults and children with BA. One of the most comprehensive studies was conducted in 650 BA patients in age from 2 to 49 years [15]. Full cessation of breathlessness and stable remission were observed after the first course of treatment in hypobaric chamber in 24.5% of children and 42.1% of adults. Treatment in hypobaric chamber had no significant effect only in 6.6% children and 14% adults. The immediate effect was even higher after repeated two or three courses of hypobaric treatment. The long-term positive effects were maintained from 1 month to several years. The most of BA patients significantly decreased the frequency of disease exacerbations, the number of breathlessness attacks, and incidence of acute respiratory infections. It was concluded that treatment in hypobaric chamber could be most efficient in children and adults with mild and moderate form of BA in phase of recovery and remission [16, 17].

Further investigation revealed that such factors as sympathoadrenal system activation, and cellular and humoral immunity normalization play important role in therapeutic mechanisms of the hypobaric treatment. These changes lead to decrease in bronchial hyperreactivity and severity of bronchoobstruction, improvement of lung ventilation, and bronchial drainage function in BA patients [18, 19].

It is obvious that sanogenic mechanisms of mountain climate and hypobaric chamber have much in common associated with exposure to low barometric pressure and PO_2 . Nevertheless, the treatment in hypobaric chamber is not widely used in clinics because of the risk of serious complications associated with the combined effect of these factors.

Since 1970s, the researchers' and practitioners' attention was attracted by the possibility of using the intermittent normobaric hypoxic training (INHT) for increasing nonspecific resistance to pathological factors in healthy and sick people. The comparative analysis of people's reaction on an equal decrease in PO_2 showed that normobaric hypoxia tolerated much better than hypobaric one [20]. Initially, INHT has been used in oncology practice for protection of patients' body against exposure to ionizing radiation during radiation therapy [21]. This method was also used in patients with fibrocavernous tuberculosis before surgery [22] and later for nonpharmacological treatment and prevention of different diseases [23–29]. Hypoxic gas mixtures containing from 10% to 16% oxygen in nitrogen have been most commonly used. Gas mixtures are inhaled in intermittent regime for maximum efficiency and exclusion of side effects. In accordance with this method, patient inhales the hypoxic gas mixture for 3–5 min and then atmospheric air for 3–5 min. The numbers of such cycles vary from 1 to 10 depending on the nature of disease and individual patient's peculiarities. The cumulative time of hypoxic gas mixture inhaling could be up to 30–60 min for a session.

Various technical devices such as anesthetic machine with semiopen breathing circuit and individual hypoxycator (Fig. 9.1) have been used in outpatient and home settings for obtaining normobaric hypoxic gas mixture identical to PO_2 levels at certain height above sea level. This device uses the principle of rebreathing and absorption of exhaled carbon dioxide. More recently, devices based on selective gas separation elements have become widely available, which allow fine adjustment of the necessary volumes of hypoxic gas mixtures with a given oxygen concentration [30].

In 1987, the scientists of AA Bogomoletz Institute of Physiology, National Academy of Sciences of Ukraine under the guidance of Prof. VA Berezovskii invented the first climatic chamber for group INHT (Fig. 9.2) and apparatus "Boreus" for individual INHT (Fig. 9.3). For many years, these devices have been used for INHT in pulmonary patients. We observed high therapeutic and preventive



Fig. 9.1 “Vershina” – the handheld hypoxicator for individual INHT (Firm “METOM”, Moscow Russia)

efficacy especially in patients with mild form of BA and in high-risk COPD patients. Different regimes of INHT were developed and tested. This provides individualization of INHT and elimination of side effects [14, 31].

In this chapter, we present the results of our studies regarding the INHT effects on respiratory function in 36 healthy individuals, 103 high-risk COPD patients, and 157 BA patients. Patients ranged in age from 21 to 59 years (women – 52.1%, men – 47.9%). INHT was performed in “Orotron” chamber. Under conditions of normal atmospheric pressure, this device creates and maintains in automatic mode the following parameters: PO_2 – 147–160 kPa, relative humidity – 60–70%, ambient temperature – 16–18°C, and content of light negative ions – up to 6,000/cm³. All patients within 2–4 weeks for 1.5 h daily received only INHT or INHT in combination with conventional therapy. The total time of hypoxic exposure in intermittent regime ranged from 21 to 42 h. Parameters of lung function were recorded in all patients before, during, and after INHT.

Fig. 9.2 “Orotron” – the climatic chamber for group INHT (Center “NORT,” Kiev, Ukraine)

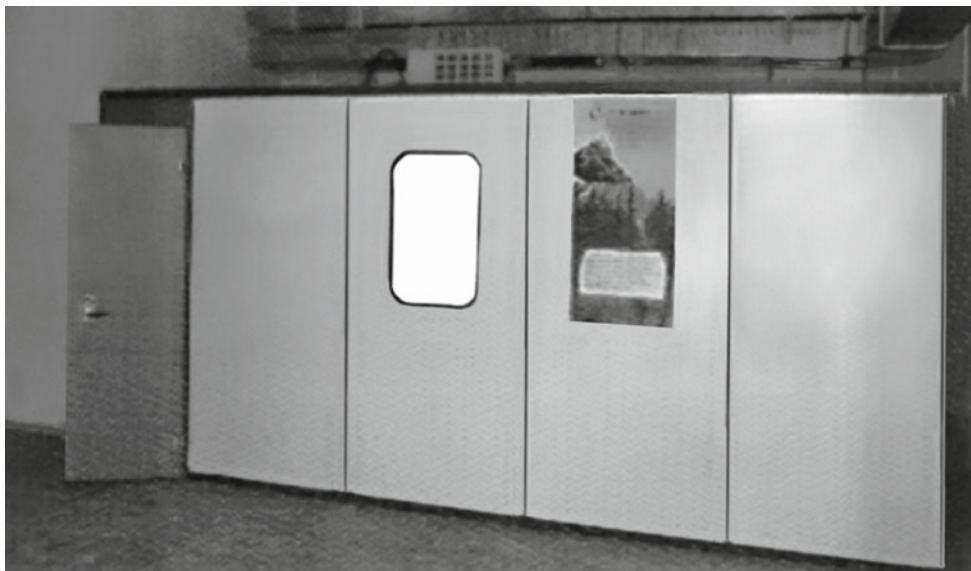


Fig. 9.3 “Boreus” – the apparatus for individual INHT (Center “NORT,” Kiev, Ukraine)

9.2 INHT and Lung Ventilation in COPD and BA Patients

We studied the healthy individuals and patients with high-risk COPD and BA to clarify the nature of changes in total and alveolar lung ventilation, as well as the status of individual mechanisms that determine their effectiveness in adaptation to INHT. The methods of spirometry, pneumotachography, and phonopulmography were used for investigating lung ventilation in five groups of subjects. The first group (healthy individuals) without lung diseases received only INHT. The second group – high-risk COPD patients – received conventional therapy in combination with INHT. The third group – high-risk COPD patients – received only INHT. The fourth group – patients with BA – received conventional therapy with INHT. The fifth group – patients with BA – received only conventional therapy.

