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Intermittent Hypoxia Alters Hypoxic Ventilatory Responses

Abstract

Intermittent hypoxic training (IHT) shows promise for prevention and treatment of some diseases and efficiently produces great advancement in athletic training. We studied (1) hypoxic ventilatory responses (HVR) in supine and sitting positions during normobaric, isocapnic, progressive hypoxia (rebreathing technique) and (2) lung ventilation and gas exchange while breathing ambient air at rest and during 5 min of breathing 11% O_2. Duel measurements were made pre- and post-15-day IHT regimen on 12 (experimental) healthy males (24,6 y.o. ± 1,9 y.o.) and on 6 (control) healthy males (24,2 y.o. ± 2,3 y.o.) given pseudo-IHT (p-IHT) without decreasing PiO_2. IHT involved rebreathing eucapnic (chemically absorbed) air as $P_{ET}O_2$ decreased to 35 mmHg, three 6–7 min sessions, three times a day, with 10 min breaks between each session over a 15 day training period. Without IHT, HVRs were the same in sitting and supine positions at low levels of hypoxic challenge (slope one-S_1: $P_{ET}O_2$ from 110–60 mm Hg) and significantly higher (by 45%) during severe hypoxia (slope two-S_2: $P_{ET}O_2$ from 60–35 mm Hg). IHT caused an increase in HVR in both sitting and supine positions: S_1 by 70 and 100 %, S_2 by 158 and 200 %, maximal lung ventilation by 35 and 78 %, respectively. There were no significant changes in the p-IHT group. IHT also caused enhanced respiratory reactions during sustained hypoxia (lung and alveolar ventilation increased by 36 and 22 %, respectively). A striking hypoxic ventilatory sensitivity was noted in subjects with hyper-reactive breathing patterns.

Two physiologic perspectives support and explain hypoxic influences. First, hypoxia causes profound disturbances of physiological systems accompanied by significant pathological shifts. Secondly, being a powerful stimulator of general nonspecific body reactivity, hypoxia promotes a cure during the course of many illnesses. Both of these aspects of hypoxic action depend on the methods of hypoxic enfluence, initial health status, and the individual peculiarities of the organism's reactivity. Intermittent hypoxic training (IHT) is now a promising trend of prevention and treatment for some diseases such as hypertension [19, 26], bronchial asthma [31], rheumatoid arthritis [21], and blood disturbances after radiation exposure [30]. In addition, IHT proved to be efficient in a number of sports for attaining the highest achievements [15, 20, 25, 28]. Increased hypoxic ventilatory response (HVR) is an essential defence mechanism against global hypoxia. Susceptibility to high altitude pulmonary edema is associated with a decreased HVR [4, 14, 23]. Attenuated carotid body hypoxic sensitivity was observed after

prolonged hypoxic exposure in cats [34]. On the other hand, an increase in HVR in healthy males has been shown after acclimatization to prolonged (1 year) altitude hypoxia [29].

Concerning the effects of very short hypoxic exposure (minutes to hours) there are contradictory results. Easton [10] and Berkenbosch, et al, [6] observed that the acute hypoxic response was depressed after 25 min of sustained hypoxia (SaO_2 = 80%) in healthy subjects. But Engwall [12] reported an increase in hypoxic ventilatory sensitivity after 4 hr acclimatization to hypoxia. This result was not dependent on the modality of hypoxic exposure (isocapnic vs.poikilocapnic). Augmentation in respiratory reactions during 8 hr of isocapnic and poikilocapnic hypoxia was observed in humans by Howard and Robbins [16].

Investigations devoted to intermittent chronic exposure to high altitudes [17, 18, 27] show that miners' intermittent chronic exposure was accompanied by physiological responses different both from the responses of acute exposure and from the responses of permanent high altitude residence. Most of these changes seem to be intermidiate between acute and chronic hypobaric hypoxia exposure. HVR and gas exchange data were not provided in these investigations.

We have investigated the influence of a 2-week course of short-term (7 min sessions, three times a day) intermittent hypoxia, which produced clinically benefitial effects, on hypoxic ventilatory sensitivity, lung ventilation, and gas exchange of healthy subjects.

