Doppelblind
randomisiert
Placebo kontrolliert

Intermittent hypoxia increases exercise tolerance in elderly men with and without coronary artery disease

Article *in* International Journal of Cardiology · September 2004

DOI: 10.1016/j.ijcard.2003.07.021 · Source: PubMed

CITATIONS
56

READS
54

7 authors, including:

Burtscher Martin
University of Innsbruck
286 PUBLICATIONS **2,557** CITATIONS
SEE PROFILE

Igor Ehrenburg
Pirogov Russian National Research Medical U...
9 PUBLICATIONS **179** CITATIONS
SEE PROFILE

Martin Faulhaber
University of Innsbruck
78 PUBLICATIONS **796** CITATIONS
SEE PROFILE

ELSEVIER

International Journal of Cardiology 96 (2004) 247–254

International Journal of Cardiology

www.elsevier.com/locate/ijcard

Intermittent hypoxia increases exercise tolerance in elderly men with and without coronary artery disease

Martin Burtscher[a,*], Otmar Pachinger[b], Igor Ehrenbourg[c], Günther Mitterbauer[a], Martin Faulhaber[a], Reinhard Pühringer[a], Elena Tkatchouk[c]

[a] *Department of Sport Science, Medical Section, University of Innsbruck, Fürstenweg 185, 6020 Innsbruck, Austria*
[b] *Division of Cardiology, Internal Medicine, University of Innsbruck, Anichstrasse 35, 6020 Innsbruck, Austria*
[c] *Clinical Research Laboratory, Hypoxia Medical Academy, 3, Ivankovskoye shosse, 123367 Moscow, Russia*

Received 24 February 2003; received in revised form 22 July 2003; accepted 25 July 2003

Abstract

Background: Intermittent hypoxia has been suggested to increase exercise tolerance by enhancing stress resistance and improving oxygen delivery. Because the improvement of exercise tolerance reduces mortality in the elderly with and without coronary artery disease intermittent hypoxia might be a valuable preventive and therapeutic tool. However, controlled studies are lacking. *Methods and results:* Sixteen males (50–70 years, 8 with and 8 without prior myocardial infarction) were randomly assigned in a double-blind fashion to receive 15 sessions of passive intermittent hypoxia (hypoxia group) or normoxia (control group) within 3 weeks. For the hypoxia group each session consisted of three to five hypoxic (14–10% oxygen) periods (3–5 min) with 3-min normoxic intervals. Controls inhaled only normoxic air in the same way. Exercise tests were performed before and after the 3-week breathing program. After 3 weeks of intermittent hypoxia peak oxygen consumption had increased compared to normoxic conditions (+6.2% vs. −3%, $p<0.001$). This improvement was closely related to the enhanced arterial oxygen content after hypoxia ($r=0.9$, $p<0.001$). Both higher haemoglobin concentration and less arterial oxygen desaturation during exercise contributed to the increase in arterial oxygen content. During sub-maximal exercise (cycling at 1 W/kg) heart rate, systolic blood pressure, blood lactate concentration, and the rating of perceived exertion were diminished after intermittent hypoxia compared to control conditions (all $p<0.05$). Changes in responses to exercise after intermittent hypoxia were similar in subjects with and without prior myocardial infarction. *Conclusions:* Three weeks of passive short-term intermittent hypoxic exposures increased aerobic capacity and exercise tolerance in elderly men with and without coronary artery disease.

Keywords: Intermittent hypoxia; Exercise tolerance; Aerobic capacity; Elderly; Coronary artery disease

1. Introduction

Intermittent hypoxia is defined as repeated episodes of hypoxia interspersed with normoxic periods [1]. Hypoxic episodes are created by exposure to natural high altitude, sojourns in hypobaric chambers or by breathing hypoxic gas mixtures in normobaric conditions. Intermittent hypoxia has been suggested to improve exercise performance, to acclimatize before going to high altitude or for prevention and treatment of various illnesses [2–7]. On the one hand, the main rationale for the clinical use of intermittent hypoxia is based on the potential cross-protective value of adaptations to one stress, which then provides resistance to another stress [8–10]. On the other hand, as is the case with acclimatization to chronic hypoxia, intermittent hypoxia is characterised by a progressive increase in ventilation, adaptations of the haematopoetic and cardio-circulatory systems to enhance oxygen delivery to the tissues, and alterations on the tissue level to optimise the utilisation of oxygen [11–13]. Both enhanced stress resistance and improved oxygen delivery are basic preconditions for increased exercise tolerance. Because the improvement of exercise tolerance reduces mortality in the elderly, in particular in patients with coronary artery disease [14,15], intermittent hypoxia might be considered to be a valuable preventive and therapeutic tool. However, beneficial and adverse effects of intermittent

* Corresponding author. Prof. Martin Burtscher, Dept. of Sport Science, Medical Section, University of Innsbruck, Fürstenweg 185, 6020 Innsbruck, Austria.
E-mail address: Martin.Burtscher@uibk.ac.at (M. Burtscher).

0167-5273/$ - see front matter © 2003 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ijcard.2003.07.021

hypoxia may vary markedly depending on the timing of hypoxic cycling, the cycle length, the degree of hypoxia and various co-stimuli like hypo- and hypercapnia, acidosis or alkalosis [1,13]. From among a broad variety of protocols, experimentally repeated short-term hypoxia with normoxic intervals with a cycle length of about 5 min, also known as interval hypoxic training, has been clinically used by Russian physicians since many years [7,16,17]. They report these passive short-term hypoxic exposures to be beneficial and well tolerated by the healthy elderly and patients with various diseases as well. However, the exclusion of control groups has been a common feature of studies employing the intermittent hypoxia protocol in the healthy and diseased elderly. Therefore, we conducted a randomised, double blind, placebo-controlled trial to investigate the effects of repeated short-term hypoxia on exercise tolerance in elderly men with and without coronary artery disease.

2. Methods

2.1. Subjects

Normally physically active men (age 50–70 years; NYHA class I and II) with or without prior myocardial infarction, living in or near Innsbruck (600 m; Austria), were invited to participate in the study. Volunteers had to undergo a routine physical examination. Subjects were excluded if they could not perform cycle exercise, or had recent myocardial infarction and/or revascularisation (<8 weeks prior to inclusion in the study), episode of instable angina, decompensated heart failure, life-threatening arrhythmias, known symptomatic aortic outflow obstruction, severe hypertension (>180/100 mm Hg) or any other severe systemic non-cardiac disease. The first 16 subjects meeting the inclusion criteria (8 with and 8 without prior myocardial infarction) comprised the study population. Finally, after stratification for prior myocardial infarction, subjects were randomly assigned in a double-blind fashion to the hypoxia group or the control group. Baseline characteristics of the study groups are shown in Table 1. Study participants were advised not to change medications, nutrition and levels and pattern of physical activity during the entire study period. The study was approved by the local ethics committee. The investigation was carried out in conformity with the ethical standards laid down in the 1964 Declaration of Helsinki. All persons gave their informed consent prior to their participation in the study.

2.2. Study protocol

Initial examination before exercise testing included medical history, data on physical activity, blood determinations (red and white blood cell count, haemoglobin concentration, haematocrite, concentrations of blood glucose, total cholesterol and HDL, triglycerides, uric acid, and blood gas analyses), electrocardiography, echocardiography, blood pressure measurements and basic pulmonary function testing.

Table 1
Baseline characteristics of the hypoxia and the control group

	Hypoxia group ($n=8$)	Control group ($n=8$)
Age (years)	59.3 (5.4)	61.3 (5.0)
Height (cm)	172.1 (3.1)	177.0 (3.3)
Body mass (kg)	77.8 (12.9)	76.1 (4.4)
Heart rate (bpm)	67.4 (6.8)	63.3 (9.7)
Systolic blood pressure (mm Hg)	144.3 (13.9)	140.8 (12.7)
Diastolic blood pressure (mm Hg)	84.0 (13.3)	82.5 (8.9)
Arterial oxygen saturation (%)	95.9 (1.3)	96.0 (1.5)
FEVC (l)	5.0 (0.8)	5.2 (0.6)
FEV_1 (%)	76.3 (7.0)	77.5 (3.9)
MVV (l/min)	153.6 (28.1)	161.4 (20.9)
Total cholesterol (mg/dl)	259.1 (41.0)	210.9 (30.5)
VO_2 peak (ml/min/kg)	30.1 (6.4)	36.9 (9.5)
Physical activity (h/week)	6.4 (4.8)	6.3 (6.5)
Current smokers, *n* (%)	1 (13)	2 (25)
Ejection fraction (%)	54.9 (8.3)	50.8 (14.8)
Hypertension, *n* (%)	3 (38)	3 (38)
Hypercholesterolaemia, *n* (%)	3 (38)	3 (38)
Diabetes, *n* (%)	0 (0)	1 (13)
Previous MI, *n* (%)	4 (50)	4 (50)
Medications, *n* (%)		
Aspirin	2 (25)	3 (38)
β-blockers	2 (25)	1 (13)
ACE inhibitors	0 (0)	2 (25)
Calcium channel blockers	1 (13)	1 (13)
Anticoagulants	1 (13)	2 (25)
Statins	2 (25)	2 (25)
Diuretics	0 (0)	2 (25)
Nitrates	1 (13)	1 (13)

Data represent means (SD) or frequencies.
Abbreviations: Forced Expiratory Vital Capacity (FEVC), Forced Expiratory Volume (FEV_1), Maximal Voluntary Ventilation (MVV), Peak Oxygen Uptake (VO_2peak), Angiotensin-Converting-Enzyme-Inhibitors (ACE-inhibitors); myocardial infarction (MI).

2.2.1. Exercise tests

Incremental symptom-limited spiro-ergometric pre-tests were performed in the week preceding the breathing program in the late morning not earlier than 2 h after breakfast. No intense physical activity was permitted during 3 days prior to the tests. Venous blood samples were taken before exercise testing. Resting respiratory and cardiovascular parameters were measured during a 5-min period in a sitting position on the cycle ergometer (Ergoline 900, Schiller, Switzerland). The starting workload was 0.5 W/kg body mass, which was increased by 0.5 W/kg every 3 min until subjects were unable to continue because of fatigue or dyspnoea. The following criteria for termination were ap-

Table 2
The 3-week breathing program

Hypoxia Group									
Days 1–5									
Duration of breathing periods (min)	3	3	3	3	3				
Fraction of oxygen (%)	14	21	14	21	14				
Days 8–12									
Duration of breathing periods (min)	4	3	4	3	4	3	4		
Fraction of oxygen (%)	12	21	12	21	12	21	12		
Days 15–19									
Duration of breathing periods (min)	5	3	5	3	5	3	5	3	5
Fraction of oxygen (%)	10	21	10	21	10	21	10	21	10

Control Group

Performed the same program breathing only normoxic air (21% of inspired oxygen fraction).

plied: angina, signs of cerebral or peripheral hypoperfusion (pallor, cyanosis, faintness, nausea), horizontal or downsloping ST-segment depression >2 mV, ST-segment elevation >2 mV (except in dyskinetic segments after infarction), onset of second- or third-degree AV block, ventricular extrasystoles >Lown 4b, complex supraventricular arrhythmias, increase in blood pressure >230 mm Hg systolic or 120 mm Hg diastolic, decrease in systolic blood pressure below the baseline value or no increase in heart rate.

Gas exchange was measured by an open spirometric system (Oxycon Alpha, Jaeger, Germany). A six-lead electrocardiogram and arterial oxygen saturation (by finger pulseoximetry) were recorded continuously. Blood lactate concentrations from the hyperaemized ear lobe, systolic blood pressure, and ratings of perceived intensity of exertion according to the "Borg scale" [18] were determined at the end of each workload.

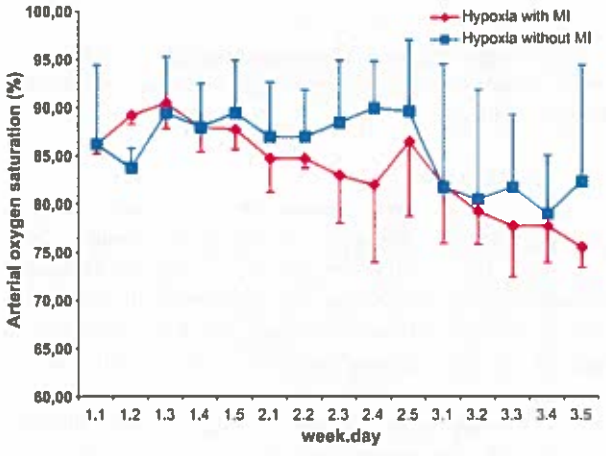


Fig. 1. Arterial oxygen saturation during the last hypoxic period of each day in subjects with ($n=4$) and without ($n=4$) prior myocardial infarction (MI) of the hypoxia group. Data represent means (SD).