Before INHT, the main parameters of lung ventilation were varied within the physiological norm in individuals who had no pulmonary diseases (Table 9.1). Minute volume of lung ventilation (V_E), tidal volume (V_T), and respiratory rate (f) did not significantly change after INHT. However, inspiratory reserve volume (IRV), maximum volume of lungs ventilation (MVV), and ratio of respiratory reserve (MVV/V_E) authentically increased. On the other hand, time of inspiration (t_i) and expiration (t_e) significantly decreased. These changes in lung ventilation were caused by adaptation of the healthy individuals to INHT. The statistically significant reduction in time of inspiration and expiration and tendency to increasing of respiratory rate in healthy peoples after INHT could be due to modifying effect of

hypoxia on the respiratory regulation mechanisms [32]. This aspect will be considered in detail below.

There were no statistically significant differences in lung ventilation between the second and third groups' patients

Table 9.1 Spirography indices in healthy individuals before (I) and after (II) INHT, ($n=36$)

Characteristics	I	II
$V_E, l \cdot \min^{-1}$	11.06 ± 0.73	11.38 ± 0.72
$f, \min^{-1}$	16.6 ± 0.8	17.7 ± 0.9
V_T, l	0.70 ± 0.03	0.65 ± 0.04
t_E, s	2.27 ± 0.12	$1.91 \pm 0.13^*$
t_I, s	1.70 ± 0.14	$1.37 \pm 0.08^*$
t_E/t_I	1.42 ± 0.08	1.57 ± 0.08
VC, l	3.99 ± 0.29	4.07 ± 0.24
VC, %	99.1 ± 4.7	102.6 ± 3.9
IRV, l	2.51 ± 0.32	$2.90 \pm 0.22^*$
ERV, l	0.55 ± 0.11	0.51 ± 0.13
FVC, l	3.44 ± 0.22	3.74 ± 0.38
FEV ₁ , l	2.98 ± 0.20	3.23 ± 0.26
FEV ₁ , %	99.3 ± 4.9	$108.1 \pm 6.4^*$
FEV ₁ /FVC, %	85.6 ± 2.1	88.1 ± 1.9
MVV, $l \cdot \min^{-1}$	78.2 ± 8.8	84.5 ± 6.0
MVV, %	76.2 ± 3.9	$83.1 \pm 3.8^*$
MVV/VC, %	19.4 ± 1.1	19.4 ± 1.1
MVV/ V_E	7.0 ± 0.8	$8.1 \pm 0.7^*$

* $p < 0.05$ – values are significantly different from the initial state

before INHT (Table 9.2). The values of vital capacity (VC), forced vital capacity (FVC), and expiratory reserve volume (ERV) increased by $9.2 \pm 2.5\%$, $6.1 \pm 2.9\%$, and $80.5 \pm 9.3\%$, respectively in 93.2% of high-risk COPD patients after 2 weeks of conventional therapy in combination with INHT. The volume that has been exhaled at the end of the first second of forced expiration (FEV₁) also achieved to upper limit of the physiological norm. It was characteristic that VC increased by 0.33 ± 0.09 ($p < 0.05$) mainly due to ERV.

The third group of high-risk COPD patients showed a steady tendency to increase in VC and FVC after INHT. The values of ERV increased by 0.22 ± 0.09 l ($p < 0.05$); FEV₁ did not differ from the second group of patients. Such dynamics in spirometry parameters pointed to improvement of lung ventilation in 81.3% of COPD patients who received INHT alone. It was achieved by improved efficiency and increased ventilatory reserves, mainly ERV.

The most significant disturbances in lung ventilation were observed in patient groups 4 and 5 before the INHT (Table 9.3). The obstructive type of disorders was dominant. Both groups of patients showed a decrease in FEV₁, FEV₁/FVC and increase in t_E . The more considerable decrease in MVV compared with VC led to decrease in MVV/VC ratios, which also reflected the severity of lung ventilation disorders. Repeated examinations indicated the different treatment efficiency in the fourth and fifth group of patients. The statistically significant differences appeared between the main indices of lung function.

Table 9.2 Spirography indices in high-risk COPD patients before (I) and after (II) INHT in combination with conventional therapy (2) and INHT only (3)

Characteristics	Group of patients			
	2 ($n=57$)		3 ($n=46$)	
	I	II	I	II
$V_E, l \cdot \min^{-1}$	13.28 ± 0.93	12.57 ± 0.76	12.02 ± 0.85	12.29 ± 0.73
$f, \min^{-1}$	17.8 ± 0.8	17.9 ± 1.1	16.4 ± 1.1	16.8 ± 1.1
V_T, l	0.76 ± 0.04	0.76 ± 0.05	0.78 ± 0.06	0.75 ± 0.04
t_E, s	1.89 ± 0.13	2.07 ± 0.15	2.45 ± 0.18	2.30 ± 0.18
t_I, s	1.53 ± 0.08	1.47 ± 0.10	1.60 ± 0.10	1.48 ± 0.08
t_E/t_I	1.26 ± 0.07	1.40 ± 0.07	1.53 ± 0.08	1.52 ± 0.08
VC, l	3.33 ± 0.19	$3.66 \pm 0.21^*$	2.97 ± 0.27	3.07 ± 0.28
VC, %	87.4 ± 4.3	$96.4 \pm 3.8^*$	87.5 ± 5.1	96.7 ± 4.8
IRV, l	2.07 ± 0.16	2.24 ± 0.19	1.79 ± 0.16	1.98 ± 0.17
ERV, l	0.41 ± 0.08	$0.74 \pm 0.11^*$	0.51 ± 0.11	$0.73 \pm 0.13^*$
FVC, l	2.96 ± 0.18	$3.14 \pm 0.18^*$	2.69 ± 0.26	2.85 ± 0.25
FEV ₁ , l	2.50 ± 0.13	$2.75 \pm 0.16^+$	2.12 ± 0.21	$2.46 \pm 0.22^*$
FEV ₁ , %	88.1 ± 3.9	$97.3 \pm 3.9^*$	82.6 ± 5.5	$96.2 \pm 5.4^*$
FEV ₁ /FVC, %	81.5 ± 1.5	$87.9 \pm 1.5^*$	79.3 ± 2.5	$87.8 \pm 1.6^*$
MVV, $l \cdot \min^{-1}$	65.7 ± 5.0	69.1 ± 5.7	59.2 ± 5.9	60.8 ± 6.5
MVV, %	66.1 ± 5.6	71.7 ± 5.5	68.0 ± 5.7	73.9 ± 5.9
MVV/VC, %	19.5 ± 1.0	17.1 ± 1.0	20.4 ± 1.1	19.4 ± 1.1
MVV/ V_E	4.9 ± 0.6	5.4 ± 0.5	5.5 ± 0.8	5.4 ± 0.7