Methods

All subjects were lacking a history of cardiovascular or pulmonary disease. Two groups of male volunteers participated in this study and gave their informed consent. All were sea-level residents. The first group (Gr.I) consisted of 12 healthy army servicemen (age 24,6 yr ± 1,9 yr, height 178 cm ± 1,9 cm, wight 71,2 kg ± 2,2 kg) who participated in IHT. The second group (Gr.II) comprised of 6 healthy male subjects (age 24,2 yr ± 2,3 yr; height 183 cm ± 2,2 cm; weight 70,4 kg ± 3,1 kg) formed the control (placebo) group (p-IHT) in which the IHT was imitated without decreasing PiO_2. All tests were executed twice: one day before IHT and one day after a 15-day IHT regime.

The sequence of the study was identical in all groups. Subjects were tested in the morning on an empty stomach. Gas exchange was determined first at rest during room air respiration. Subjects lay in a supine position and breathed into a mouthpiece through a low-resistance, open circuit with a uni-directional valve, a volume meter coupled to the inspiratory limb, and a tap for sampling expired gas from a 5-liter mixing bag. Measurements were begun after a 10 minute acclimation period for relaxed adjustment to the apparatus. Values for inspired minute ventilation (V_I) and respiratory frequency (f, breaths/min) were obtained from the volume meter VEB MLW (DDR). From analysis of the mixed expired gases in the mixing bag, O_2 uptake (VO_2, STPD) and CO_2 production (VCO_2, STPD) were calculated.

$P_{ET}O_2$ and end-tidal CO_2 concentration ($P_{ET}CO_2$) were continuously monitored at the mouth with a medical mass spectrometer MX62-02 (USSR) which was calibrated before and after each test with standardized gases that had been assayed by the Scholander technique. Measurements were performed while the subject breathed room air and then repeated after five minutes of hypoxia, induced by

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S_2, l · min^{-1} · mm Hg^{-1}	
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V_E(50), l · min^{-1}	
max V_E, l · min^{-1}	
min $P_{ET}O_2$, mm Hg	

p_1 – level of signific
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breathing 11% oxygen. After 10 minutes of rest, hypoxic ventilatory drives were tested in a supine position and 10 minutes later in a sitting position.

A rebreathing technique was used. HVR was measured during isocapnic hypoxia. The subjects breathed into a spirometer in which the O_2 concentration fell with time. The initial gas composition consisted of 20,9% O_2, 79,1% N_2. $P_{ET}CO_2$ was maintained at a resting room air value by regulation of the CO_2-product absorption rate. Rebreathing was carried out for about 5 or 6 minutes, until a $P_{ET}O_2$ = 40–35 mm Hg was reached. The ventilatory responses were analyzed by relative minute ventilation (V_E) to $P_{ET}O_2$. Curves were hyperbolic in shape. The piecewise linear approximation technique was used for analysis of the curves [32]. This method enabled the independent analysis of the slopes during the first phase of slowly increasing ventilation (S_1) and during the second phase of sharply increasing ventilation (S_2). Fracture point coordinates and peak readings of the parameters were also analyzed (Fig. 1). IHT was administered using normobaric isocapnic progressive hypoxia (rebreathing technique beginning with room air and continuing to the 40–35 mm Hg range) during 15 days of three-per-day, 6–7 minute sessions with 15 minute breaks. Statistics were performed using Student's matched pair test.

Results

The ventilatory responses to hypoxic stimulus were found to be similar in sitting and supine positions at low-level hypoxic challenge (Fig. 1, Tabl. 1). However, as

Table 1. Ventilatory responses to isocapnic progressive hypoxia in young healthy males before and after 15 days of hypoxic training