Table 3
Haematological parameters of the hypoxia and the control group before and after the 3 week breathing program

	Hypoxia group ($n=8$)		Control group ($n=8$)		p-value
	Before	After	Before	After	
RBC (10^6/ml)	4.89 (0.24)	5.08 (0.19)	4.94 (0.41)	4.77 (0.41)	0.02
Hb (g/dl)	14.4 (0.8)	15.0 (0.7)	14.6 (0.9)	14.6 (1.0)	0.04
Hct (%)	44.1 (2.5)	44.3 (3.0)	45.0 (4.1)	43.8 (3.8)	0.38
MCV (fl)	90.3 (2.6)	87.3 (6.5)	91.2 (4.9)	92.0 (4.8)	0.22
MCH (pg)	29.4 (0.9)	29.5 (1.6)	29.6 (1.8)	30.7 (1.3)	0.73
MCHC (g/dl)	32.6 (1.0)	33.9 (1.1)	32.5 (2.1)	33.4 (1.6)	0.59

Data represent means (SD). p-values for differences in changes between groups.
Abbreviations: Red Blood Cell Count (RBC), Haemoglobin (Hb), Haematocrit (Hct), Mean Cell Volume (MCV), Mean Cell Haemoglobin (MCH), Mean Cell Haemoglobin Concentration (MCHC).

2.2.2. Breathing program

After completion of the pre-tests, the 3-week breathing program (Table 2), consisting of five session per week, took place. For the hypoxia group, each session consisted of three to five hypoxic (14–10% inspired fraction of oxygen; HypoxyComplex HypO2, HypoMed, Moscow) periods, each lasting 3–5 min with 3-min normoxic intervals. Hypoxic and normoxic air was inhaled via face mask in a sitting position. The control group performed the program (inhaling only normoxic air) in the same way. The breathing protocol was adapted to that proposed by the Clinical Research Laboratory of the Hypoxia Medical Academy in

Table 4
Cardiovascular and ventilatory responses to sub-maximal exercise (1 W/kg) of the hypoxia and the control group before and after the 3-week breathing program

	Hypoxia group ($n=8$)		Control group ($n=8$)		p-value
	Before	After	Before	After	
Heart rate (bpm)	112 (18.5)	103 (16.9)	96 (11.9)	94 (11.3)	0.03
Systolic blood pressure (mm Hg)	165 (36.9)	156 (33.3)	163 (16.9)	164 (11.0)	0.02
Rate pressure product	18,986 (6593)	16,380 (5419)	15,746 (3033)	15,443 (2386)	0.02
Oxygen consumption (ml/min/kg)	15.6 (1.3)	15.4 (1.4)	16.2 (0.7)	15.5 (1.2)	0.35
Respiratory exchange ratio	0.84 (0.08)	0.85 (0.07)	0.83 (0.07)	0.82 (0.06)	0.60
Minute ventilation (l/min)	35.8 (7.6)	36.6 (7.2)	35.7 (3.5)	32.8 (2.9)	0.06
Arterial oxygen saturation (%)	95.4 (1.4)	97.0 (0.9)	96.8 (1.3)	97.0 (1.3)	<0.01
Arterial oxygen content (ml/l)	186.3 (11.0)	197.6 (10.3)	191.8 (11.1)	192.4 (13.8)	<0.01
Blood lactate concentration (mmol/l)	2.8 (0.6)	2.3 (0.5)	2.3 (0.5)	2.4 (0.6)	<0.01
Perceived exertion	12.4 (1.2)	11.0 (1.2)	11.6 (1.2)	11.8 (1.3)	<0.01

Data represent means (SD). p-values for differences in changes between groups.

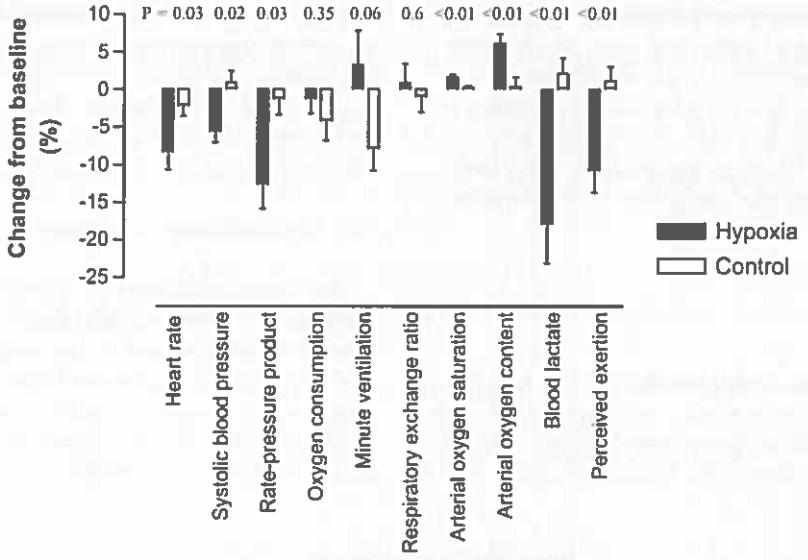


Fig. 2. Changes (in percentages) from baseline of cardiorespiratory responses at sub-maximal workload (1 W/kg) after the 3-week breathing program of the hypoxia ($n=8$) and the control group ($n=8$). Data represent means (SEM). p-values for differences in changes between groups.

Moscow [7]. The breathing program was carried out at the Department of Sports Science (Medical Section) of the University Innsbruck and the entire program was under the supervision of two physicians. Start and termination of breathing periods were announced and controlled by instructors. Arterial oxygen saturation and heart rate were monitored continuously by a pulseoximeter attached to a finger tip, which, however, was invisible for the study subjects themselves. Incremental spiro-ergometric tests were repeated 3 days after completion of the breathing program in the same way as the pre-tests.

Table 5
Cardiovascular and ventilatory responses at maximal exercise of the hypoxia and the control group before and after the 3-week breathing program

	Hypoxia group ($n=8$)		Control group ($n=8$)		p-value
	Before	After	Before	After	
Exercise time (min)	9.3 (2.4)	9.7 (2.5)	10.6 (2.6)	10.7 (2.7)	0.40
Workload (W)	189 (57.1)	209 (53.6)	224 (53.7)	224 (56.7)	0.07
Heart rate (bpm)	162 (16.5)	162 (12.1)	147 (15.5)	146 (16.2)	0.71
Systolic blood pressure (mm Hg)	213 (36.2)	211 (24.5)	218 (32.1)	218 (39.6)	0.73
Rate pressure product	34,661 (7939)	33,994 (4399)	32,161 (7037)	31,961 (8576)	0.78
Oxygen consumption (ml/min)	2330 (586)	2475 (546)	2813 (747)	2729 (765)	<0.001
Minute ventilation (l/min)	88.0 (14.5)	102.3 (13.3)	100.1 (19.7)	102.2 (22.8)	0.03
Arterial oxygen saturation (%)	94.9 (1.9)	96.6 (1.3)	94.5 (1.2)	94.9 (0.6)	<0.01
Arterial oxygen content (ml/l)	185.3 (10.6)	196.8 (9.6)	187.2 (9.6)	188.2 (13.2)	<0.01
Blood lactate (mmol/l)	8.4 (1.8)	6.6 (2.0)	7.8 (1.5)	7.3 (1.8)	0.04

Data represent means (SD). p-values for differences in changes between groups.

2.3. Statistics

The calculated power of the study, based on the observations of our recent study [5] for the chosen sample size, amounted to 85% (Alpha = 0.05). Data are presented as means (SD or SEM) or frequencies as appropriate. Differences in haematological changes and

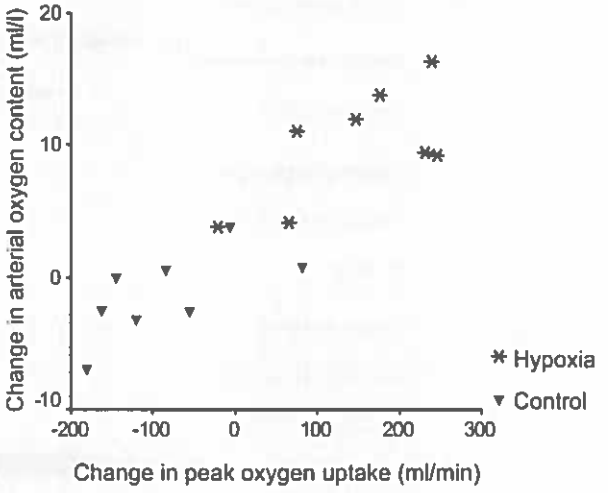


Fig. 3. Relationship between the changes in peak oxygen consumption and the arterial oxygen content in the hypoxia and control group after the 3-week breathing program. $R^2=0.8$, $p<0.001$.

changes in cardiorespiratory and metabolic responses to exercise between groups were evaluated by repeated-measures ANOVA. Correlation analyses (Pearson) were applied to examine the relation between two continuous variables. A p-value of less than 0.05 (two-tailed) was considered to indicate statistical significance. Data analyses were conducted with the use of the SPSS statistical-software package.

3. Results

All study participants completed the 3-week breathing program. Intermittent hypoxia was well tolerated by the elderly with and without coronary artery disease. Inhaling hypoxic air resulted in slightly lower arterial oxygen saturation in subjects with prior myocardial infarction (Fig. 1). ECG recordings, performed when arterial oxygen saturation fell below 85% for the first time, did not reveal any ST-segment or T-wave changes. Besides dizziness and sleepiness during the breathing sessions (in the hypoxia and the placebo group as well), no side effects occurred.

3.1. Haematological parameters

Red blood cell count (+3.9%) and haemoglobin concentration (+4.2%) increased during 3 weeks of intermittent hypoxia when compared to the control group (−3.4% and 0.0%) ($p=0.02$ and $p=0.04$) (Table 3). Changes regarding haematocrite, mean cell volume, mean cell haemoglobin and mean cell haemoglobin concentration during the 3 weeks did not differ between groups.

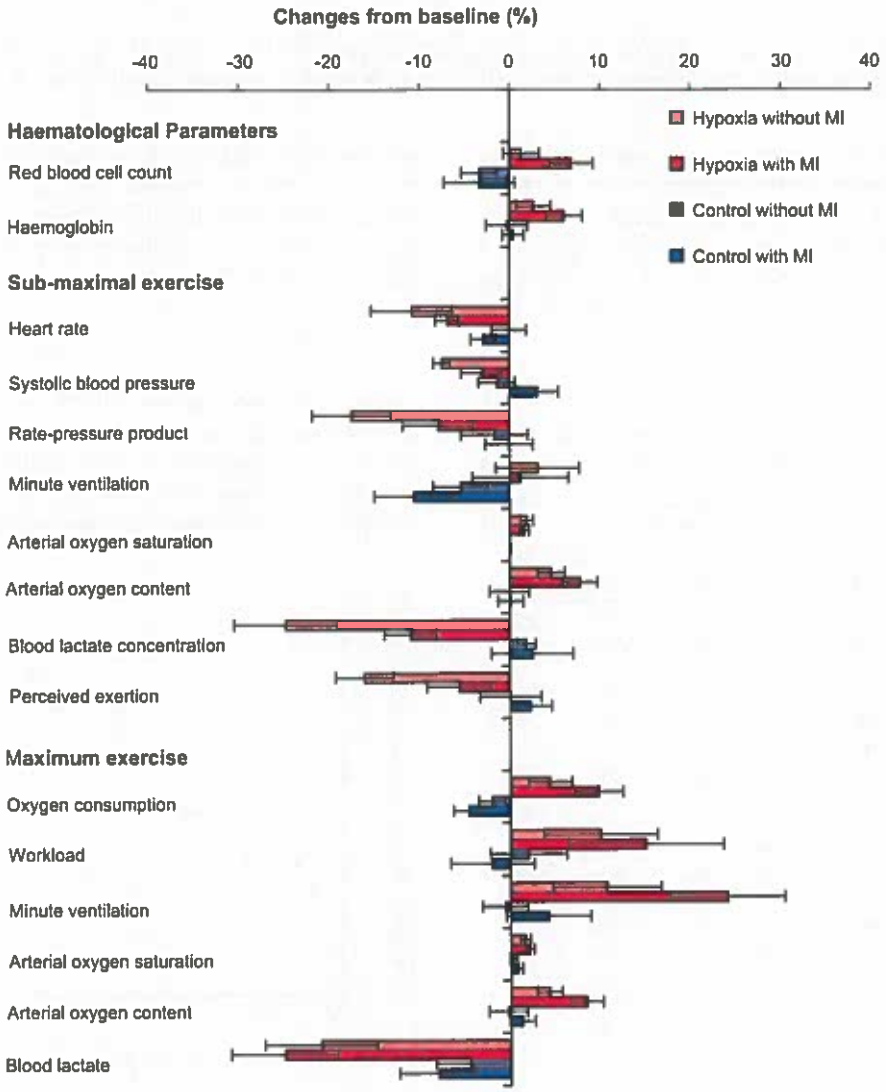


Fig. 4. Changes (in percentages) from baseline for sub-groups with ($n=4$) and without ($n=4$) prior myocardial infarction (MI) of the hypoxia and the control group. All variables with p-values <0.1 for differences in changes between the hypoxia and the control group are shown. Data represent means (SEM).