* $p < 0.05$ – values are significantly different from the initial state

Table 9.3 Spirography indices in BA patients before (I) and after (II) INHT in combination with conventional therapy (4) and conventional therapy only (5)

Characteristics	Group of patients			
	4 (<i>n</i> =85)		5 (<i>n</i> =72)	
	I	II	I	II
$V_E, l \cdot \min^{-1}$	11.64±0.64	13.61±0.77	12.84±1.01	12.11±0.84
$f, \min^{-1}$	16.8±0.8	17.0±0.9	14.8±0.9	14.5±0.6
V_T, l	0.77±0.06	0.84±0.06	0.87±0.06	0.71±0.04
t_E, s	2.21±0.15	2.40±0.19	2.39±0.19	2.10±0.17
t_I, s	1.61±0.10	1.55±0.90	1.67±0.22	1.58±0.13
t_E/t_I	2.21±0.15	2.40±0.19	2.19±0.16	2.25±0.18
VC, l	3.14±0.19	3.26±0.20	3.96±0.37	4.07±0.24
VC, %	80.6±4.1	88.2±4.2*	82.6±3.7	87.5±3.8
IRV, l	2.08±0.16	1.94±0.18	2.37±0.22	2.32±0.32
ERV, l	0.40±0.10	0.55±0.08	0.51±0.13	0.77±0.13
FVC, l	2.89±0.20	2.91±0.18	3.44±0.22	3.58±0.34
FEV ₁ , l	2.02±0.14	2.34±0.16**	2.81±0.27	3.07±0.21
FEV ₁ , %	71.8±4.5	82.2±4.8**	73.4±5.3	80.3±4.1
FEV ₁ /FVC, %	70.2±2.4	80.1±2.5**	68.2±1.8	74.6±1.9*
MVV, l · min ⁻¹	61.2±5.4	65.3±5.4	76.9±8.6	80.1±6.1
MVV, %	64.0±4.7	66.6±4.9	69.3±5.1	71.5±5.6
MVV/VC, %	16.3±1.9	20.5±1.4*	17.4±1.7	20.3±1.2*
MVV/ V_E	5.6±0.5	5.2±0.4	5.9±0.5	6.5±0.3

* $p < 0.05$, ** $p < 0.01$ – values are significantly different from the initial state

The fourth group of patients had a significant increase in V_E from 11.64±0.64 to 13.61±0.77 l and VC from 80.6±4.1% to 88.2±4.2% ($p < 0.05$). The speed characteristics of pulmonary ventilation increased more significantly. The values of FEV₁ increased by 0.32±0.08 l, FEV₁/FVC by 10.4±2.3%, and MVV/VC reached up to 20.5±1.4% ($p < 0.05$). Higher rates of lung ventilation parameters after INHT in combination with conventional therapy were achieved in these patients mainly by improving the respiratory tract aerodynamic properties. There was also some positive dynamic in spirometry parameters in fifth group of patients after conventional therapy. But these changes were 25–38% less ($p < 0.05$) than those in patients group 4.

Thus, INHT induced the adaptive changes in lung ventilation and increased its effectiveness in healthy individuals. INHT increased the lung ventilation reserves and improved the respiratory tract aerodynamic properties in patients with COPD and BA. These effects of INHT led to efficiency gains of conventional therapy by 25–30%.

9.3 INHT and Alveolar Ventilation in COPD Patients

Given the fact that efficiency of lung ventilation is determined by not so much the total lung ventilation but the alveolar ventilation, we investigated the dynamic of alveolar ventilation (V_A) in patients with COPD before and after

course of INHT in relation to changes of V_T and functional residual capacity (FRC). We used the method of pulmophonography for these purposes [33].

The patients had different ratio of V_T and FRC and, consequently, the value of V_A before INHT. The values of V_T , FRC, and alveolar ventilation were within the physiological norm in 25% of patients (Table 9.4). Enhanced alveolar hyperventilation due to increased V_T took place in 40% of patients. Alveolar hypoventilation due to significant increase in FRC and decrease in V_T were observed in 35% of patients.

The various changes of V_T and FRC were identified in all patients after 2 weeks of INHT. It was reflected in dynamics of alveolar ventilation. But the nature and severity of these changes were different. The value of V_T decreased by 0.54±0.11 ($p < 0.05$), and FRC increased by 0.43±0.16 ($p < 0.05$) in the first group of patients. As a result, the V_A decreased by 0.10±0.02 ($p < 0.05$) and approached to the physiological level. In the second group of patients, V_T increased by 0.24±0.09 but FRC decreased by 0.16±0.05 ($p < 0.05$). This led to a moderate increase in V_A . In the third group of patients, V_T and FRC significantly increased by 0.28±0.06 and 0.21±0.06 ($p < 0.05$), respectively. It was accompanied by increased V_A , albeit to a lesser extent, than in the second group of patients.

Increased FRC reduced the excessive V_A in hyperventilation patients after INHT. The more significantly increased V_T led to improvement of the alveolar ventilation in hypoventilation patients. As a result of such changes of V_T and FRC, 76% of

Table 9.4 Values of V_T , FRC, and V_A measured with a pulmophonography method in high-risk COPD patients with initial alveolar hyperventilation, normoventilation, and hypoventilation before (I) and after (II) INHT

Group of patients	Stages of research	V_T , un.	FRC, un.	V_A , un.
Hyperventilation ($n=34$)	I	1.93 ± 0.17	6.91 ± 0.16	0.29 ± 0.019
	II	$1.38 \pm 0.11^*$	$7.34 \pm 0.04^*$	$0.19 \pm 0.002^*$
Normoventilation ($n=21$)	I	1.43 ± 0.05	7.34 ± 0.03	0.20 ± 0.004
	II	$1.67 \pm 0.20^*$	$7.19 \pm 0.07^*$	$0.24 \pm 0.003^*$
Hypoventilation ($n=30$)	I	0.94 ± 0.10	7.12 ± 0.13	0.14 ± 0.002
	II	$1.22 \pm 0.12^{**}$	$7.33 \pm 0.09^{**}$	$0.17 \pm 0.002^*$

* $p < 0.05$, ** $p < 0.01$ – values are significantly different from the initial state

Table 9.5 Unevenness of the total and alveolar lung ventilation in high-risk COPD patients measured with a pulmophonography method before (I) and after (II) INHT, ($n=85$)

Lung ventilation	Coefficient of unevenness, un.		
	Range of physiological norm	I	II
Total ventilation of the right lung	$0.53 \div 0.60$	0.70 ± 0.04	$0.54 \pm 0.03^{**}$
Alveolar ventilation of the right lung	$0.42 \div 0.54$	0.74 ± 0.05	$0.53 \pm 0.03^*$
Total ventilation of the left lung	$0.61 \div 0.78$	1.08 ± 0.05	$0.82 \pm 0.04^*$
Alveolar ventilation of the left lung	$0.49 \div 0.62$	0.81 ± 0.06	$0.58 \pm 0.05^*$

* $p < 0.05$, ** $p < 0.01$ – values are significantly different from the initial state

COPD patients with initial alveolar hyper- and hypoventilation reached up to physiological level by the end of INHT. Our results suggest that INHT could decrease or eliminate the alveolar ventilation impairment in COPD patients.