Parameters	Position	GROUP I (with HT) N = 12			GROUP II (placebo) N = 6		
		before	after	p	before	after	p
S_1, l·min^{-1}·mm Hg^{-1}	sit	0,10±0,02	0,17±0,05	NS	0,12±0,06	0,13±0,07	NS
	sup	0,08±0,01	0,16±0,06	NS	0,11±0,09	0,11±0,04	NS
	p_1	NS	NS		NS	NS	
S_2, l·min^{-1}·mm Hg^{-1}	sit	0,43±0,03	1,11±0,06	=0,001	0,46±0,05	0,51±0,06	NS
	sup	0,30±0,03	0,90±0,08	=0,001	0,31±0,04	0,36±0,04	NS
	p_1	<0,01	=0,05		<0,02	<0,05	NS
FP (V_E), l·min^{-1}	sit	13,0±1,1	18,3±2,8	<0,05	13,5±2,1	14,5±0,9	NS
	sup	11,3±0,56	13,2±1,5	<0,01	12,2±1,0	12,8±1,0	NS
	p_1	NS	NS		NS	NS	
FP ($P_{ET}O_2$), mm Hg	sit	79,0±5,4	61,0±4,1	<0,01	72,0±3,2	64,3±3,5	NS
	sup	7,8±1,1	59,6±2,3	NS	66,6±3,0	65,7±4,3	NS
	p_1	=0,001	NS		NS	NS	
V_E(50), l·min^{-1}	sit	26,2±1,8	30,0±3,4	NS	24,5±2,0	22,2±2,0	NS
	sup	13,3±1,1	20,0±2,6	<0,02	17,4±2,1	17,6±1,9	NS
	p_1	=0,001	<0,05		<0,05	NS	
max V_E, l·min^{-1}	sit	31,0±2,1	42,0±5,8	NS	28,4±2,6	29,0±1,9	NS
	sup	17,6±1,7	31,4±2,6	<0,001	22,1±3,0	20,5±2,1	NS
	p_1	=0,001	NS		<0,1	<0,01	
min $P_{ET}O_2$, mm Hg	sit	38,1±1,7	37,6±2,2	NS	40,6±2,0	44,3±4,1	
	sup	34,0±1,2	35,3±1,7	NS	40,2±2,9	42,2±3,7	NS
	p_1	<0,05	NS		NS	NS	

p_1 – level of significance of differences between sitting and supine position (Student's t-test)

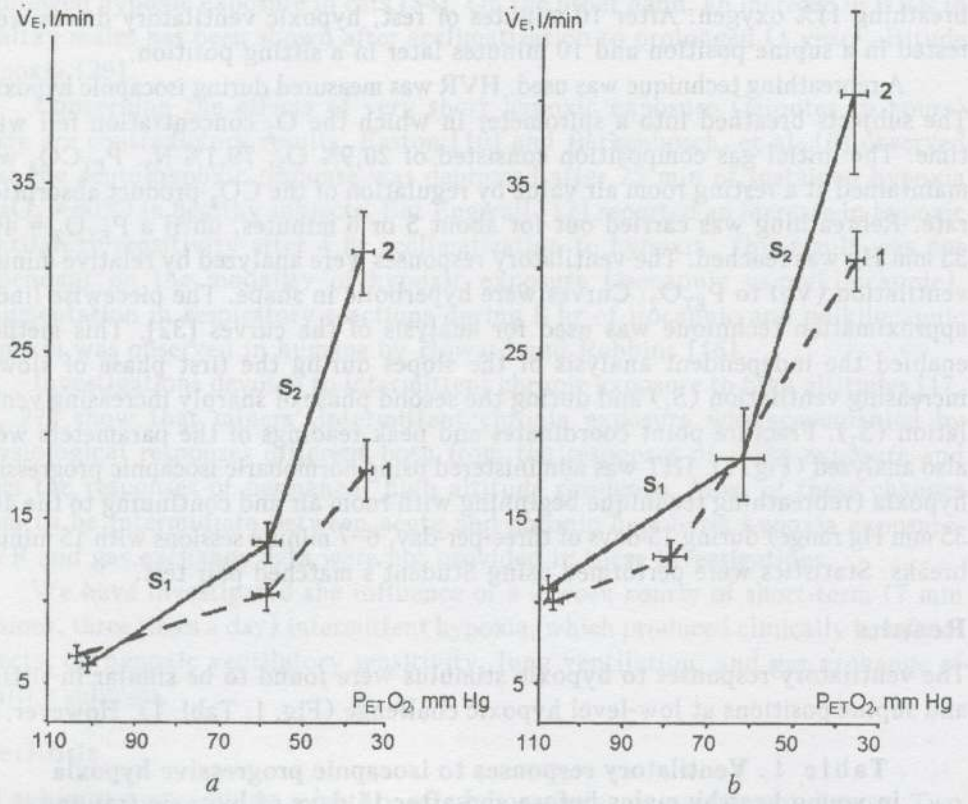
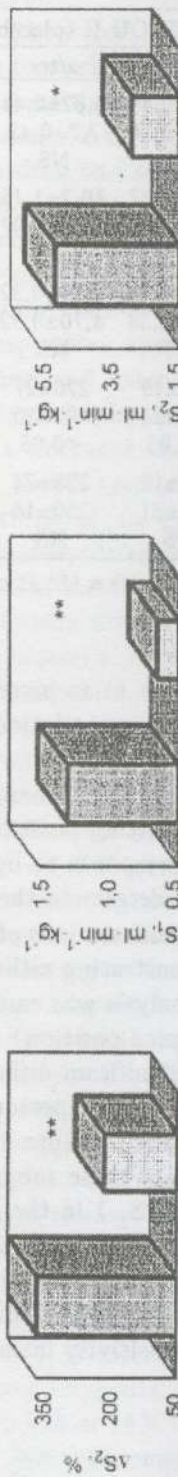
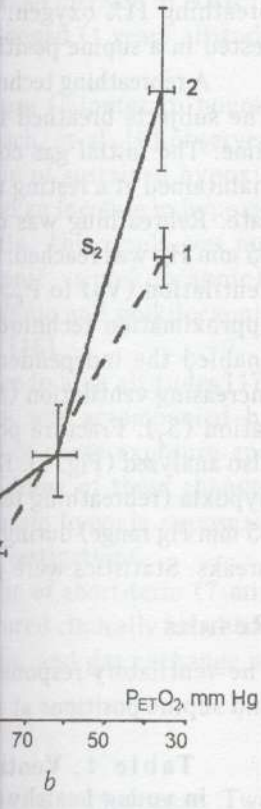