3.2. Sub-maximal exercise

Sub-maximal exercise responses were clearly influenced by 3 weeks of intermittent hypoxia (Table 4, Fig. 2). The mean values of heart rate (−8.3%), systolic blood pressure (−5.5%), rate pressure product (−13.7%), blood lactate concentration (−17.9%) and rate of perceived exertion (−11.3%) were diminished at the workload of 1 watt/kg in subjects who were exposed to intermittent hypoxia when compared to the control group (heart rate: −2.4%, systolic blood pressure: +0.6%, rate pressure product: −1.9%, blood lactate: +4.3%, rate of perceived exertion: +1.7%) (all $p<0.05$). Arterial oxygen saturation (+1.7%) and arterial oxygen content (=exercising arterial oxygen saturation times resting haemoglobin concentration times 1.36) (+6.1%) were increased after intermittent hypoxia compared to controls (+0.4%, +0.3%) ($p<0.01$). Correlation analyses revealed a significant relation between the heart-rate decrease and the arterial oxygen-content increase after intermittent hypoxia ($r=-0.7$, $p<0.05$).

3.3. Maximum exercise

None of the exercise tests (pre- and re-tests) had to be terminated prematurely because of ischaemic events, severe arrhythmias or high blood pressure values. General fatigue, leg pain and dyspnoea were the reasons for termination of exercise testing. Dyspnoea was the cause of exercise termination in three subjects of the hypoxia group and two of the control group during the pre-tests and in none of the hypoxia group and again in two of the control group at the re-tests. Changes in exercise responses at peak workload after the 3-week breathing program are shown in Table 5. Whereas the peak workload (+10.6%) tended to be enhanced after 3 weeks of intermittent hypoxia compared to the control group (0.0%) ($p=0.07$) peak oxygen uptake had also increased (+6.2% vs. −3.0%) ($p<0.001$). Additionally, minute ventilation (+16.3%), arterial oxygen saturation (+1.8%) and arterial oxygen content (+6.2%) at the peak workload had increased compared to control conditions (minute ventilation: +1.1%, arterial oxygen saturation: +0.4%, arterial oxygen content: +0.5%) (all $p<0.05$). Maximal blood lactate concentration (−21.4%) remained lower in the hypoxia group when compared to the control group (−6.4%) ($p=0.04$). Correlation analyses revealed a close relationship between the changes in peak oxygen consumption and those in arterial oxygen content after hypoxia ($r=0.9$, $p<0.01$) (Fig. 3). Besides, less oxygen desaturation during exercise after intermittent hypoxia was related to increased minute ventilation ($r=-0.8$, $p<0.05$).

3.4. Responses of sub-groups

For variables with a p-value <0.1 for differences in changes between the hypoxia and the control group, changes from baseline are shown separately for subjects with and without prior myocardial infarction (Fig. 4). Because of the small sub-sample sizes we did not statistically evaluate differences between sub-groups. It can be seen clearly that each of the two sub-groups responded in a similar fashion to hypoxia or placebo. Nevertheless, a tendency towards more pronounced changes with regard to haematological parameters and responses to maximum exercise after hypoxia could be observed in subjects with prior myocardial infarction. Changes with regard to responses to sub-maximal exercise tended to be less pronounced in these subjects, particularly in those taking beta-blockers.

4. Discussion

4.1. Haematological parameters

The 3-week intermittent hypoxia effected a small but significant increase in red blood cell count and haemoglobin concentrations, indicating improved oxygen-carrying capacity. These results may be surprising because single hypoxic exposures up to 60 min were shown not to stimulate erythropoietin production [19]. On the other hand, Gulyaeva et al. demonstrated that the erythropoietin response also depends on the repetition of hypoxic exposure [20]. Using a similar intermittent hypoxia protocol as we did, they found a marked erythropoietin response after the 4th hypoxic session. Applying a similar protocol for 2 weeks also Bernardi et al. reported haematological changes comparable to those of the presented study [21]. The fact that haematocrite did not increase with haemoglobin concentration may be considered as a favourable effect that avoids an increase of blood viscosity. The slightly increased hypoxic stimulus in subjects with prior myocardial infarction (Fig. 1) could well explain the tendency of an enhanced erythropoietic response observed in this sub-group (Fig. 4).

4.2. Sub-maximal exercise

Responses to sub-maximal exercise after 3 weeks of intermittent hypoxia are characterized by diminished values of heart rate, systolic blood pressure, blood lactate and rate of perceived exertion and increases in arterial oxygen saturation and arterial oxygen content. Minute ventilation and oxygen uptake at the workload of 1 W/kg did not change. Because of the close relationship between arterial systemic oxygen delivery (arterial oxygen content times cardiac output) and oxygen uptake, limb blood flow and cardiac output will decline when arterial oxygen content rises at the same oxygen uptake [22,23]. Thus, the decreased exercising heart rate after intermittent hypoxia could well be explained by the increased arterial oxygen content as indicated by the relation between the heart rate decrease and arterial oxygen content increase after intermittent hypoxia.

The reduction in heart rate dependent on the arterial oxygen content may be mediated by a decline in the relative sympathetic tone. Both the reduced vagal withdrawal and decreased sensitivity of beta-adrenoceptors were reported after intermittent hypoxia [21,24]. These effects seem to be less marked in subjects with prior myocardial infarction, especially in those taking beta-blockers. Reduced heart rate and also systolic blood pressure values caused lower rate pressure products after intermittent hypoxia at similar sub-maximal workloads, indicating a decrease in myocardial oxygen consumption [25]. Because both the healthy and the diseased showed similar changes after intermittent hypoxia, and furthermore, maximum systolic blood pressure did not change, a negative adaptation, secondary to compromised left-ventricular function or decreased myocardial blood flow in patients with coronary artery disease, is unlikely.

Because the rate of lactate appearance in the blood was shown to be closely correlated to sympatho-adrenergic activity in normoxia and hypoxia [26–28], lower blood lactate levels after intermittent hypoxia may be partly attributed to a lesser beta-adrenergic stimulation of glycogenolysis [29,30]. Although the mechanisms of adaptation remain speculative, all these changes observed after intermittent hypoxia indicate improved aerobic capacity and tolerance to sub-maximal exercise. This is also supported by the fact of the lower rate of perceived exertion after intermittent hypoxia. These results are comparable with those shown after more prolonged daily hypobaric hypoxia (3–5 h/day for 17 days), suggesting that shorter total hypoxic exposures effect similar adaptations when applied progressively in alternating hypoxic and normoxic intervals [3].

4.3. Maximum exercise

Peak oxygen uptake increased after intermittent hypoxia accompanied by a rise of the haemoglobin concentration and maximal minute ventilation with lower arterial oxygen desaturation during exercise. The peak workload, however, showed only a tendency to increase. Enhanced oxygen consumption by both respiratory and leg muscles may have contributed to the improvement of peak oxygen uptake [31]. Peak oxygen consumption incline was repeatedly shown to be due to increases in arterial oxygen content by raising the haemoglobin concentration and/or preventing arterial oxygen desaturation [32–35]. In fact, correlation analyses between the observed changes in peak oxygen uptake and arterial oxygen content after intermittent hypoxia revealed an excellent fit (Fig. 3). Thus, 81% of the variation in changes of the peak oxygen uptake can be explained by the changes in the arterial oxygen content. The higher haemoglobin concentration may result from the hypoxia-related stimulation of erythropoiesis [20]. Thus, the slightly lower arterial oxygen saturation during intermittent hypoxia may have been responsible for the somewhat higher haemoglobin concentration and accompanying peak oxygen consumption in the sub-group with prior myocardial infarction. The diminished arterial oxygen desaturation during exercise is closely related to the increased ventilation after intermittent hypoxia as also demonstrated in previous studies [36]. Despite the higher peak workloads heart rate, systolic blood pressure and the rate pressure product did not change, indicating slower inclines of these parameters with workload. An even diminished maximum rate pressure product despite higher workloads was reported in healthy men after intermittent hypoxia with exercise [12]. The authors considered a hypoxia-related positive adaptation with potentially cardio-protective implications. The question remains whether exercise under hypoxic conditions would be more effectively than passive hypoxia. It is interesting to note that maximal blood lactate concentrations remained lower despite the somewhat higher peak workloads. This phenomenon, described as the lactate paradox, is known to occur after acclimatization to hypoxia [37]. Although re-tests were performed only 3 days after terminating the breathing program our previous study indicate that the hypoxia-related adaptations may be preserved for about 1 month without repeating hypoxic exposures [5].

In conclusion, aerobic capacity and exercise tolerance had increased after 3 weeks of passive intermittent hypoxia. The perceived rating of exertion, blood lactate accumulation and myocardial oxygen consumption, as indicated by the diminished rate-pressure product, were reduced during sub-maximal exercise, and peak oxygen uptake had increased after intermittent hypoxia. These changes in aerobic capacity and responses to exercise seem to be closely related to the hypoxia-induced rise in the arterial oxygen content and the consequently reduced sympathetic activation by exercise stress. Thus, intermittent hypoxia may be a valuable and safe tool to increase aerobic capacity and exercise tolerance in elderly men with and without coronary artery disease.

References

[1] Neubauer JA. Physiological and pathophysiological responses to intermittent hypoxia. J Appl Physiol 2001;90:1593–9.
[2] Casas M, Casas H, Pages T, et al. Intermittent hypobaric hypoxia induces altitude acclimation and improves the lactate threshold. Aviat Space Environ Med 2000;71:125–30.
[3] Rodriguez FA, Casas H, Casas M, et al. Intermittent hypobaric hypoxia stimulates erythropoiesis and improves aerobic capacity. Med Sci Sports Exerc 1999;31:264–8.
[4] Zhuang J, Zhou Z. Protective effects of intermittent hypoxic adaptation on myocardium and its mechanisms. Biol Signals Recept 1999; 8:316–22.
[5] Burtscher M, Tsvetkova AM, Tkatchouk EN, et al. Beneficial effects of short term hypopxia. Hypoxia into the Next Millennium. In: Roach RC, Wagner PD, Hackett PH, editors. Advances in Experimental Medicine and Biology, vol. 474; 1999. p. 371–2.
[6] Aleshin IA, Tinkov AN, Kots YI, et al. Treatment of cardiovascular diseases by means of adaptation to periodic hypoxia in pressure chamber. Ter Arkh 1997;69:54–8.
[7] Tkatchouk EN, Gorbatchenkov AA, Kolchinskaya AZ, et al. Adapta-