We also studied the alveolar ventilation distribution in four standard regions (i.e., superior, inferior, anterior, and posterior) of the right and left lung in COPD patients before and after INHT by means of phonopulmography method. Interesting results were obtained in hyperventilation (first group) and hypoventilation (second group) patients.

Significant disturbances in regional lung ventilation were observed in hyperventilation patients before the INHT. The total alveolar hyperventilation predominantly in posterior and superior regions was typical for the dominant lung of these patients. The alveolar hyperventilation in superior and posterior region and normal levels of alveolar ventilation in inferior and anterior regions were observed in nondominant lung. This type of regional ventilation distribution was the least favorable, since the maximum ventilation was in superior and posterior regions, which had the lowest level of perfusion even in physiological conditions. The alveolar ventilation was dramatically lower in inferior, anterior, and posterior regions of both lungs in second group of COPD patients before INHT. Disturbances of the regional ventilation were most pronounced in nondominant lung. INHT optimized the regional ventilation in the first group of patients due to significant decrease of the alveolar ventilation in posterior (by 0.23 ± 0.06), superior (by 0.18 ± 0.04), and, to a lesser extent, inferior (by 0.12 ± 0.04) and anterior regions (by 0.12 ± 0.03) of dominant lung. Changes of the alveolar ventilation in all regions of nondominant lung did

not exceed $0.08\text{--}0.06$. The values of regional ventilation indices approached to the physiological level in both lungs in the first group of patients by the end of INHT.

INHT moderately increased the alveolar ventilation in inferior region (by 0.04 ± 0.01) and, to a lesser extent, in anterior and posterior regions of dominant lung in the second group of patients. Alveolar ventilation of nondominant lung increased in all regions, but maximum increase was noted in anterior (by 0.05 ± 0.01) and posterior (by 0.04 ± 0.01) regions.

The indices of regional ventilation unevenness were within the physiological norm in patients with normal ventilation before INHT. But adaptation to INHT was accompanied by redistribution of regional ventilation. There was a decrease of alveolar ventilation in superior and posterior regions and a moderate increase in inferior and anterior regions of dominant lung. There was a trend toward a moderate increase of alveolar ventilation in all regions of nondominant lung.

It is known that COPD patients with normal or even increased level of lung ventilation may still have severe disorders of gas exchange. Manifestations of respiratory failure are frequently associated with abnormal distribution of air in lungs or unevenness of lung ventilation. That is why we determined the degree of unevenness distribution of total and alveolar ventilation in right and left lungs in patients with COPD before and after INHT.

The total and alveolar lung ventilation unevenness was evident in all COPD patients before INHT. The highest degree of unevenness was typical for the left lung (Table 9.5). We observed a significant decrease of lung ventilation unevenness after INHT. The unevenness coefficient of total and

Table 9.6 Respiratory tract aerodynamic characteristics in high-risk COPD patients before (I) and after (II) INHT in combination with conventional therapy (1), before (III) and after (IV) INHT only (2)

Characteristics	Group of patients			
	1 (n = 57)	II	2 (n = 43)	IV
R_{awl} , mmAq · l ⁻¹ · s ⁻¹	11.45 ± 1.18	9.07 ± 0.98	12.77 ± 1.20	10.91 ± 1.11
R_{awE} , mmAq · l ⁻¹ · s ⁻¹	10.37 ± 1.22	9.88 ± 1.04	9.81 ± 1.32	8.01 ± 1.40
G_{awl} , mmAq ⁻¹ · l · s	0.11 ± 0.02	0.22 ± 0.05	0.14 ± 0.03	0.20 ± 0.06
G_{awE} , mmAq ⁻¹ · l · s	0.14 ± 0.02	0.19 ± 0.04	0.15 ± 0.02	0.16 ± 0.04
FEF_{max} , l · s ⁻¹	5.01 ± 0.35	5.92 ± 0.39*	5.58 ± 0.75	5.42 ± 0.69*
$FEF_{25\%}$, l · s ⁻¹	4.79 ± 0.33	5.45 ± 0.37*	4.31 ± 0.38	5.08 ± 0.41
$FEF_{50\%}$, l · s ⁻¹	3.47 ± 0.23	4.00 ± 0.28*	3.90 ± 0.34	4.87 ± 0.23*
$FEF_{75\%}$, l · s ⁻¹	1.95 ± 0.18	2.04 ± 0.17	2.01 ± 0.25	2.51 ± 0.27
$FEF_{50\%}/FEF_{75\%}$	189.2 ± 10.3	198.8 ± 8.9	207.6 ± 16.5	178.1 ± 8.7*

* $p < 0.05$ – values are significantly different from the initial state

alveolar ventilation decreased by 22.9% and 21.6% in right lung and by 24.1% and 28.4% in left lung, respectively. The distribution of lung ventilation between right and left lung was improved mainly due to the increased ventilation in right lung after INHT. Consequently, the number of patients with absolute or relative dominance of right lung ventilation increased from 47% to 57%. The data indicated that the unevenness of regional lung ventilation in COPD patients was expressed more often in hyperventilation of superior and posterior regions and/or hypoventilation in inferior and anterior regions. Such changes in regional ventilation were the least favorable.

In summary, INHT improved or normalized the lung regional ventilation in 78% COPD patients. As a result, it restored the physiological level of ventilation distribution between right and left lung and reduced the severity of ventilation unevenness in each lung.

9.4 INHT and Airway Resistance in COPD and BA Patients

Bronchial obstruction is one of the important links in pathogenesis of pulmonary functional impairments in COPD and BA patients. The nature, severity, and reversibility of bronchial obstruction to a large extent determine the efficiency of therapeutic measures, as well as estimating the patient's quality of daily life and well-being. In this context, the particular interest was paid to the possibility of bronchial obstruction correction in patients with chronic pulmonary diseases by INHT. This issue was investigated in four groups of patients. The high-risk COPD patients who received conventional therapy in combination with INHT were included in group 1. The second group of COPD patients received only INHT. The third group of patients with BA received INHT in combination with conventional therapy. The fourth group of patients with BA received only conventional therapy.

Investigation of airway resistance was performed by pneumotachography method.