Fig. 1. Hypoxic ventilatory responses before (1) and after (2) intermittent hypoxic training: *a* – supine position; *b* – sitting position; S_1 – phase of slowly increasing ventilation; S_2 – phase of sharply increasing ventilation.

revealed by high-level hypoxia (S_2) , the HVR demonstrated significant differences between these positions. S_2 in sitting versus supine position in Gr.I and Gr.II was higher by 43 and 48%, respectively. The peak meanings of V_E at $P_{ET}O_2$ = 50 mm Hg were also significantly higher in the sitting position. Five minutes of breathing with an hypoxic gas mixture (11% O_2 in N_2) did not evoke significant changes in parameters of lung ventilation in any group (Tabl. 2). We did not find any increase in V_E, f or V_A. As a result, oxygen consumption fell by 22% (Gr.I) and 25% (Gr.II) under hypoxia. No changes were observed in CO_2 production.

IHT caused considerable shifts of ventilatory sensitivity to the hypoxic stimulus. First an increase in HVR was observed in Gr.I both in sitting and supine position: S_1 by 70 and 100%; S_2 by 158 and 200%; and maxV_E by 35 and 78%, respectively. Greatest alterations were expressed in the supine position. No significant changes were found in Gr.II (Tabl.1). Changes in lung ventilation and gas exchange were observed when breathing a constant hypoxic mixture after IHT (Table. 2). In the contrary of the first investigation, Gr.I revealed a significant increase of V_E and V_A when inhaling 11% O_2 by 36 and 22%, respectively. This increased ventilation prevented the fall in oxygen consumption: VO_2 did not change during hypoxia, and CO_2 purging increased. Responses to inhalation of 11% O_2 after 15 days of p-IHT remained unchnaged in Gr.II subjects. We suggest therefore, that IHT caused