tion to interval hypoxia with the purpose of prophylaxis and treatment. Hypoxia Med J 1994;11:308–28.
[8] Banasiaka KJ, Xiab Y, Haddad GG. Mechanisms underlying hypoxia-induced neuronal apoptosis. Prog Neurobiol 2000;62:215–49.
[9] Meerson F, Pozharov V, Minyailenko T. Superresistance against hypoxia after preliminary adaptation to repeated stress. J Appl Physiol 1994;76:1856–61.
[10] Meerson FZ, Malyshev YI, Zamotrinsky AV. Differences in adaptive stabilisation of structures in response to stress and hypoxia relate with the accumulation of hsp70 isoforms. Mol Cell Biochem 1992;111:87–95.
[11] Bisgard GE, Neubauer JA. Peripheral and central effects of hypoxia on the control of ventilation. In: Dempsey JA, Pack A, editors. Regulation of Breathing. 2nd ed. New York, NY: Marcel Dekker; 1995. p. 617–68.
[12] Bailey DM, Davies B, Baker J. Training in hypoxia: modulation of metabolic and cardiovascular risk factors in men. Med Sci Sports Exerc 2000;32:1058–66.
[13] Clanton TL, Klawitter PF. Adaptive responses of skeletal muscle to intermittent hypoxia: the known and the unknown. J Appl Physiol 2001;90:2476–87.
[14] Gordon DJ, Ekelund LG, Karon JM, et al. Predictive value of the exercise tolerance test for mortality in North American men: the lipid research clinics mortality follow-up study. Circulation 1986;74:252–61.
[15] Bijnen FC, Feskens EJ, Caspersen CJ, et al. Baseline and previous physical activity in relation to mortality in elderly men: the Zutphen elderly study. Am J Epidemiol 1999;150:1289–96.
[16] Meerson FZ, Ustinova EE, Orlova EH. Prevention and elimination of heart arrhythmias by adaptation to intermittent high altitude hypoxia. Clin Cardiol 1987;10:783–9.
[17] Ustinova EE, Saltykova VA, Didenko VV, et al. Effect of adaptations to periodic and continuous hypoxia in disorders of electrical stability of the heart in postinfarction cardiosclerosis. Bull Exp Biol Med 1988;105:533–5.
[18] Borg G. Psychophysical bases of perceived exertion. Med Sci Sports Exerc 1982;14:377–81.
[19] Knaupp W, Khilnani S, Sherwood J, et al. Erythropoietin response to acute normobaric hypoxia in humans. J Appl Physiol 1992;73:837–40.
[20] Gulyaeva NV, Tkatchouk EN. Effects of normobaric hypoxic training on immunoreactive erythropoietin and transferrin levels in blood serum of healthy volunteers. Hypoxia Med J 1998;6:13–7.
[21] Bernardi L, Passino C, Serebrovskaya Z, et al. Respiratory and cardiovascular adaptations to progressive hypoxia. Effect of interval hypoxic training. Eur Heart J 2000;22:879–87.
[22] Ferretti G, Kayser B, Schena F, et al. Regulation of perfusive O_2 transport during exercise in humans: effects of changes in haemoglobin concentration. J Physiol 1992;455:679–88.
[23] Roach RC, Koskolou M, Calbert J, et al. Arterial O_2 content and tension in regulation of cardiac output and leg blood flow during exercise in humans. Am J Physiol 1999;276:H438–45.
[24] Meerson FZ, Kopylov IN, Baldenkov GN. Increase of alpha 1-adrenoreactivity of the rat heart in adaptation to periodic hypoxia. Bull Exp Biol Med 1991;111:570–2.
[25] Raven PB, Potts JT. Cardiovascular responses to exercise and training. In: Harries M, Williams C, Stanish WD, et al, editors. Oxford Textbook of Sports Medicine. Oxford: University Press; 1998. p. 32–45.
[26] Mazzeo RS, Bender PR, Brooks GA, et al. Arterial catecholamine response during exercise with acute and chronic high altitude exposure. Am J Physiol 1991;261:E419–24.
[27] Reeves JT, Wolfel EE, Green HJ, et al. Oxygen transport during exercise at altitude and the lactate paradox: lessons from operation Everest II and Pikes peak. Exerc Sport Sci Rev 1992;20:275–96.
[28] Brooks GA, Wolfel EE, Groves BM, et al. Muscle accounts for glucose disposal but not blood lactate appearance during exercise after acclimatization to 4.300 m. J Appl Physiol 1992;72:2435–45.
[29] Green H, Sutton J, Wolfel E, et al. Altitude acclimatization and energy metabolic adaptations in skeletal muscle during exercise. J Appl Physiol 1992;73:2701–8.
[30] Brooks GA, Butterfield GE, Wolfe RR, et al. Decreased reliance on lactate during exercise after acclimatization to 4.300 m. J Appl Physiol 1991;71:333–41.
[31] Harms CA, Dempsey JA. Cardiovascular consequences of exercise hyperpnea. Exerc Sport Sci Rev 1999;27:37–62.
[32] Ekblom B, Goldberg A, Gullbring B. Response to exercise after blood loss and reinfusion. J Appl Physiol 1972;33:175–80.
[33] Thomson JM, Stone JA, Girsburg A, et al. O_2 transport during exercise following blood reinfusion. J Appl Physiol 1982;53:1213–9.
[34] Knight DR, Schaffartzik W, Poole DC, et al. Effects of hyperoxia on maximal leg O_2 supply and utilisation in man. J Appl Physiol 1993;75:2586–94.
[35] Harms CA, McClaran SR, Nickele GA, et al. Exercise-induced arterial hypoxaemia in healthy young women. J Physiol 1998;507(2):619–28.
[36] Ricart A, Casas H, Casas M, Pages T, et al. Acclimatization near home? Early respiratory changes after short-term intermittent exposure to simulated altitude. Wilderness Environ Med 2000;11:84–8.
[37] Hochachka PW. The lactate paradox: analysis of underlying mechanisms. Ann Sports Med 1989;11:184–8.

Doppel verblindete randomisierte Placebo kontrollierte Studie

ELSEVIER

CrossMark

Alzheimer's & Dementia: Translational Research & Clinical Interventions 3 (2017) 114-122

Alzheimer's & Dementia

Featured Article

Intermittent hypoxic–hyperoxic training on cognitive performance in geriatric patients

Urike Bayer[a], Rudolf Likar[b], Georg Pinter[a], Haro Stettner[c], Susanne Demschar[b], Brigitte Trummer[b], Stefan Neuwersch[b], Oleg Glazachev[d], Martin Burtscher[e,*]

[a]Department of Geriatrics, Klinikum Klagenfurt, Klagenfurt, Austria
[b]Department of Anesthesiology and Intensive Care Medicine, Klinikum Klagenfurt, Klagenfurt, Austria
[c]Department of Statistics, Alpen-Adria University Klagenfurt, Klagenfurt, Austria
[d]Research Centre, I.M. Sechenov First Moscow State Medical University, Moscow, Russia
[e]Department of Sport Science, Medical Section, University of Innsbruck, Innsbruck, Austria

Abstract

Introduction: Intermittent hypoxic–hyperoxic training (IHHT) may complement a multimodal training intervention (MTI) for improving cognitive function and exercise tolerance in geriatric patients.

Methods: Thirty-four patients (64–92 years) participated in this randomized controlled trial. Before and after the 5- to 7-week intervention period (MTI + IHHT vs. MTI + ambient air), cognitive function was assessed by the Dementia-Detection Test (DemTect) and the Sunderland Clock-Drawing Test (CDT), and functional exercise capacity by the total distance of the 6-Minute Walk Test (6MWT).

Results: DemTect and CDT indicated significantly larger improvements after MTI + IHHT (+16.7% vs. −0.39%, $P < .001$) and (+10.7% vs. −8%, $P = .031$) which was also true for the 6MWT (+24.1% vs. +10.8%, $P = .021$).

Discussion: IHHT turned out to be easily applicable to and well tolerated by geriatric patients up to 92 years. IHHT contributed significantly to improvements in cognitive function and functional exercise capacity in geriatric patients performing MTI.

Keywords: Intermittent hypoxia; Geriatric patients; Cognitive performance; Dementia; Exercise tolerance; Multimodal training

1. Introduction

As a consequence of the steadily growing life expectancy, the number of people suffering from cognitive dysfunction is increasing steeply. Not surprisingly, more and more anti-dementia drugs, such as memantine and cholinesterase inhibitors, have been developed. However, beneficial effects seem to be rather small in relation to the potential adverse effects of pharmacological therapy [1–3].

In contrast, several clinical trials report on the positive consequences of short-term interventions with physical activity for cognitive function in old people [4–6]. The meta-analyses performed by Colcombe and Kramer demonstrated that a multimodal training intervention (MTI), which includes cardiovascular fitness training combined with strength training, showed larger improvements than aerobic training alone [7].

Nevertheless, there is still a great demand for new strategies for the prevention and treatment of dementia. Recently, it would seem that intermittent hypoxic training (IHT) may represent such a strategy. IHT represents a noninvasive, easily applicable method based on repeated resting exposures to an oxygen-deficient gas mixture interspersed by

*Corresponding author. Tel.: +43 (0)512 507 45896; Fax: +43 (0)512 507 2656.
E-mail address: martin.burtscher@uibk.ac.at

http://dx.doi.org/10.1016/j.trci.2017.01.002

normoxic periods [8]. In contrast to moderate hypoxia, exposure to severe hypoxia, that is, 5% O_2, was found to have deleterious consequences in Wistar rats [9]. Also, obstructive sleep apnea with brief and frequently recurrent cycles of hypoxia is well known to be associated with systemic hypertension, stroke, and adverse cardiac events [10]. In addition, chronic hypoxia was shown to have hazardous effects on organ structure and function, may provoke cerebral and myocardial ischemia, and plays a crucial role in regulating tumor growth and metastasis [11]. Short intermittent intervals of moderate hypoxia, however, that is, 12% O_2, cause moderate stress followed by beneficial adaptations [12]. IHT may provoke beneficial effects by preconditioning subsequently protecting the heart and/or the brain against deleterious consequences of ischemia reperfusion [13]. Although the excessive production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) represents an important mechanism of cell damage during hypoxia and reoxygenation in mitochondria initiating cellular death pathways, IHT may optimize mitochondrial metabolism, thus preventing adverse consequences of excess mitochondrial ROS generation [14,15]. In addition, IHT stimulates endothelial nitric oxide (NO) production that leads to vasodilatation, opens reserve capillaries [16], and induces the production of vascular endothelial and fibroblast growth factors to stimulate endothelial proliferation [17]. In clinical research, Burtscher et al. and Katayama et al. showed that hypoxic training improved exercise tolerance in patients suffering from chronic diseases such as cardiovascular disease, chronic obstructive pulmonary disease (COPD) or metabolic diseases [18–20]. There is also evidence that IHT may protect against neurodegenerative changes and even increase cognitive functions in experimental Alzheimer's disease in rats [21]. To our knowledge, Schega et al. were the first to investigate the positive effects of IHT on cognitive function in elderly subjects aged between 60 and 70 years [22].

Very recently, a modified IHT mode, intermittent hypoxic–hyperoxic training (IHHT), has been proposed as being associated with even more beneficial effects than IHT. The normoxic periods are replaced by moderate hyperoxic periods with 30%–40% oxygen resulting in a faster recovery of oxygen desaturation [23]. The hypoxic–hyperoxic treatment has been claimed to be more effective and produces a faster membrane-stabilizing effect in cells of the heart, liver, and brain compared to IHT in a study with male Wistar rats [24]. A very recent study reported that IHHT improved exercise performance in athletes with overtraining syndrome [25]. The case study of Susta et al. reported a significant improvement of cardiopulmonary efficiency and lactate removal after 3 weeks of daily IHHT [26]. Glazachev showed that IHHT can even improve exercise tolerance, aerobic capacity, and cardiometabolic profile in patients with stages II–III of the New York Heart Association (NYHA II–III) without any additional exercise [27]. None of these studies reported adverse side effects.

Thus, we hypothesized that IHHT performed in parallel with an MTI would produce greater improvements of exercise tolerance and cognitive function in geriatric patients than an MTI alone. The aim of the present study was to evaluate the applicability of IHHT in patients attending in an MTI in a geriatric daily clinic and to investigate its effects on exercise tolerance and cognitive function.

2. Methods

2.1. Participants and randomization

Geriatric patients between 60 and 100 years, who attended in the multimodal training program of the Geriatric Daily Clinic in Klagenfurt (Carinthia, Austria), were invited to participate in this double-blind, randomized, stratified, and placebo-controlled study. Finally, 41 patients between 64 and 92 years participated in the study. The double-blinded study setting was ensured by the fact that neither patients nor therapists were aware about the type of breathing program. All volunteers underwent a routine physical examination. Subjects were not included if they were not able to walk without any staff assistance or suffered from severe dementia with a score of Mini–Mental State Examination (MMSE) less than 12 points, uncontrolled hypertension (systolic blood pressure [BP] > 180 mm Hg and/or diastolic BP > 100 mm Hg), COPD III–IV, decompensated heart failure (NYHA III–IV), or previous intracerebral bleeding. The first 41 patients meeting the inclusion criteria comprised the study population. After obtaining informed and written consent, study participants were assessed by the MMSE which is a practical test for grading the cognitive state of a patient [28]. Thereafter, participants were randomly assigned to either the hypoxia group (HG) or the normoxia group (NG). Subjects were stratified by age (60–80, 81–100 years), gender (male, female), and cognitive function (MMSE 12–21, 22–30 points). Finally, the data of 34 of the 41 included patients who successfully completed the whole study programme were taken for the outcome analysis as shown in Fig. 1.

All participants were advised not to change medications, nutrition, and physical activity during the whole study period; only single doses of emergency medication in cases of high blood pressure and pain attacks were accepted, as documented in the medical recordings of the Geriatric Day Clinic.

The study was approved by the local ethics committee and performed in accordance with the ethical standards of the Declaration of Helsinki in 1975.