The total airway resistance in high-risk COPD patients, who had no clinical signs of bronchial obstruction, was 11–12 mmAq · l⁻¹ · s⁻¹ in phase of inspiration (R_{awl}) and 9–10 mmAq · l⁻¹ · s⁻¹ in phase of expiration (R_{awE}). The mean values of respiratory conductance were 0.11–0.14 mmAq⁻¹ · l · s (G_{awl}) and 0.14–0.15 mmAq⁻¹ · l · s (G_{awE}), respectively. The maximum instantaneous flow achieved during a FVC maneuver (FEF_{max}) and the average flow from the point where 25%, 50%, and 75% of the FVC has been exhaled ($FEF_{25\%}$, $FEF_{50\%}$, $FEF_{75\%}$) did not extend beyond the lower level of physiological norm. There were no significant differences in these indices between the first and second groups of COPD patients before INHT (Table 9.6).

The values of R_{awl} , R_{awE} did not change significantly in both groups of high-risk COPD patients after INHT, but FEF_{max} , $FEF_{25\%}$, and $FEF_{50\%}$ were moderately increased. This was related to the improvement of upper respiratory tract aerodynamic properties and the increased effort of respiratory muscles. The overall changes of these parameters in COPD patients of group 1 and 2 were similar, and there was no statistically significant intergroup difference. But if the combination of INHT with the conventional therapy allowed to achieve the positive results in 91.8% of patients, whereas when only INHT was used, 78.9% of patients had such positive outcomes.

There was a significant airflow limitation in third and fourth groups of BA patients before treatment began. The airway resistance was increased up to 14–15 mmAq · l⁻¹ · s⁻¹, and the value of respiratory conductance did not exceed 0.08 mmAq⁻¹ · l · s. All indices of “flow-volume” curve were lower, but $FEF_{75\%}$ decreased more significantly. This indicated an increase of peripheral airways resistance (Table 9.7).

Significant improvement was found in all basic characteristics of the airway function in the third group of patients after INHT in combination with conventional therapy. Positive dynamics was significantly lower in the fourth group of patients who received only conventional therapy. Intergroup

Table 9.7 Respiratory tract aerodynamic characteristics: (1) in BA patients before (I) and after (II) INHT in combination with conventional therapy; (2) in BA patients before (III) and after (IV) INHT only (2)

Characteristics	Group of patients			
	1 (n=47)	II	2 (n=33)	IV
R_{awl} , mmAq · l ⁻¹ · s ⁻¹	14.35 ± 1.55	10.47 ± 0.95*	15.41 ± 1.44	13.01 ± 0.85*
R_{awE} , mmAq · l ⁻¹ · s ⁻¹	13.83 ± 1.91	10.55 ± 1.21*	14.01 ± 1.81	12.84 ± 1.91*
G_{awl} , mmAq ⁻¹ · l · s	0.08 ± 0.01	0.11 ± 0.02	0.07 ± 0.01	0.10 ± 0.01
G_{awE} , mmAq ⁻¹ · l · s	0.09 ± 0.01	0.11 ± 0.01	0.10 ± 0.01	0.11 ± 0.02
FEF_{max} , l · s ⁻¹	4.12 ± 0.35	4.84 ± 0.33**	4.32 ± 0.30	5.01 ± 0.49*
$FEF_{25\%}$, l · s ⁻¹	3.23 ± 0.33	4.24 ± 0.34*	3.08 ± 0.21	3.59 ± 0.38
$FEF_{50\%}$, l · s ⁻¹	2.03 ± 0.23	2.87 ± 0.28*	2.11 ± 0.32	2.65 ± 0.56*
$FEF_{75\%}$, l · s ⁻¹	0.98 ± 0.13	1.36 ± 0.16*	1.15 ± 0.23	1.42 ± 0.15*
$FEF_{50\%}/FEF_{75\%}$	262.7 ± 39.6	213.8 ± 15.8	263.5 ± 34.8	212.4 ± 28.8

* $p < 0.05$, ** $p < 0.01$ – values are significantly different from the initial state

differences for some indices reached from 27% to 52%. These facts indicated that there was an obvious bronchodilation effect of INHT in BA patients. This effect was more evidence in those BA patients, who received only INHT.

The efficacy of bronchodilation effect in BA patients after INHT was largely determined by duration and severity of disease, the presence of steroid dependence, and concomitant pathology. Our data show that individual selection of INHT allows to decrease the level of airflow obstruction in 88.7% of mild BA patients. Notably, the degree and duration of the positive effects of INHT on airway function and respiratory resistance in patients with chronic pulmonary diseases were not less than those achieved in mountains.

9.5 Effect of INHT on Respiratory Pattern in COPD and BA Patients

Changes in patient's respiratory pattern are very important in both diagnostic and prognostic assessment [34, 35]. It is known that frequent and shallow breathing is the least effective compensatory reaction. Development of tachypnea may be the first and only symptom of the respiratory distress syndrome and sudden death during sleep. On the other hand, the normalization in the structure and parameters of the respiratory cycle demonstrates the efficacy of therapeutic measures undertaken and the favorable course of disease.

Existing data about change in respiratory pattern in healthy men were obtained at the sea level and during high-altitude adaptation. This problem was studied also in patients during short-time adaptation to hypobaric hypoxia. The direct effects of hypoxic exposure were mainly examined in these studies. But the questions about nature and persistence of the changes in respiratory pattern during and after INHT in patients with COPD and BA remain opened [36].

We studied the dynamics of volumetric, temporal, and spatial parameters of respiratory pattern in COPD and BA

patients under INHT. The following key indicators of respiratory pattern [37] were analyzed: V_E , V_T , f , t_{tot} (total duration of respiratory cycle), t_I (duration of inspiratory phase), t_E (duration of expiratory phase), t_I/t_{tot} (proportion of inspiration phase in total duration of respiratory cycle) or “useful cycle” of breathing, t_E/t_I (time respiratory quotient), V_I/t_I (mean rate of inspiratory flow), V_E/t_E (mean rate of expiratory flow), $V_{I,max}/t_I$ (maximum rate of inspiratory flow), and $V_{E,max}/t_E$ (maximum rate of expiratory flow).

Preliminary analysis of the initial respiratory pattern structure allowed allocating two groups of patients before INHT (Table 9.8). The values of V_E , V_T , f , and t_I were higher in the second group of patients, but $V_{E,max}/t_E$ and t_E/t_I ratios were higher in the first group.

Changes in respiratory pattern had a stenoventilation type in the first group of patients after INHT. We found increased V_E and f by 2.21 ± 0.74 l ($p < 0.05$) and 2.6 ± 0.7 min⁻¹ ($p < 0.05$), respectively. The total duration of respiratory cycle was less by 0.62 ± 0.14 s ($p < 0.05$) due to decreased t_I and to a lesser extent t_E . The t_E/t_I and t_I/t_{tot} ratios were stable because of proportional reduction in time of inspiration and expiration. The mean rate of inspiratory flow increased due to reduction of t_I while V_T remained at a constant level.