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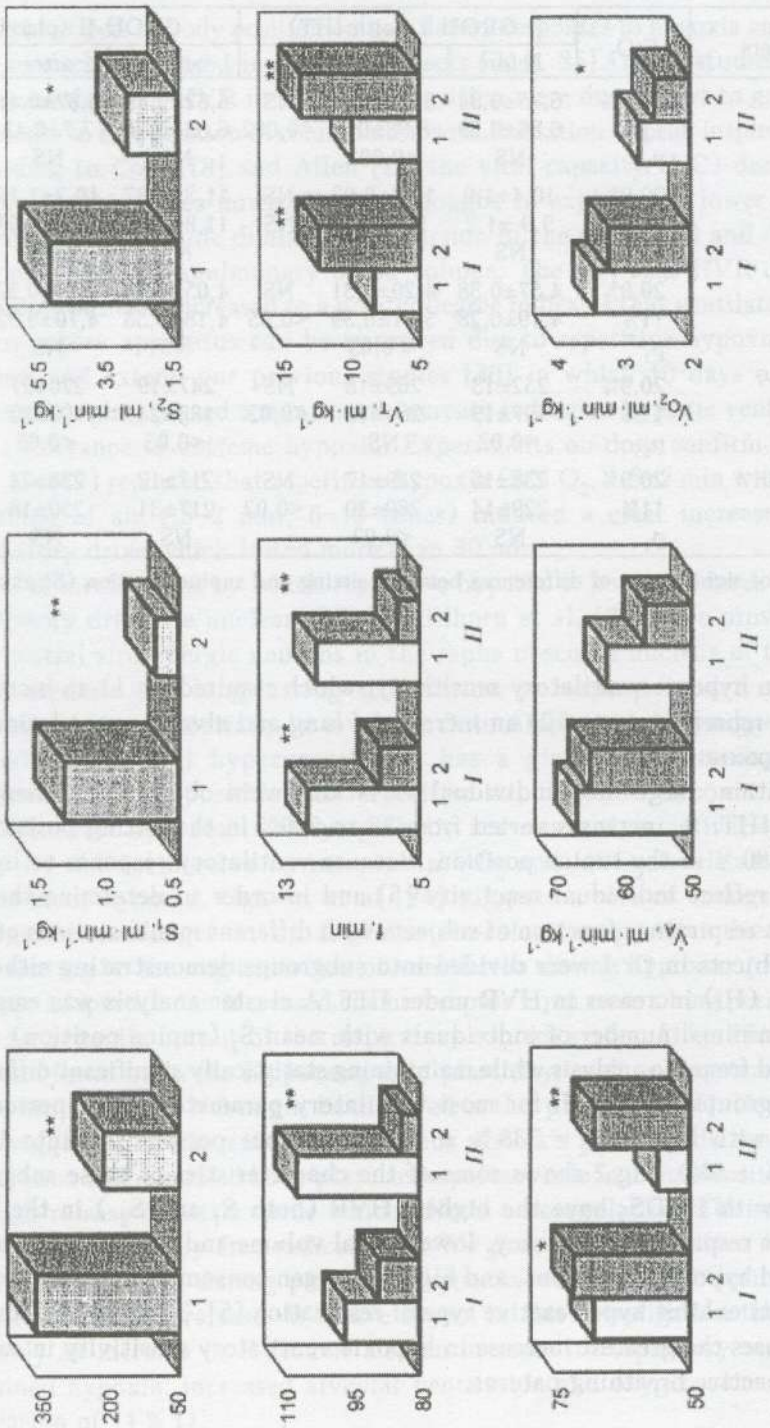

Fig. 2. Hypoxic ventilatory responses, lung ventilation and gas exchange in males with high (1, n = 5) and low (2, n = 4) respiratory reactivity: *I* — normoxia, *II* — hypoxia.
* P < 0,05 between 1 and 2; ** P < 0,01.

Table 2. Lung ventilation and gas exchange in young healthy males during 5 min breathing with gas mixture (11% O_2 in 79% N_2) before and after 15 days of intermittent hypoxic training

Parameters	FiO_2	GROU 1 (with IHT)			GROU II (placebo)		
		before	after	p	before	after	p
V_E, $l \cdot min^{-1}$	20,9%	6,75±0,34	6,62±0,53	NS	6,82±0,49	6,82±0,41	NS
	11%	6,86±0,29	8,98±0,6	<0,002	6,83±0,76	7,7±0,43	NS
	p_1	NS	<0,002		NS	NS	
f, min^{-1}	20,9%	10,4±1,0	10,3±0,92	NS	11,3±0,87	10,2±1,16	NS
	11%	9,9 ±1,2	11,9±1,4	NS	11,8±1,36	11,2±0,97	NS
	p_1	NS	NS		NS	NS	
V_A, $l \cdot min^{-1}$	20,9%	4,57±0,38	4,20±0,31	NS	4,05±0,28	4,17±0,32	NS
	11%	4,19±0,28	5,11±0,39	<0,05	4,18±0,58	4,70±0,32	NS
	p_1	NS	< 0,05		NS	NS	
Vo_2, $ml \cdot min^{-1}$	20,9%	252±13	269±18	NS	247±19	270±27	NS
	11%	197±19	264±19	<0,02	185±24	197±20	NS
	p_1	<0,02	NS		<0,05	<0,05	
Vco_2, $ml \cdot min^{-1}$	20,9%	238±15	229±17	NS	217±13	236±24	NS
	11%	229±14	289±20	<0,02	217±31	250±18	NS
	p_1	NS	<0,02		NS	NS	