2.2. Study protocol

2.2.1. Multimodal training intervention

All study participants were included in the same MTI of the Geriatric Day Hospital in Klagenfurt, Austria. The baseline characteristics of both groups are shown in Table 1. The whole therapy unit for all patients includes 15–20 days of

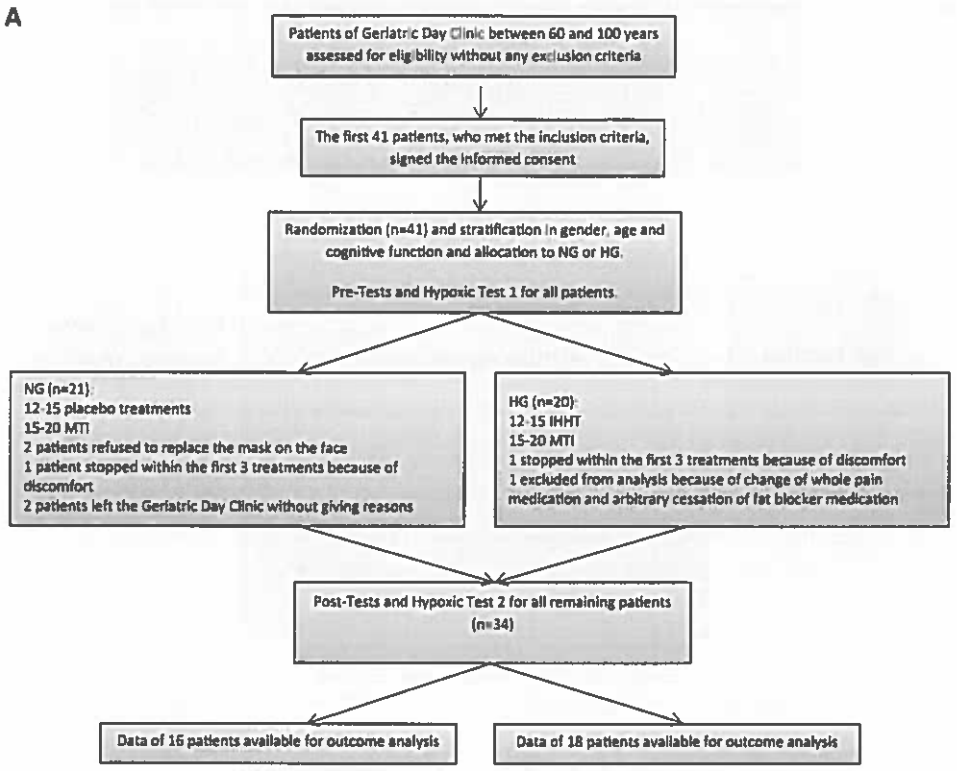


Fig. 1. (A) Process of inclusion, randomization, stratification, and (B) training program and outcome analysis. Abbreviations: 6MWT, 6-Minute Walk Test; CDT, Clock-Drawing Test; DemTect, Dementia-Detection Test; FiO_2, inspiratory oxygen fraction; IHHT, intermittent hypoxic–hyperoxic training; HG, hypoxic group; HT1, hypoxic test 1; HT2, hypoxic test 2; MMSE, Mini–Mental State Examination; NG, normoxic group; NRS, numeric rating scale for pain.

therapy, depending on the needs of each patient, with an individual treatment plan of 2–3 days of therapy per week over a period of 5–7 weeks (Fig. 1). All therapy units had been documented in the medical recordings of the hospital. Because of the holistic detection of sick people by a multiprofessional geriatric team, an optimal therapy concept with three focal points was created for each patient. The present study has been integrated into this therapy plan over a period of half a year.

The everyday MTI included physiotherapy, occupational therapy, and cycling. The daily 30-minute physiotherapy program consisted of individually tailored strength training on a leg press (3 × 20 repetitions), functional exercises, and a combination of balance and reaction training. Functional exercises were performed on a stepper and the combined balance and reaction training with the use of a computer-aided multifunction (MFT) Challenge Disc (MFT Bodyteamwork, Austria), Airex Balance-beam, and Airex Balance-pad-plus (AIREX, Switzerland). The occupational therapy focused for 60 minutes on the training of strength, flexibility, and coordination of fingers and arms using various devices complemented by cognitive training carried out on a one hand computer (RehaCom Cognitive Therapy Software; UK). The 20-minute cycling program was performed on the rehabilitation trainer MOTOmed viva 1 (RECK, Germany) in a sitting position with a pedaling rate between 28 and 32 at a very low to low resistance. A more effective cardiovascular fitness training on the cycle ergometer was not possible due to the high age and the multimorbidity of the patients. The heart rate of patients was controlled by a nurse and did not exceed 120 beats/minute during the whole cycling period.

2.2.2. *IHHT program*

Concurrent with the MTI, the IHHT using the ReOxy breathing therapy device (AI Mediq S.A., Luxembourg) was performed. This device delivers a gas mixture with an oxygen content of 10%–30% in nitrogen and continuously monitors arterial oxygen saturation (SpO_2) and pulse rate and stores all recorded data. Blood pressure was measured before and after every procedure. To establish an individually tailored IHHT, as recommended by the instructions of AI Mediq S.A., all patients had to take part in the same hypoxic test (HT1) which lasted for 5–10 minutes: all participants breathed a hypoxic gas mixture with low oxygen (12% O_2) (cf. 8, 18–20) through a face mask while sitting in an armchair for 5–10 minutes. SpO_2 and pulse rate were measured by a pulse oximeter, which was invisible to the patients. Following this, on each therapy day, HG patients underwent a repeated exposure to hypoxic gas mixtures

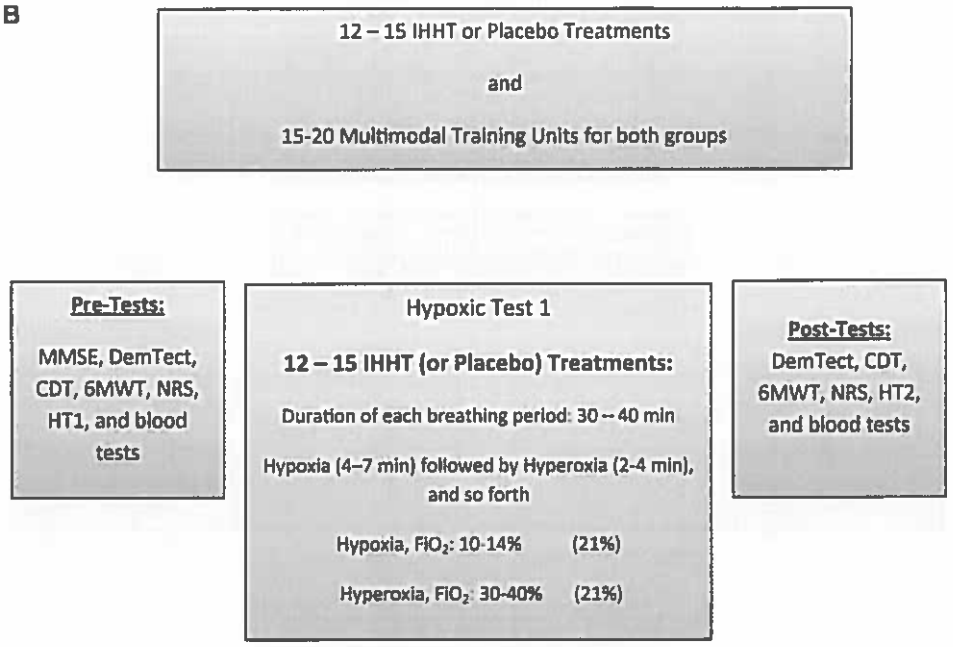


Fig. 1. (*continued*).

(10%–14% O_2) lasting 4–7 minutes, followed by a 2- to 4-minute exposure to a hyperoxic gas mixture (30%–40%) through the face mask (cf. 24–26). Each session lasted 30–40 minutes and included 4–8 hypoxia–hyperoxia cycles, depending on the individual responses and state of health. The therapy was constantly adjusted by the ReOxy breathing therapy device to the individually measured values of oxygen saturation and pulse rate in HT1. Individual minimal SpO_2 and maximal pulse rate data in HT1 were used as preset key parameters to be installed into device software for further therapy sessions. While a patient is receiving the hypoxic gas mixture, SpO_2 and pulse rate are constantly monitored and transmitted to a monitoring device which compares the current value of SpO_2 with the preset value of the individual's minimum SpO_2. When reaching the minimum SpO_2, the hyperoxic gas mixture is supplied up to restoring baseline resting SpO_2, again followed by administering a hypoxic gas mixture [29].

After performing the same HT1, patients in the NG were exposed to the same breathing program as the HG but only breathing a normoxic gas mixture (placebo). Treatment differences were only visible to the two study nurses who provided the therapy and operated the devices. The study participants and the therapist were not informed about the kind of treatment provided.

During the whole stay in the geriatric daily clinic, 12–15 hypoxic or normoxic treatment procedures were performed for both groups 2–3 times a week over a period of 5–7 weeks, always together with the MTI on the same day (Fig. 1). At the end, both groups performed a second hypoxic test (HT2).

2.2.3. Assessments

For the purpose of stratification, all patients were assessed with the MMSE at the beginning of the study, before all treatments started. All other assessments, including the cognitive testing with the Dementia-Detection Test (DemTect) and the Sunderland Clock-Drawing Test (CDT), the evaluation of the functional exercise capacity with the 6-Minute Walk Test (6MWT), and the measurement of the pain situation with the numeric rating scale (NRS) were held at the beginning and at the end of all treatments and therapy units. The taking of blood samples was held in the same way, at the beginning and at the end (Fig. 1).

2.2.4. Cognitive testing

The DemTect is a highly sensitive screening instrument to identify patients with MCI and patients with dementia in early stages [30]. A cognitive screening by the DemTect is claimed to be more reliable than screening by the MMSE, and in particular, in the area of incipient and slightly more advanced cognitive disorders, the DemTect is far superior to the MMSE [31]. The CDT is also a valid and reliable screening test for dementia and cognitive impairment [32]. In our study, we used the free-drawn method.

2.2.5. Evaluation of functional exercise capacity and measurement of pain

The 6MWT was used to assess the functional exercise capacity of the study participants. It was carried out according to the guidelines for the 6-Minute Walk Test of

Table 1
Baseline characteristics of the hypoxic and normoxic groups

Variable	Hypoxic group (n = 18)	Normoxic group (n = 16)	P values
Gender (m, f)	m 5 (28%)/f 13 (72%)	m 2 (12.5%)/f 14 (87.5%)	.25**
Age (years)	80.9 (7.9)	83.4 (5.5)	.14
Height (cm)	163.7 (8.3)	163.2 (8.5)	.43
Weight (kg)	72.0 (9.3)	66.8 (12.3)	.09
BMI (kg/m^2)	27.0 (3.9)	25.0 (3.6)	.07
MMSE score	24.9 (3.8)	24.5 (3.9)	.36
Therapy days (n)	18.3 (2.4)	17.5 (2.6)	.16*
Systolic blood pressure (mm Hg)	137.2 (18.9)	134.6 (15.9)	.38
Diastolic blood pressure (mm Hg)	77.5 (6.9)	77.9 (8.7)	.42*
Oxygen saturation (%)	94.2 (6.2)	93.7 (7.5)	.42
Oxygen saturation, HT (%)	81.4 (2.8)	83.9 (5.5)	.27*
Total cholesterol (mg/dL)	231.2 (46.2)	215.9 (58.1)	.09*
Regular medication, n (%)			
Anticoagulants	9 (50)	10 (62.5)	.35**
β blockers	7 (38.9)	8 (50)	.38**
ACE inhibitors	7 (38.9)	6 (37.5)	.61**
AT II inhibitors	6 (33.3)	3 (18.8)	.29**
Calcium channel blockers	5 (27.8)	1 (6.3)	.12**
Statins	1 (5.6)	4 (25)	.13**
Diuretics	8 (44.4)	9 (56.3)	.37**
Nitrates	1 (5.6)	1 (6.3)	.73**

Abbreviations: BMI, body mass index; MMSE, Mini–Mental State Examination; HT, hypoxic test 1; SD, standard deviation.

NOTE. Data represent means (SD) or frequencies (%). P values for differences between groups are based on the use of the Welch test if values are normally distributed or on the use of the Mann–Whitney U test (*) if values are not normally distributed. **P values calculated by the Exact Fisher–Yates Test.

the American Thoracic Society [33]. We assessed pain with the 11-point NRS. It was shown to the study subjects with 0 representing "no pain" and 10 representing "pain as bad as you can imagine" [34].

2.3. Statistical methods

Data are presented as means and standard deviation or frequencies. The Kolmogorov–Smirnov test was used to test normal distribution of data. Correlation between variables and its significance was determined by the nonparametric Spearman rank correlation coefficient r_S. Frequencies were compared by the Fisher–Yates test (exact Fisher test). Significance of differences was tested by use of the Wilcoxon–Mann–Whitney (U) test and in the case of normally distributed data by the Welch test. A P value $\leq$.05 is considered to indicate statistical significance. Statistical evaluations were performed in R (version 2.7.0 resp. 3.2.3, 2015; The R Foundation for Statistical Computing, ISBN 3-900051-07-0, http://cran.r-project.org) and (elementary statistics and some figures) in HP-RPL (Version 2.08, 2006; Hewlett-Packard Company, San Diego, CA 92123, USA).

3. Results

Both the hypoxic and normoxic sessions were well tolerated. Aside from sleepiness and slight dizziness during the hypoxic treatments, absolutely no side effects were reported. Small gastrointestinal infections and minor infections of the upper respiratory tract occurred in both groups, but they all fully recovered within several days and all patients continued with the training interventions within a week. Mean values of minimum arterial oxygen saturation (measured by pulse oximetry) during the HTs are shown in Table 2.