The respiratory pattern changed in isoventilation type in patients group 2 after INHT. We found a typical decrease in f by 2.46 ± 0.46 min⁻¹ ($p < 0.01$) and increase in V_T by 0.13 ± 0.06 l ($p < 0.01$), whereas the value of V_E remained unchanged. The decrease in respiratory rate led to increase in t_{tot} by 0.72 ± 0.10 s, mainly due to increase in t_E by 0.32 ± 0.12 s ($p < 0.05$) and to lesser extent t_I . The t_E/t_I and t_I/t_{tot} ratios did not change, but $V_{E,max}/t_E$ significantly increased.

As a result of these multidirectional changes in respiratory pattern, significant differences in V_T and f values were detected between the first and second groups of patients after INHT. Respiratory pattern in group 1 patients was characterized by more frequent and less deep breathing. The similar

Table 9.8 Characteristics of stenoventilation (1) and isoventilation (2) types of adaptive changes in breathing pattern in high-risk COPD patients before (I) and after (II) INHT

Characteristics	1 (n=26)		2 (n=28)	
	I	II	I	II
$V_E, \text{l} \cdot \text{min}^{-1}$	11.02 ± 0.72	$13.23 \pm 0.81^*$	12.68 ± 0.53	12.86 ± 0.69
f, min^{-1}	16.48 ± 0.81	$18.17 \pm 0.95^*$	17.10 ± 0.70	$14.64 \pm 0.75^*$
V_T, l	0.66 ± 0.05	0.73 ± 0.05	0.74 ± 0.05	$0.88 \pm 0.07^*$
t_{tot}, s	3.64 ± 0.11	$3.26 \pm 0.18^*$	3.76 ± 0.17	$4.15 \pm 0.12^*$
t_E, s	1.50 ± 0.07	$1.30 \pm 0.08^*$	1.63 ± 0.08	1.70 ± 0.11
t_I, s	2.14 ± 0.17	1.86 ± 0.12	2.12 ± 0.11	$2.43 \pm 0.16^*$
t_E/t_I	1.45 ± 0.11	1.42 ± 0.06	1.32 ± 0.06	1.43 ± 0.07
t_I/t_{tot}	0.40 ± 0.02	0.40 ± 0.02	0.42 ± 0.39	$0.39 \pm 0.02^*$
$V_I/t_I, \text{l} \cdot \text{s}^{-1}$	0.49 ± 0.04	$0.60 \pm 0.05^*$	0.49 ± 0.02	0.55 ± 0.04
$V_E/t_E, \text{l} \cdot \text{s}^{-1}$	0.37 ± 0.04	0.42 ± 0.03	0.38 ± 0.02	0.40 ± 0.03
$V_{I\text{max}}/t_I, \text{l} \cdot \text{s}^{-1}$	0.69 ± 0.06	$1.14 \pm 0.34^*$	0.67 ± 0.04	$0.93 \pm 0.14^*$
$V_{E\text{max}}/t_E, \text{l} \cdot \text{s}^{-1}$	0.66 ± 0.39	1.13 ± 0.33	0.54 ± 0.17	$1.03 \pm 0.16^*$

* $p < 0.05$ – values are significantly different from the initial state

volume of lung ventilation in group 2 patients was achieved by deeper and fewer breaths.

The mean inspiratory flow increased much significantly in the first group of patients, but the maximum expiratory flow values were recorded in the second group. The increase in mean expiratory flow was associated with improved airway aerodynamic properties and respiratory conductance. However, the increase in mean inspiratory flow reflected not only changes in respiratory muscles efforts but also to a larger extent the changes in central respiratory regulation. The frequency of basal respiratory pattern recovery was 0.96 in COPD patients who received INHT in combination with conventional therapy. This index did not exceed 0.63 in patients who received only conventional therapy.

Our results suggested that changes in volumetric, temporal, and spatial parameters of respiratory pattern in COPD patients after INHT were different in nature. They depended on the individual characteristics of respiratory biomechanics and status of central mechanisms of respiratory regulation. Adaptation to INHT restored the basal respiratory pattern in COPD patients, which was the best in physiological and energetic sense.

9.6 INHT and Respiratory Regulation in Healthy Individuals and COPD Patients

The above-discussed investigation of lung function in healthy individuals and COPD patients led us to assume that INHT affected not only at the level of executive organs (lungs, bronchi, respiratory muscles, etc.) but also at the level of central respiratory regulation. One of the few methods to study the central control of respiration is the phase analysis of respiratory cycles [37–39].

Accordingly, we applied the method in high-risk COPD patients and in healthy individuals. The first group of COPD patients received conventional therapy in combination with

INHT and the second group received INHT only. The healthy individuals also received INHT. As indicators of central inspiratory activity (CIA), the value of maximal inspiratory pressure in the airway (PI_{max}) and the mean rate of inspiratory flow (V_I/t_I) were used [40, 41]. These indicators allow obtaining information about level and intensity of respiratory chemosensory stimulation – “a respiratory drive” – which is directly proportional to CIA. Excitability threshold of the “turn off” inspiration mechanism had been determined from the “useful cycle” of respiration (t_I/t_{tot}) [42].

It was found that PI_{max} was significantly higher in both groups of COPD patients than in healthy individuals before INHT (Table 9.9). This indicated a higher initial level of the central inspiratory activity in COPD patients. But V_I/t_I , which was usually directly proportional to CIA, did not increase. The t_I/t_{tot} ratio showed a tendency to increase the excitability threshold of the “turn off” inspiration mechanism in COPD patients. Healthy individuals had the higher level of V_I/t_I than COPD patients. This pointed to a relatively higher level of respiratory chemosensory stimulation in healthy individuals before INHT.

The mean values of PI_{max} and t_I/t_{tot} were decreased and V_I/t_I was increased in all COPD patients after INHT alone or in combination with conventional therapy. No statistically significant differences in these parameters between both groups of COPD patients indicate the direct involvement of INHT in these effects. However, the differences in degree and direction of PI_{max} and V_I/t_I changes in COPD patients who had no clinical and functional signs of bronchial obstruction might be related not only to respiratory regulation mechanisms but also to latent pulmonary functional impairment.

Our results in healthy individuals confirmed the direct influence of INHT on the central respiratory regulation. There was moderate but statistically significant decrease in PI_{max} and V_I/t_I in healthy individuals after INHT. But the t_I/t_{tot} ratio and therefore level of the excitability threshold of the “turn off” inspiration mechanism remained stable.

Table 9.9 Some characteristics of respiratory regulation in high-risk COPD patients before (I) and after (II) INHT in combination with conventional therapy (1), INHT only (2), and in healthy individuals (3)

Groups of patients	Stage of research	$PI_{\max}$, mm Aq.	V_I/t_p , l · s ⁻¹	t_I/t_{tot}
1 (n=37)	I	10.13±0.97	0.481±0.010	0.453±0.019
	II	7.11±0.60*	0.545±0.009*	0.411±0.008*
2 (n=33)	I	9.97±0.82	0.492±0.007	0.432±0.018
	II	7.08±0.55*	0.539±0.008	0.413±0.009
3 (n=36)	I	8.14±0.61	0.648±0.015	0.421±0.007
	II	6.50±0.49*	0.570±0.010*	0.403±0.017

* $p < 0.05$ – values are significantly different from the initial state

These changes indicated the decrease in CIA level and intensity of the respiratory chemosensory stimulation after INHT.