p_1 – level of significance of differences between sitting and supine position (Student's t-test)

an increase in hypoxic ventilatory sensitivity, which resulted in: 1) an increase of HVR during rebreathing, and 2) an increase of lung and alveolar ventilation with sustained hypoxia.

In addition, large inter-individual variations were observed in changes in HVR under IHT. S_2 increases varied from 28 to 500% in the sitting position and from 88 to 780 % in the supine position. Because ventilatory response to hypoxic stimuli may reflect individual reactivity [5] and in order to determine the main differences in respiratory function of subjects with different manifestations of HVR reactions, subjects in Gr.I were divided into subgroups demonstrating either low (Lo) or high (Hi) increases in HVR under IHT. A cluster analysis was employed such that a minimal number of individuals with mean S_2 (supine position) values were excluded from the analysis while maintaining statistically significant differences between subgroups Lo and Hi for most ventilatory parameters. Five persons fell into Hi-ΔS_2 with IHT (ΔS_2 = 338 % ± 18 %) and four persons fell into Lo-ΔS_2 (ΔS_2 = 109 % ± 9%). Fig.2 shows some of the characteristics of these subgroups. Individuals with Hi-DS_2 have the highest HVR (both S_1 and S_2) in the initial state, highest respiratory frequency, lowest tidal volume and V_A/V_E ratio both in normoxic and hypoxic conditions, and highest oxygen consumption under hypoxia. These subjects exhibit hyperreactive type of respiration [5]. Thus we can conclude that IHT causes the greatest increase in hypoxic ventilatory sensitivity in subjects with hyperreactive breathing paterns.

Discussion

Our data have demonstrated significant differences in hypoxic sensitivity of healthy persons before and after intermittent hypoxic influences. While these differences

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were observed in both sitting and supine positions, the influence of IHT was manifested more vividly in the supine position. No changes were observed in control subjects.

The effects of body position on ventilatory responses to hypoxia and hypercapnia have been characterized in normal subjects [3, 9, 35]. These studies showed that the lower slopes of HVR in the supine position were due in part to greater air flow impedance in this position in combination with limitation of peak inspiratory pressure. According to Cotes [8] and Allen [2], the vital capacity (VC) decreases by 7 % when the subject lies down. Factors thought to explain the lower values in the supine position include diminished excursion of the chest wall and/or diaphragm and/or longer intrapulmonary blood volume. The fact that HVR during IHT in the supine position increased to a greater degree indicates that ventilatory limitations of respiratory apparatus can be improved due to repetitive hypoxia. The results confirm and extend our previous studies [30] in which 10 days of intermittent hypoxic training caused a significant increase in human hypoxic ventilatory slopes and a tolerance to extreme hypoxia. Experiments on dogs confirm our results as well. Cao [7] reported that repetitive hypoxia (9 % O_2, 1,5–2 min with intermittent breathing of air 1,5–2 min, 6–13 times) induced a clear increase in normoxic ventilatory drive which lasted more than 30 min.

The mechanisms by which repetitive hypoxic exposure induces an increase in ventilatory drive are unclear. While Millhorn et al. [22] have provided evidence that central sirotonergic neurons in the raphe obscurus nucleus of the brain stem could mediate the long-lasting stimulation of respiratory drive, many other mechanisms may potentially be involved. Soto-Arape et al. [33] suggest that during hypoxia the initial hyperventilation has a glutamate-releasing component. Furthermore, it is possible that repetitive exposures to hypoxia may raise the metabolic rate as a result of sympathetic nervous system activation [7]. In this study we did not observe an increase in VO_2 and VCO_2 levels after a course of intermittent hypoxia. Ogawa, et al [24] suggests a role of endogenous NO as a retrograde messenger in an L-glutamate-releasing positive feedback system contributing to the augmentation of ventilation during hypoxia. As seen in high-altitude adaptation, an increased chemoreceptor input over a long period can further increase synaptic output of the respiratory control system [11]. This phenomenon is a manifestation in the hippocampus of plasticity, such as long-term potentiation in the hippocampus. NO might be involved in this plasticity [24]. However, Grimes [13] suggests that the autonomic nervous system's nitric oxide synthase positive innervation in the carotid body plays an important role in chemosensitivity primarily through release of nitric oxide which affects vasoregulation. The response to NO could be modified by free radicals [1]. We propose that reactive oxygen species which are produced during periods of hypoxia-reoxygenation during IHT play a specific role in NO release. We have shown in this investigation that IHT caused not only an increase in HVR but also an increase in respiratory reactions during sustained hypoxia: increased alveolar ventilation and oxygen consumption under inhalation of 11 % O_2.