3.1. Cognitive function

Testing of cognitive function by DemTect and CDT did not reveal any significant differences between groups before starting the intervention (Table 2). But after the IHHT combined with MTI, the HG showed a notable increase in cognitive function measured with the DemTect and the CDT. In contrast, no positive changes in the NG after the placebo treatments combined with MTI were detected. The score of the DemTect remained almost the same as that at the start and the score of the CDT even decreased slightly. There was a significant difference in cognitive function between the HG and NG groups regarding the CDT and the DemTect (Tables 2 and 3). The cause of missing values in these tests (one person in the DemTect and four persons in the CDT) was the inability of the patients to write and draw.

3.2. Functional exercise capacity and pain

The functional exercise capacity was measured by the total distance of the 6MWT. After the IHHT or placebo treatments combined with the MTI, both groups showed an increase in the total distance but in the HG, the increase was higher as depicted in Tables 2 and 3. Using the 11-point NRS for the evaluation of the pain situation, there was no statistically significant difference at the beginning between the HG and the NG. After all treatments, the pain situation improved in both groups but just failed to become statistically significant between groups (Tables 2 and 3).

A highly significant correlation was found between the changes of the distance of the 6MWT and the DemTect score and also between the 6MWT and the CDT (Fig. 2, Table 3). We also found a significant negative correlation between the differences of the NRS score and the DemTect score ($r = -0.35$, $P < .05$) and also between the NRS score and the CDT score ($r = -0.44$, $P < .05$) only for the overall group but not for the subgroups. Cognitive recovery did correlate neither with the subject's age nor with the degree of desaturation or the change of desaturation.

Table 2
Cognitive function, functional exercise capacity and pain assessment, cardiorespiratory and biochemical data before and after the intervention

Variable	Hypoxic group (n = 18)		Normoxic group (n = 16)		P values
	Pre	Post	Pre	Post	
DemTect	11.2 (3.5)	14.2 (3.7)	11.4 (4.1)	11.3 (3.6)	**<.001***
CDT	7.8 (3.0)	8.4 (3.0)	7.5 (2.3)	6.9 (2.6)	**.038***
6MWT (m)	234.3 (94.8)	290.7 (83.2)	250.6 (94.3)	277.7 (96.3)	**.045***
NRS	4.3 (2.4)	2.7 (1.9)	2.9 (2.7)	1.9 (2.0)	**.061***
Pulse rate (bpm)	66.5 (8.5)	66.1 (8.5)	73.5 (8.0)	67.8 (5.5)	**.076***
Systolic blood pressure (mm Hg)	136.4 (17.9)	132.5 (14.7)	134.6 (15.9)	129.5 (16.4)	.41
Diastolic blood pressure (mm Hg)	80.8 (18.3)	73.3 (5.9)	77.9 (8.7)	72.9 (6.7)	.36*
Oxygen saturation (%)	94.2 (6.2)	98.3 (1.2)	93.7 (7.5)	97.7 (1.8)	.36*
Oxygen saturation, HT (%)	81.4 (2.8)	87.1 (7.6)	83.9 (5.5)	85.8 (7.5)	.27
Total cholesterol (mg/dL)	231.2 (46.2)	220.6 (42.4)	215.9 (58.1)	213.1 (62.1)	**.08**
HDL (mg/dL)	59.2 (14.6)	56.9 (15.0)	54.9 (12.1)	53.8 (11.1)	.24
LDL (mg/dL)	143.9 (40.9)	137.3 (35.2)	130.6 (47.4)	125.6 (41.8)	.31*
Triglycerides (mg/dL)	140.3 (59.2)	131.8 (55.8)	158.6 (100.1)	159.3 (118.6)	.26
Erythrocytes ($\times 10^6/\mu L$)	4.6 (0.5)	4.5 (0.5)	4.2 (0.5)	4.1 (0.5)	.36*
Hemoglobin (g/dL)	13.3 (1.3)	13.5 (1.2)	12.4 (1.4)	12.6 (1.5)	.46
TNF alpha (ng/L)	11.3 (5.3)	12.5 (5.6)	10.3 (3.3)	10.7 (3.1)	**.08***
Interleukin-6 (pg/mL)	8.5 (3.5)	9.2 (5.9)	8.2 (2.6)	8.2 (2.2)	.24

Abbreviations: DemTect, Dementia-Detection Test; CDT, Clock-Drawing Test; 6MWT, 6-Minute Walk Test; NRS, numeric rating scale for pain; TNF alpha, tumor necrosis factor alpha; HT, hypoxic test; SD, standard deviation.

NOTE. Data are means (SD). P values for differences between groups are based on the use of the Welch test if values are normally distributed or on the use of the Mann–Whitney U test (*) if values are not normally distributed. Bold text indicates P values <0.1.

3.3. Blood tests and cardiorespiratory parameters

A slight decrease in systolic and diastolic pressure, total cholesterol, HDL, LDL, and triglycerides was observed but with no statistically significant difference between the groups. The amount of erythrocytes, hemoglobin, and interleukin-6 remained pretty much the same with no significant difference. The arterial oxygen saturation and the tumor necrosis factor alpha increased slightly but also with no statistically significant difference between the two groups (Table 2).

4. Discussion

To our knowledge, this is the first study that has investigated the tolerability and the effects on cognitive function of IHHT plus MTI in geriatric patients suffering from mild-to-moderate dementia with a mean age of more than 80 years.

4.1. IHHT applicability

One important aim of the present study was to investigate whether IHHT is tolerable and applicable to geriatric patients performing an MTI. Some patients even desaturated down to 75% SaO_2 during the hypoxia periods, but this low oxygen saturation only lasted several seconds because of the subsequently delivered hyperoxia. Neither adverse health problems nor feelings of remarkable discomfort were reported during the whole hypoxic intervention as was true for the normoxic breathing sessions. These findings are in accordance with those reported by Burtscher et al. [18,20] and Schega et al. [22], who used intermittent hypoxia in healthy elderly and those suffering from COPD.

4.2. IHHT effects on cognitive function and functional exercise capacity

As demonstrated by other authors [35,36], our short-term MTI in the NG did not result in improved cognitive function. Although the distance in the 6MWT increased by 10.8% in the NG, the increase in functional exercise capacity was not associated with improvement in cognitive performance. Thus, the increase in cognitive function in the HG might mainly be due to the IHHT.

These findings are similar to those reported by Schega et al. [22]. However, in contrast, Schega et al. found positive effects on cognitive function also related to the physical training alone. An explanation for the lack of improvement in cognitive performance after physical training alone in our study could be the low resilience of very old patients because the patients in Schega et al's study were not older than 70 years and therefore more able to tolerate physical training. This is in concordance to the conclusion of the meta-analysis of Colcombe and Kramer, who found that patients aged between 66 and 71 years seemed to benefit most from exercise [7]. For the study participants who were older than 80 years, it was probably not possible to achieve a training intensity that was high enough to cause such clear cognitive effects. Thus, MTI combined with IHHT seems to be an appropriate method to improve

Table 3
Changes of test results (DemTect, CDT, 6MWT and NRS) from pre to post for the hypoxic and normoxic groups and correlations between changes of the overall group

Variable	Delta pre–post		*P* value (Mann–Whitney *U* test)
	Hypoxic group	Normoxic group	
DemTect	+3 (+16.7%)	−0.07 (−0.39%)	**<.001**
CDT	+1.07 (+10.7%)	−0.8 (−8%)	**.03**
6MWT (m)	+56.26 (+24.1%)	+27.13 (+10.8%)	**.02**
NRS	−1.56 (−15.6%)	−1.0 (−10%)	**.07**

Correlations between changes of both groups	Spearman rank correlation coefficient (r_S) Both groups	*P* value
6MWT–DemTect	+0.57	**<.001**
6MWT–CDT	+0.42	**.01**
NRS–DemTect	−0.35	**.02**
NRS–CDT	−0.44	**.007**

Abbreviations: DemTect, Dementia-Detection Test; CDT, Clock-Drawing Test; 6MWT, 6-Minute Walk Test; NRS, numeric rating scale for pain. Bold text indicates *P* values <0.1.

both cognitive function and functional exercise capacity in very old patients. Glazachev, in his study, even reported an increased exercise tolerance and aerobic capacity without any exercising [27]. Just as the baseline data of the LIFE Cognition study revealed that physical performance directly correlates to cognitive performance [37], so too in our study the improvements in cognitive function within the overall group were significantly correlated with the increase in the functional exercise capacity determined by the 6MWT (Fig. 2) confirming the importance of exercise training for improvement of cognitive function.

There are several studies showing positive structural effects of physical training on brain structure and function. Aerobic fitness training can induce a significant increase in brain volume, in gray- and white-matter regions [38] and increases the hippocampal volume in older adults [39]; it also influences the brain-derived neurotrophic factor (BDNF), which seems to play an important role in memory and learning [40,41].

Similar effects may result from hypoxic treatments. Zhu et al. found that IHT leads to more newborn neurons and enhances the expression of the BDNF in the hippocampus [42], and Satriotomo et al. reported that hypoxic preconditioning increased the BDNF expression in rats after 4 and 10 weeks, especially in the group receiving treatments three times a week [43]. Malyshev et al. suggested that the protective neuronal mechanisms of adaptation to hypoxia may be related to a restriction of oxidative stress in the hippocampus, the limitation of a decrease in NO production induced by β-amyloid, stimulation of antioxidants, heat shock proteins, and increased density of the vascular network in the brain, which are suggested as key pathogenic factors of Alzheimer's disease [44]. Some of these adaptations might be

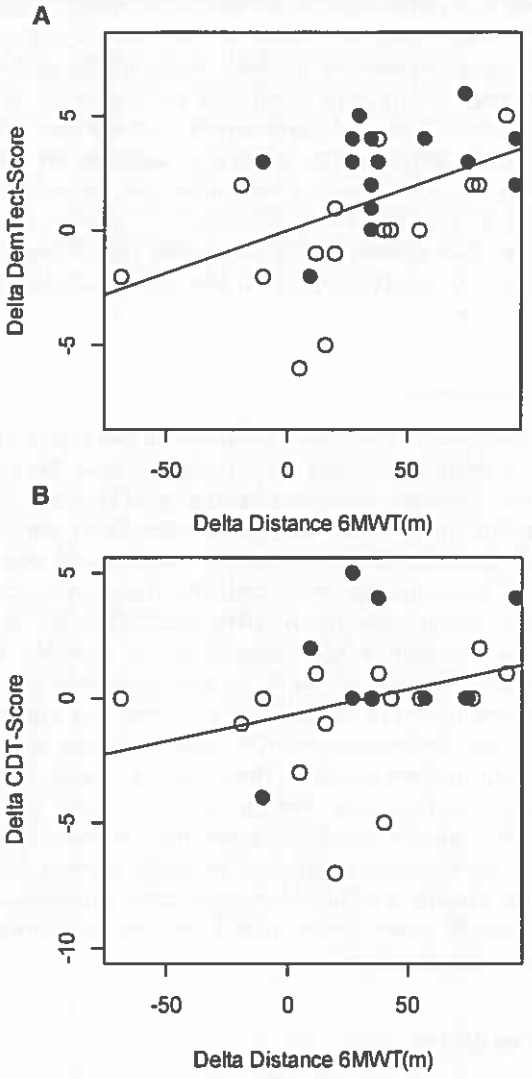


Fig. 2. Correlation between the changes (A) in the distance of the 6-Minute Walk Test (6MWT) and the Dementia-Detection Test Scores (DemTect) and (B) in the distance of 6MWT and the Clock-Drawing Test (CDT) scores. Hypoxic group: filled circles; normoxic group: open circles. (A) r = 0.57, $P < .01$ and (B) r = 0.42, $P = .01$.

caused by the hypoxia-related erythropoietin (EPO) production in the brain. EPO has been reported to activate signaling cascades initiating improved resistance of the brain to ischemia-reperfusion stress by stabilizing mitochondrial membranes, reduced formation of reactive oxygen and nitrogen species, and likely also by suppression of the production of proinflammatory cytokines and of neutrophil infiltration [45].

As physical activity requires some time to increase cognitive function and studies with a long-term intervention of more than 3 months showed the best effects [7], IHHT seems to already have positive effects after some weeks. Thus, we suggest that our MTI was too short to show measurable increases after several weeks but MTI + IHHT did.

Another explanation for the efficacy of IHHT on cognitive function may be related to the reduction of pain, which was measured by the NRS. Although the pain situation improved in both groups, the pain reduction in the HG tended to be more pronounced. Our findings reveal that beside the increment of exercise capacity, the reduction of pain is also highly associated with an increase in cognitive performance. Schiltenwolf et al. showed that chronic pain impairs cognitive function [46]. Thus, treating pain, for example, by IHHT, also could increase cognitive function.