Conclusion and Perspectives

Results of our studies indicated that INHT increased reserves of lung ventilation, restored the physiological level of alveolar ventilation in 78% of patients with COPD, optimized the regional air distribution in lungs, and decreased by 25–30% the lung ventilation unevenness. INHT also resulted in improvement of airway function due to reduction by 31–37% of bronchial resistivity in BA patients. INHT changed the functional state of central respiratory regulation in COPD patients and healthy individuals. It contributed to more complete restoration of the optimal structure of respiratory pattern, due to the normalization of respiratory biomechanics, as well as the declined level of central inspiratory activity and intensity of the respiratory chemosensory stimulation.

It is obvious that sanogenic mechanism of INHT in pulmonary patients includes the complex adaptive changes in nervous, endocrine, and humoral regulation. These changes not only increase the resistance to hypoxia but also have a marked sanogenic and healing effects [43–45]. In addition, INHT increases the overall and immunological reactivity, reduces the severity of bronchial obstruction, increases the ventilatory reserve, normalizes the level of alveolar ventilation and pulmonary microcirculation, and optimizes the ventilation-perfusion relationships and intrapulmonary gas exchange [46–50].

Duration and severity of disease, presence of comorbidity, and steroid dependence are apparently the important factors determining INHT effectiveness and expression of sanogenic effect in patients with chronic pulmonary diseases. Our analysis of INHT efficacy in patients with BA by the criterion of broncholytic effect intensity showed that if duration of disease was less than 5 years, this effect was seen in 82.3% of adult patients, from 5 to 10 years in 68.0%, and over 10 years in 57.8% of the patients. This effect was only detected in 33.4% of cases, if patients had a persistent steroid dependence. Careful definition of indications and individual selection of INHT regime could allow the positive effect reaching up to 87% of adults and 92% of children [51–55].

Finally, INHT significantly improves the health of people and reduces the morbidity with temporary disability in patients. INHT is compatible with the traditional methods of treatment and prevention of pulmonary diseases and is able to potentiate the action of other pharmacological and biophysical sanogenic factors. The further development and improvement of the methodology and technical support will allow INHT to emerge as an important nonpharmacological therapy for care and rehabilitation of patients with pulmonary diseases.

References

1. Sirotinin MM. Life at altitudes and altitude sickness. Kiev: AS of UkrSSR; 1939. pp. 225, [In Ukrainian].
2. Ado AD. Experience in conducting of bronchial asthma epidemiological studies. In: Planning and implementation of socio-hygienic and epidemiological studies of bronchial asthma. Leningrad: All-Union Sci & Research Inst of Pulm. 1973. p. 23–7 [In Russian].
3. Serebrovskaya TV. Intermittent hypoxia research in the former Soviet Union and the Commonwealth of Independent States: history and review of the concept and selected applications. High Alt Med Biol. 2002;3:205–21.
4. Brimkulov NN. The alpine climatotherapy of bronchial asthma patients. Ter Arkh. 1991;63:25–30 [In Russian].
5. Boboev AT, Gadaev AG, Razikov AA. The rehabilitation of bronchial asthma patients in a mountain climate. Vopr Kurortol Fizioter Lech Fiz Kult. 1999;1:37–8 [In Russian].
6. Cogo A, Basnyat B, Legnani D, et al. Bronchial asthma and airway hyperresponsiveness at high altitude. Respiration. 1997;64:444–9.
7. Menz G. Effect of sustained high altitude on asthma patients. Expert Rev Respir Med. 2007;1:219–25.
8. Schultze-Werninghaus G. Effects of high altitude on bronchial asthma. Pneumologie. 2008;62:170–6.
9. Yakushenko MI. Features of children adaptation to mountain climate and efficacy of bronchial asthma treatment in mountain climate. In: Alpine climatotherapy in internal medicine. Bishkek: Kyrgyz Sci & Research Inst of Cardiol. 1991. p. 90–3 [In Russian].
10. Simon HU, Grotzer M, Nikolaizik WH, et al. High altitude climate therapy reduces peripheral blood T lymphocyte activation, eosinophilia, and bronchial obstruction in children with house-dust mite allergic asthma. Pediatr Pulmonol. 1994;17:304–11.
11. Njå F, Røksund OD, Svidal B, et al. Asthma and allergy among schoolchildren in a mountainous, dry, non-polluted area in Norway. Pediatr Allergy Immunol. 2000;11:40–8.
12. Berezovskii VA, Deñega VG, Nosar VI, et al. Effect of artificial mountain climate on respiration and circulation in coal miners with chronic dust bronchitis. Fiziol Zh. 1985;31:619–23 [In Russian].