But these reactions (like HVR moderation) differed from one individual to another. Our previous studies demonstrated considerable inter-individual differences regarding adaptation both to intermittent- and high-altitude hypoxia [29,30]. Two

opposing strategies of respiratory adaptive processes were distinguished: an active «aerobic» strategy, characterized by enhanced ventilatory reactions to hypoxia, a «fight-for-oxygen» response with low anaerobic glycolysis processes; and a passive «anaerobic» strategy with gradually declining ventilatory reactions to hypoxia with considerably enhanced anaerobic glycolysis. The present investigation confirms these two strategies for ventilatory adaptation and adds new data on the body's response to sustained short-term hypoxia.

In summary, our results indicate that IHT caused an increase in HVR and enhanced respiratory reactions during sustained hypoxia. A striking hypoxic ventilatory sensitivity was noted in subjects with hyper-reactive breathing patterns.

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ВПЛИВ ПЕРІОДИЧНИХ ГІПОКСИЧНИХ ПОДРАЗНЕНЬ НА ЧУТЛИВІСТЬ ДИХАННЯ ЛЮДИНИ ДО ГІПОКСІЇ

Метод періодичних гіпоксичних подразнень останнім часом став все ширше застосовуватись для запобігання та лікування деяких хвороб, а також в спортивній практиці в комплексі тренувальних заходів. Механізм позитивної дії інтервального гіпоксичного тренування (ІГТ), зокрема, на функцію дихання, багато в чому залишається нез'ясованим. Ми вивчали чутливість системи дихання до гіпоксичного подразника, легеневу вентиляцію та газообмін в нормальних умовах та при диханні газовою сумішшю з 11 % кисню до і після 15-денного курсу ІГТ у 12 здорових чоловіків (24,6 років ± 1,9 років), а також у 6 чоловіків (24,2 роки ± 2,3 роки) контрольної групи, яким імітували дію ІГТ без зниження вмісту кисню у вдихуваному повітрі. ІГТ проводили методом еукапнічного зворотнього дихання зі зміною P_AO_2 від 110 до 35 мм рт.ст. на протязі 6–7 хвилин, тричі на день з 10-хвилинними перервами. Перед початком тренування вентиляторна відповідь (HVR) на гіпоксичний подразник малої величини (S_1, P_AO_2 від 110 до 60 мм рт.ст.) не відрізнялась в двох положеннях тіла (сидячи та лежачи), але була на 45 % вища в положенні сидячи при суворій гіпоксії (S_2, P_AO_2 від 60 до 35 мм рт.ст). ІГТ викликала підвищення HVR в обох положеннях: S_1 – відповідно на 70% та 100%, S_2 – на 158% та 200%, а також значне збільшення максимальної вентиляції легень (на 35% та 78%, відповідно). Спостерігалось також підвищення реакції легеневої та альвеолярної вентиляції на вдихування гіпоксичної суміші (на 36% та 22%, відповідно). Найбільші зміни параметрів дихання було виявлено у осіб з гіперреактивним типом вентиляції. Обговорюються можливі механізми виявлених реакцій.

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Стан деяк
ланок ада
з експери

Моде
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Вступ

У механізмах ад
які виникають
тальної та анте
діляється ролі
4]. При цьому
стреслімітуючи
ня експеримент
таційно-пристос
утробної гіпокс

Методика

Моделювання
женням основн
слідження пров
строками вагіт
вагітні кролиці
робною гіпоксі

Вивчали п
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Про зміни
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(ПОЛ) і антио
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