4.3. Limitations

There are at least five limitations in our study. First, the intervention period may probably have been too short to improve cognitive function by MTI alone. However, this enabled us to demonstrate that IHHT plus MTI can effectively improve cognitive function in old patients even during the relatively short intervention period. Second, the use of IHHT and MTI in this group of patients with a high compliance is probably only possible with much effort on the part of trained supervisors and not easy to translate to a real-life situation. Third, the mechanisms of IHHT remain largely speculative, but its demonstrated efficacy will stimulate further research on this issue. Fourth, due to the small number of male patients, we did not perform sex-specific analyses, and thus, the results may primarily be valid for females. Finally, we did not measure EPO concentrations that might have been related to improvements in cognitive performance.

5. Conclusion

IHHT has proved to be easily applicable to and well tolerated by geriatric patients aged up to 92 years, even when they suffered from moderate dementia. IHHT contributed significantly to improvements in cognitive performance and functional exercise capacity in geriatric patients performing MTI.

Acknowledgments

The authors wish to thank all volunteers who participated in the study. Also, the authors thank AiMediq SA, Luxembourg, for supplying two ReOxy devices and equipment at cost. Additionally, the authors thank the nurses of the Geriatric Day Clinic Draginja Catiz, Rosemarie Mayer, and Dagmar Dornik, who coordinated all appointments and collected blood samples for the outcome analysis and Dr. Evgenia Terziev, Christine Lübke, Gerd Tragner, Sonja Türk, Franz Smolnig, and Waltraud Genser for the assessments and positive cooperation.

RESEARCH IN CONTEXT

1. Systematic review: Embase and PubMed databases were searched using various combinations of search terms including "hypoxia, hyperoxia, exercise, training, elderly, cognitive impairment, dementia" to identify and evaluate the accumulated knowledge on the applicability and effects of intermittent hypoxic–hyperoxic training (IHHT) in geriatric patients.
2. Interpretation: We demonstrated that IHHT has proved to be easily applicable to and well tolerated by geriatric patients up to 92 years of age and that IHHT contributed significantly to improvements in cognitive performance and functional exercise capacity in these patients. The efficacy of IHHT on cognitive performance in geriatric patients may be related (1) to neuronal mechanisms of adaptation to hypoxia, (2) to improved exercise tolerance, and/or (3) to the reduction of pain.
3. Future directions: Because mechanisms of IHHT remain largely speculative, its demonstrated efficacy will stimulate further research to better understand responsible mechanisms and to substantiate causal links.

References

[1] Feldman HH, Ferris S, Winblad B. Effect of rivastigmine on delay to diagnosis of Alzheimer's disease from mild cognitive impairment: the InDDEx study. Lancet Neurol 2007;6:501–12.
[2] Petersen RC, Thomas RG, Grundman M, Bennett D, Doody R, Ferris S, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. N Engl J Med 2005;352:2379–88.
[3] Jiang J, Jiang H. Efficacy and adverse effects of memantine treatment for Alzheimer's disease from randomized controlled trials. Neurol Sci 2015;36:1633–41.
[4] Lautenschlager NT, Cox KL, Flicker L, Foster JK, van Bockxmeer FM, Xiao J, et al. Effect of physical activity on cognitive function in older adults at risk of Alzheimer's disease. JAMA 2008; 300:1027–37.
[5] Barnes DE, Santos-Modesitt W, Poelke G, Kramer AF, Castro C, Middleton LE, et al. The Mental Activity and eXercise (MAX) Trial: A randomized controlled trial to enhance cognitive function in older adults. JAMA Intern Med 2013;173:797–804.
[6] Langlois F, Minh Vu TT, Chasse K, Dupuis G, Kergoat MJ, Bherer L. Benefits of physical exercise training on cognition and quality of life in frail older adults. J Gerontol B Psychol Sci Soc Sci 2013;68:400–4.
[7] Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults: a meta-analytic study. Psychol Sci 2003;14:125–30.
[8] Neubauer JA. Invited review: physiological and pathophysiological responses to intermittent hypoxia. J Appl Physiol 2001;90:1593–9.
[9] Joyeux-Faure M, Slanke-Labesque F, Lefebvre B, Béguin P, Godin-Ribuot D, Ribuot C, et al. Chronic intermittent hypoxia increases infarction in the isolated rat heart. J Appl Physiol (1985) 2005; 98:1691–6.

[10] Lévy P, Ryan S, Oldenburg O, Parati G. Sleep apnoea and the heart. Eur Respir Rev 2013;22:333–52.
[11] Michiels C. Physiological and pathological responses to hypoxia. Am J Pathol 2004;164:1875–82.
[12] Serebrovskaya TV, Manukhina EB, Smith ML, Downey HF, Mallet RT. Intermittent hypoxia: cause of or therapy for systemic hypertension? Exp Biol Med 2008;233:627–50.
[13] Kolar F, Ostadal B. Molecular mechanisms of cardiac protection by adaptation to chronic hypoxia. Physiol Res 2004;53 S3–13.
[14] Thompson JW, Dave KR, Young JI, Perez-Pinzon MA. Ischemic preconditioning alters the epigenetic profile of the brain from ischemic intolerance to ischemic tolerance. Neurotherapeutics 2013;10:789–97.
[15] Suzontova TG, Arkhipenko YuV. Intermittent hypoxia in resistance of cardiac membrane structures: role of reactive oxygen species and redox signalling. In: Xi L, Serebrovskaya TV, eds. Intermittent Hypoxia: From Molecular Mechanisms to Clinical Applications. Hauppauge, NY: Nova Science Publishers; 2009:113–50. Chapter 5.
[16] Manukhina EB, Vanin AF, Malyshev IYu, Mallet RT. Intermittent hypoxia-induced cardio- and vasoprotection: Role of NO stores. In: Xi L, Serebrovskaya TV, eds. Intermittent Hypoxia: From Molecular Mechanisms to Clinical Applications. Hauppauge, NY: Nova Science Publishers; 2009:79–112. Chapter 4.
[17] El'chaninova SA, Korenyak NA, Pavlovskaya LI, Smagina IV, Makarenko VV. The effect of interval hypoxic hypoxia on the vascular endothelial growth factor and basic fibroblast growth factor concentrations in the peripheral blood. Hum Physiol 2004;30:705–7.
[18] Burtscher M, Haider T, Domej W, Linser T, Gatterer H, Faulhaber M, et al. Intermittent hypoxia increases exercise tolerance in patients at risk or with mild COPD. Respir Physiol Neurobiol 2009;165:97–103.
[19] Katayama K, Matsuo H, Ishida K, Mori S, Miyamura M. Intermittent hypoxia improves endurance performance and submaximal exercise efficiency. High Alt Med Biol 2003;4:291–304.
[20] Burtscher M, Pachinger O, Ehrenbourg I, Mitterbauer G, Faulhaber M, Pühringer R, et al. Intermittent hypoxia increases exercise tolerance in elderly men with and without coronary artery disease. Int J Cardiol 2004;96:247–54.
[21] Manukhina EB, Goryacheva AV, Barskov IV, Viktorov IV, Guseva AA, Pshennikova MG, et al. Prevention of neurodegenerative damage to the brain in rats in experimental Alzheimer's disease by adaptation to hypoxia. Neurosci Behav Physiol 2010;40:737–43.
[22] Schega L, Peter B, Törpel A, Mutschler H, Isermann B, Hamacher D. Effects of intermittent hypoxia on cognitive performance and quality of life in elderly adults: a pilot study. Gerontology 2013;59:316–23.
[23] Glazachev O. Optimization of clinical application of interval hypoxic training. Biomed Eng 2013;47(3):134–7.
[24] Arkhipenko YV, Sazontova TG, Zhukova AG. Adaptation to periodic hypoxia and hyperoxia improves resistance of membrane structures in heart, liver, and brain. Bull Exp Biol Med 2005;140(3):278–81.
[25] Susta D, Dudnik E, Glazachev O. A program based on repeated hypoxia–hyperoxia exposure and light exercise enhances performance in athletes with overtraining syndrome. Clin Physiol Funct Imaging 2015; http://dx.doi.org/10.1111/cpf.12296.
[26] Susta D, Kellett M, Glazachev O. The effects of intermittent hypoxic-hyperoxic training on high intensity intermittent performance: a case study. Sports Med Res Pract J: ISSN 2223-2524
[27] Glazachev O. Intermittent hypoxia–hyperoxia exposure improves cardiometabolic profile, exercise tolerance and quality of life: a preliminary study in cardiac patients. Eur J Prev Cardiol EJPC-D-15-00334.
[28] Folstein MF, Folstein SE, McHugh PR. Mini mental state. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–98.
[29] Glazachev O, Platonenko A, Spirina G. Vorrichtung Zur Biologisch Regelbaren Auswahl von Individuellen Verlaufen für Eine Intervall-hypoxie-therapie (hypoxietraining): Gebrauchsmusters Nr DE De202012012602, 06.08.2013; Tag der Eintragung 01.06.2012 Gebrauchsmusterinhaber AI MEDIQ S.A., Luxembourg, LU.
[30] Kalbe E, Kessler J, Calabrese P, Smith R, Passmore AP, Brand M, et al. DemTect: a new, sensitive cognitive screening test to support the diagnosis of mild cognitive impairment and early dementia. Int J Geriatr Psychiatry 2004;19:136–43.
[31] Kohn N, Kalbe E, Georg H, Kessler J. Vergleich MMST und DemTect: Spezifität und Sensitivität bei primär kognitiven Störungen. Aktuelle Neurologie 2007;34 (Article in German).
[32] Agrell B, Dehlin O. The clock-drawing test. Age and Ageing 1998; 27:399–403.
[33] American Thoracic Society ATS Statement: Guidelines for the Six-Minute Walk Test. Official Statement of the American Thoracic Society, approved by the ATS Board Of Directors; 2002
[34] Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain. Arthritis Care Res 2011;63:S240–52.
[35] Baker LD, Frank LL, Foster-Schubert K, Green PS, Wilkinson CW, Mc Tiernan A, et al. Effects of aerobic exercise on mild cognitive impairment. A controlled trial. Arch Neurol 2010;67:71–9.
[36] Suzuki T, Shimada H, Makizako H, Doi T, Yoshida D, Tsutsumimoto K, et al. Effects of a multicomponent exercise on cognitive function in older adults with amnestic mild cognitive impairment: a randomized trial. BMC Neurol 2012;12:128.
[37] Sink KM, Espeland MA, Rushing J. The LIFE Cognition Study: design and baseline characteristics. Clin Interv Aging 2014;9:1425–36.
[38] Colcombe SJ, Erickson KI, Scalf PE, Kim JS, Prakash R, McAuley E, et al. Aerobic exercise training increases brain volume in aging humans. J Gerontol A Biol Sci Med Sci 2006;61:1166–70.
[39] Brinke LF, Bolandzadeh N, Nagamatsu LS. Aerobic exercise increases hippocampal volume in older women with probable mild cognitive impairment: a 6-month randomised controlled trial. Br J Sports Med 2015;49:248–54.
[40] Huang EJ, Reichardt LF. Neurotrophins: roles in neuronal development and function. Annu Rev Neurosci 2001;24:677–736.
[41] Zimmer P, Oberste M, Bloch W. Influence of exercise on the central nervous system—molecular and cellular mechanisms. Dtsch Z Sportmed 2015;66:42–9 (Article in German).
[42] Zhu XH, Yan HC, Zhang J, Qu HD, Qiu XS, Chen L, et al. Intermittent hypoxia promotes hippocampal neurogenesis and produces antidepressant-like effects in adult rats. J Neurosci 2010;30:12653–63.
[43] Satriotomo I, Vinit S, Flom AL. Repetitive acute intermittent hypoxia increases bdnf and trkb expression in respiratory motor neurons: dose effects. FASEB J. Available at: www.fasebj.org/cgi/content/meeting_abstract/24/1_MeetingAbstracts/799.16; 2010. Accessed December 22, 2016.
[44] Malyshev IY, Wiegant F, Mashina SY, Torshin VI, Goryacheva AV, Khomenko IP, et al. Possible use of adaptation to hypoxia in Alzheimer's disease: a hypothesis. Med Sci Monit 2005;11:HY31–8.
[45] Nguyen AQ, Cherry BH, Scott GF, Ryou MG, Mallet RT. Erythropoietin: powerful protection of ischemic and post-ischemic brain. Exp Biol Med (maywood) 2014;239:1461–75.
[46] Schiltenwolf M, Akbar M, Hug A, Pfüller U, Gantz S, Neubauer E, et al. Evidence of specific cognitive deficits in patients with chronic low back pain under long-term substitution treatment of opioids. Pain Physician 2014;17:9–20.