13. Berezovskii VA, Deĭnega VG. Physiological mechanisms of the mountain climate sanogenic effects. Kiev: Naukova Dumka; 1988. pp. 224, [In Ukrainian].
14. Berezovskii VA, Levashov MI. Introduction to orotherapy. Kiev: Academy of Hypoxia Problems, RF; 2000. pp. 56, [In Ukrainian].
15. Bulatov PC, Uspenskaja EP, Egorov MI, et al. Immediate and long-term results of barotherapy bronchial asthma and high-risk bronchial asthma patients. In: Bronchial asthma. Leningrad: All-Union Sci & Research Inst of Pulm. 1977. p. 81–2 [In Russian].
16. Alemanova GD. Application of hypoxibarotherapy in rehabilitation of children suffering from bronchial asthma. Pediatrics. 2010;1: 67–70 [In Russian].
17. Balabolkin II, Alemanova GD. Clinical and immunological rehabilitation by application of hypobaric hypoxic stimulation in bronchial asthma child and adolescent. Pediatrics. 2010;2:90–6 [In Russian].
18. Meerson FZ, Frolov BA, Smagin EA, et al. Effect of adaptation to hypoxia on immediate and delayed type of allergic reactions. In: Adaptation and resistance of organism in mountains conditions. Kiev: Naukova Dumka 1986. p. 56–65 [In Ukrainian].
19. Bulakhov AN, Nikolaeva AG, Dotsenko EA, et al. Relaxation of the smooth muscles of bronchus under hypobaric hypoxia and its adaptation to that condition. Fiziol Zh. 2003;49:53–7 [In Ukrainian].
20. Dotsenko YI. Comparison of the effectiveness of intermittent normobaric hypoxitherapy and hypobarotherapy in clinic of chronic nonspecific lung diseases. In: Interval hypoxic training (efficacy, mechanisms of action). Kiev: State Inst of Physical Culture 1992. p. 65–8 [In Ukrainian].
21. Strelkov RB, Chizhov AI. Intermittent normobaric hypoxia in prevention, treatment and rehabilitation. Yekaterinburg: Ural Worker; 2001. pp. 400, [In Russian].
22. Radionov BV. Importance of training in preparation for pneumectomy of patients with fibro-cavernous pulmonary tuberculosis. Thesis for Ph.D. degree in Medical Science, Kiev; 1972. p. 26 [In Ukrainian].
23. Berezovskii VA, Levashov MI, Gridina TN. The use of an artificial mountain climate for treating and rehabilitating chronic bronchitis patients. Vrach Delo. 1990;12:34–6 [In Ukrainian].
24. Aleksandrov OV, Struchkov PV, Vinitskaia RS, et al. Clinico-functional effect of a course of interval normobaric hypoxic therapy in patients with chronic obstructive bronchitis and bronchial asthma. Ter Arkh. 1999;71:28–32 [In Russian].
25. Serebrovska TV, Mankovska MI, Lysenko GI, et al. The method of intermittent hypoxic effects in combined treatment of patients with bronchial asthma. Lik Sprava. 1998;6:104–8 [In Ukrainian].
26. Ivanova IP, Nepomniashchikh VM, Shirinskii VS, et al. Normobaric hypoxo-therapy of patients with bronchial asthma. Klin Med (Mosk). 2001;79:36–9 [In Russian].
27. Kolchinskaja AZ, Tsyganova EN, Ostapenko LA. Normobaric interval hypoxic training in medicine and sports. Moscow: Meditsina; 2003. pp. 407, [In Russian].
28. Vogel 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.
29. Haider T, Casucci G, Linser T, et al. Interval hypoxic training improves autonomic cardiovascular and respiratory control in patients with mild chronic obstructive pulmonary disease. J Hypertens. 2009;27:1648–54.
30. Lopata VO, Berezovskii LMI, et al. Classification and review of technical devices for hypoxia therapy. Fiziol Zh. 2003;49:100–5 [In Ukrainian].
31. Berezovskii VA, Levashov MI. Natural and instrumental orotherapy and rehabilitation patients with pulmonary diseases. Ukr Pulm Zh. 2005;3(suppl):15–8 [In Russian].
32. Breslav IS, Glebovskii VD. Regulation of respiration. Leningrad: Nauka; 1981. pp. 280, [In Russian].
33. Nemirovskii LI. Pulmophonography. Moscow: Meditsina; 1981. pp. 160, [In Russian].
34. McFadden JP, Price RC, Eastwood HD, et al. Raised respiratory rate in elderly patients: a valuable physical sign. Br Med J. 1982;284:626–7.
35. Gravelin TR, Weg JG. Respiratory rate as an indicator of acute respiratory dysfunction. JAMA. 1980;244:1123–5.
36. Krivoshchekov SG, Divert GM, Divert VE. Individual characteristics of external respiration during intermittent normobaric hypoxia. Fiziol Cheloveka. 2006;32:62–9 [In Russian].
37. Breslav IS. Breathing patterns: physiology, extremes conditions, and pathology. Leningrad: Nauka; 1984. pp. 206, [In Russian].
38. Grodins FS, Yamachiro SM. What is the pattern of breathing regulated for? Oxford: Centr Nerv Contr Mech Breath Proc Int Symp; 1979. p. 169–76.
39. Haas F, Distenfeld S, Axen K. Effects of perceived musical rhythm on respiratory pattern. J Appl Physiol. 1986;61:1185–91.
40. Gautier H. Control of the pattern of breathing. Clin Sci. 1980;8:343–8.
41. Gautier H, Milic-Emili J, Miserocchi G, et al. Pattern of breathing and mouth occlusion pressure during acclimatization to high altitude. Respir Physiol. 1980;40:365–77.
42. Rossi M, Maestrelli P. The effect of ventilatory drive in chronic obstructive lung disease. In: Clinical respiratory physiology. Bratislava: Slovak Acad of Sci. 1983. p. 44–54.
43. Kolchinskaja AZ. Mechanisms of the interval hypoxic training action. Hypoxia Med J. 1993;1:5–8 [In Russian].
44. Ksenofontova IV, Uianaeva AI, Aĭrapetova NS, et al. Interval hypoxic training as a method of prophylaxis of meteopathic reactions in patients with bronchial asthma: guide for physicians. Vopr Kurortol Fizioter Lech Fiz Kult. 2006;4:54–6 [In Russian].
45. Tlupova TG, Borukaeva IK. Application of interval hypoxitherapy for improvement of the respiratory functional system and visual functions in patients with bronchial asthma. Bull Regen Med. 2008;5:32–5 [In Russian].
46. Berezovskii VA, Levashov MI. Artificial mountain climate: some mechanisms of therapeutic action. Vopr Kurortol Fizioter Lech Fiz Kult. 1993;3:23–6 [In Russian].
47. Levashov MI, Berezovskii VA. Pulmonary circulation in patients with COPD under the influence of hypoxic gas mixtures and artificial mountain climate. In: Intermittent normobaric hypoxia. Reports of the Acad. of Hypoxia Problems. RF. Moscow. 1997;1:188–95 [In Russian].
48. Ragozin ON, Balykin MV, Charikova EI, et al. The analysis of a spectrum of rhythms of parameters external breath and cardiovascular system at the patients with bronchial asthma on a background normobaric hypoxitherapy. Fiziol Zh. 2001;47:36–9 [In Ukrainian].
49. Krivoshchekov SG, Divert GM, Divert VE. Effect of short-term intermittent normobaric hypoxia on the regulation of external respiration in humans. Fiziol Cheloveka. 2002;28:45–51 [In Russian].
50. Leutin VP, IaG P, Divert GM, et al. Changes in the central regulation of respiratory function after a single session of intermittent normobaric hypoxia. Fiziol Cheloveka. 2003;29:13–5 [In Russian].
51. 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].
52. Berezovskii VA, Gorban EM, Levashov MI, et al. Technology to improve of the organism resistance by means of hypoxitherapy. Method Recom of the MHU. Kyiv; 2000. p. 23 [In Ukrainian].
53. Poddubnaya RY, Grineva OM, Bykov AT, et al. Intermittent normobaric hypoxo-therapy in complex of sanatorium treatment and rehabilitation of persons with bronchopulmonary diseases. In: Intermittent normobaric hypoxo-therapy. Reports of the Academy of Hypoxia Problems. RF. Moscow. 1999;3:215–9 [In Russian].
54. Karash YM, Strelkov RB, Chizhov AY. Normobaric hypoxia in treatment, prophylaxis and rehabilitation. Moscow: Meditsina; 1988. pp. 352, [In Russian].
55. Borukaeva IK. Effectiveness of hypoxic therapy in patients with chronic obstructive pulmonary disease. Vopr Kurortol Fizioter Lech Fiz Kult. 2009;2:16–8 [In Russian].