HIGH ALTITUDE MEDICINE & BIOLOGY
Volume 9, Number 1, 2008

DOI: 10.1089/ham.2008.1053

Effects of Intermittent Hypoxia Training on Exercise Performance, Hemodynamics, and Ventilation in Healthy Senior Men

VALERIY B. SHATILO,[1] OLEG V. KORKUSHKO,[1] VADIM A. ISCHUK,[1] H. FRED DOWNEY,[2] and TATIANA V. SEREBROVSKAYA[3]

ABSTRACT

Shatilo, Valeriy B., Oleg V. Korkushko, Vadim A. Ischuk, H. Fred Downey, and Tatiana V. Serebrovskaya. Effects of intermittent hypoxia training on exercise performance, hemodynamics, and ventilation in healthy senior men. *High Alt. Med. Biol.* 9:43–52, 2008.—The efficacy and safety of intermittent hypoxia training (IHT) were investigated in healthy, 60- to 74-yr-old men. Fourteen men (Gr 1) who routinely exercised daily for 20 to 30 min were compared with 21 (Gr 2) who avoided exercise. Their submaximal work-load power values before the IHT training were 94 ± 3.7 and 66 ± 3.1, respectively. Before and after 10 days of IHT, the ventilatory response to sustained hypoxia (SH; 12% O_2 for 10 min), work capacity (bicycle ergometer), and forearm cutaneous perfusion (laser Doppler) were determined. During SH, no negative electrocardiogram (ECG) changes were observed in either group, and the ventilatory response to SH was unaltered by IHT. In Gr 1, IHT (normobaric rebreathing for 5 min, final Sa_{O_2} = 85% to 86%, followed by 5 min normoxia, 4/day) produced no changes in hemodynamic indixes and work capacity. In Gr 2, IHT decreased blood pressure (BP) by 7.9 ± 3.1 mmHg ($p < 0.05$) and increased submaximal work by 11.3% ($p < 0.05$) and anaerobic threshold by 12.7% ($p < 0.05$). The increase in HR and BP caused by a 55 W-work load was reduced by 5% and 6.5%, respectively ($p < 0.05$). Cutaneous perfusion increased by 0.06 ± 0.04 mL/min/100 g in Gr 1 and by 0.11 ± 0.04 mL/min/100 g in Gr 2 ($p < 0.05$). Hyperemia recovery time increased significantly by 15.3 ± 4.6 sec in Gr 1 and by 25.2 ± 11.2 sec in Gr 2. Thus, healthy senior men well tolerate IHT as performed in this investigation. In untrained, healthy senior men, IHT had greater positive effects on hemodynamics, microvascular endothelial function, and work capacity.

Key Words: intermittent hypoxia; old age; ventilation; hemodynamics; exercise performance

INTRODUCTION

Aging is associated with loss of muscle mass, decrease of muscle blood flow, dilatation of alveoli, enlargement of air spaces, reduction of hypoxic ventilatory sensitivity, and other changes that limit physical activity (Korkusko et al., 1982; Janssens et al., 1999; Serebrovskaya et al., 2000; Dela and Kjaer, 2006). Luckner et al. (2006) proposed that age-

[1]Institute of Gerontology, Kiev, Ukraine.
[2]University of North Texas Health Science Center, Fort Worth, Texas, USA.
[3]Bogomoletz Institute of Physiology, Kiev, Ukraine.

related disturbances in microcirculatory homeostasis play a key role in the pathophysiology of multiple organ dysfunction syndromes. Today is well known that physical activity reduces cardiovascular disease risk in older adults (Klieman et al., 2006). Multivariate analysis demonstrated that a sedentary lifestyle associated with aging is related to mortality (Al-Khalili et al., 2007). Conforming to the laws of nature, the vigor of adult maturity is replaced by the increasing fragility of old age, but elderly individuals desire the same full and active life as younger adults in spite of biologically inescapable decreases in physiological processes and reserves.

Intermittent hypoxia training (IHT) has been demonstrated to enhance the physical performance of athletes (see reviews, Sergeev, 1962; Gippenreiter and West, 1996; Serebrovskaya, 2002) and older individuals (Kolesnikova and Serebrovskaya, 2001), even patients with heart disease (Burtscher et al., 2004). Although the first use of IHT for training of pilots and climbers was described more than 70 years ago (Gurvich and Fainberg, 1938), in the last decade of the 20th century, interest in IHT has been revived, mainly in Russia and other eastern European countries. Recently, IHT has been advocated for the prevention and treatment of some diseases, such as bronchial asthma (Serebrovskaya et al., 2003a), coronary heart disease (del Pilar Valle et al., 2006), myocardial infarction (Burtscher et al., 2004), essential hypertension (Simonenko et al., 2003; Mukharliamov et al., 2006), Parkinson's disease (Serebrovskaya et al., 2003b), and obesity (Balykin et al., 2004).

Various mechanisms for the beneficial effects of IHT have been hypothesized (Bernardi et al., 2001; Serebrovskaya, 2002). It has been shown that by enhancing stress resistance and improving oxygen delivery, IHT is an effective stimulus for evoking respiratory, cardiovascular, and metabolic adaptations, which increase exercise tolerance (Neubauer, 2001; Burtscher, 2004). Reeves and Gozal (2005) have shown that intermittent hypoxia induces alterations in respiratory control that reflect various types of ventilatory plasticity. Thus, it is likely that IHT would also be a particularly beneficial therapy to slow or reverse the effects of aging. Therefore, the purpose of this study was to evaluate the safety of IHT in healthy senior men and, more specifically, to test the hypothesis that IHT improves indixes of ventilation, hemodynamics, and exercise performance in exercise-trained and untrained subjects.

METHODS

This work was officially approved and authorized by the Ethics Committee for Human Experiments of the Institute of Gerontology.

Subjects

The efficacy and safety of IHT were investigated in two groups of aged, healthy volunteers with different levels of physical activity, who gave their informed consent. All subjects were sea-level residents and nonsmokers. Most subjects consumed one to three alcoholic drinks weekly. The subjects were in good health with no evidence of cardiovascular or pulmonary disease. Group 1 (Gr 1) consisted of 14 healthy men (age 67.4 ± 2.0 yr; weight 64.5 ± 3.1 kg; height 171 ± 2 cm; body mass index 22.2 ± 0.9) in good physical condition. These subjects exercised daily for 20 to 30 min at an average energy cost of 500 kcal and had submaximal $\dot{V}_{O_2}$ of 23.7 ± 1.0 mL/kg^{-1}/min^{-1}. Group 2 (Gr 2) consisted initially of 22 healthy but sedentary men (age 61.0 ± 1.5 yr; weight 69 ± 3 kg; height 169 ± 2 cm; body mass index 24.2 ± 1.0) who, unlike their exercise-trained counterparts, avoided exercise and had peak $\dot{V}_{O_2}$ of 18.2 ± 0.3 mL/kg^{-1}/min^{-1} ($p < 0.05$). One subject of this group could not pass the first hypoxia test and was excluded from subsequent investigation, so for the remainder of the investigation Gr 2 was comprised of 21 sedentary men.

Experimental protocol

Initially, a sustained hypoxia test was administered to all subjects. Those who performed satisfactorily on this test (see Results) continued in the study and received 10 days of IHT. A sustained hypoxia test was again administered after 10 days of IHT. In addition, these subjects underwent tests for hematology assessment, exercise capacity, and forearm microvascular reactivity during the next 2 days

after the hypoxic test, before initiation of IHT, and on the days following 10 days of IHT. The tests were performed during the early morning with the subjects fasting. First, venous blood was drawn from the median antecubital vein to provide hematology assessment. Then anaerobic threshold was determined. On the next day the forearm cutaneous perfusion test was provided and, after that, physical work capacity was evaluated. The same protocol was realized after 10 days of IHT course.

Intermittent hypoxia training (IHT)

IHT was performed in the morning, from 10 till 12 AM, 2 h after a light breakfast. With the subjects in a sitting position, normobaric, isocapnic hypoxia was administered for 5 min 4 times/day for 10 days with a Hypotron (modified closed spirometer with CO_2 absorption) (Serebrovskaya, 1995). The four periods of hypoxia were separated by three 5-min periods of room-air inspiration. Initial inspired gas composition (F_i) was 20.9% O_2 and 79.1% N_2. Partial pressure of expiratory carbon dioxide (P_{ETCO_2}) was continuously monitored at the mouth with a medical mass spectrometer (MX62-03, Ukraine), which was calibrated before and after each test with standardized gases that had been assayed by the Scholander technique. During the first 1 to 1.5 min of rebreathing, F_{iO_2} fell progressively with body utilization of O_2 until it reached 12%. During the remaining 3.5 to 4 min of IHT, O_2 and CO_2 were added gradually as needed to maintain F_{iO_2} at 12% and P_{ETCO_2} at its prehypoxia value. S_{aO_2} at conclusion of IHT was 85% to 86%. P_{ETCO_2} was maintained at the initial pretest pressure for each subject, typically 38 to 40 mmHg, throughout the training period. Subjects easily endured the hypoxia periods without any distress or side effects. ECG and ventilation were continuously monitored during IHT, and arterial pressure was measured at 2-min intervals.

Analytical procedures

Sustained hypoxia test. After a 30-min rest, the subject in a sitting position inspired a hypoxic gas mixture (12% O_2, 88% N_2). Before and during the test, ventilation, arterial pressure (BP), heart rate (HR), S_{aO_2} (pulsoximeter), and ECG were recorded. The test lasted 10 min or was interrupted if one of the following disturbances was observed: (1) dizziness, nausea, precordial chest pain, or other negative subjective feelings, (2) an increase in HR of more than 30%, (3) a decrease in S_{aO_2} to lower than 80%, (4) a rise of systolic BP of more than 30%, (5) ECG signs of ischemia or frequent extrasystoles (more than 6/min), or AV conduction defects (see Results).

Blood analysis. Blood was sampled from a finger puncture for routine hematology assessment of erythrocyte and leukocyte count, blood hemoglobin and glucose concentration, and content of alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, creatinine, urea, albumin, and total cholesterol.

Forearm cutaneous perfusion test. Forearm cutaneous perfusion was measured using a BLF 21 D laser instrument (Transonic Systems, Inc., USA) at room temperature (22°C) with the subject in a sitting position and after resting in that position for at least 30 min. Microvascular reactivity (MVR) was evaluated from the maximal postocclusive reactive hyperemia (PORH) following 3-min forearm ischemia produced by cuff inflation. The time required for forearm flow to return to normal was also measured. Similar procedures have been used by other investigators (e.g., Luckner et al., 2006; Zdolsek et al., 2006).

Exercise tests. A bicycle ergometer test was used to evaluate anaerobic threshold and physical work capacity. Anaerobic threshold was estimated from ventilatory gas exchange indixes during continuously accelerated load (the increase by 12.5 W every minute up to pulse rate [HR = 200 − age] was reached). HR was monitored continuously from the ECG, and arm BP was measured intermittently by sphygmomanometry, with a microphone placed over the brachial artery to detect Korotkoff sounds. V_{O_2} and lung ventilation parameters were monitored with the Oxycon-4 System (Mijnhardt, the Netherlands). All recordings were made by the same technicians, and the spirometric values were corrected for body temperature, atmospheric pressure, and humidity. Anaerobic threshold was calculated as Wasserman (1987) has described. Physical work capacity

was determined the next day. Subjects completed 5 min of work at 25 W. The load was then increased every 5 min by15 W until the individual's maximum tolerable level was reached (i.e., to volitional exhaustion). Peak V_{O_2} was determined, using an oxygen analyzer, the Oxycon-4 System, as the highest value of O_2 consumption during maximum effort.

Statistical analyses. All values are expressed as means ± SE. Treatment means were compared statistically with the ANOVA test. Correlations were identified by the least-squares method and expressed as linear regression slopes. Differences were considered significant for $p < 0.05$.

RESULTS

To ensure that the senior subjects could safely tolerate IHT, each first underwent the sustained hypoxia test to assess individual tolerance of hypoxia. None of the subjects showed changes in ECG during or after this sustained hypoxic test. In some patients, single extrasystoles were observed, but this was not considered a reason for stopping the test or excluding the subjects from the investigation. During first administration of the sustained hypoxia test, three subjects of Gr 1 (21%) and 15 subjects of Gr 2 (68%) could not pass the test completely because Sa_{O_2} fell lower than 80% before 10 min of breathing 12% O_2 had elapsed. For these subjects, the duration of the test was 8.7 ± 0.4 min. One subject of Gr 1 and 3 subjects of Gr 2 complained of shortness of breath, weakness, or dizziness at 7 or more min of the procedure, and the test was then stopped. One subject of Gr 2 revealed an increase in blood pressure above 30% during the 3rd to 5th min, and this patient was excluded from further exposure to hypoxia. For the remaining subjects who completed the 10-min test, their final S_{aO_2} was 81.0 ± 0.6%. After this initial sustained hypoxia test, 14 subjects in Gr 1 and 21 subjects in Gr 2 received IHT.

During IHT, most subjects felt no distress. Three of the 35 subjects complained of tinnitus, dizziness, or mild chest discomfort on days 1 and 2 of IHT. However, measured variables (arterial pressure, heart rate, pulmonary ventilation indexes, blood S_{aO_2}, ECG) did not reflect any substantial changes, and these subjects continued in the investigation. After completion of IHT, no changes in ECG were observed.

Cardiorespiratory data measured during sustained hypoxia tests are presented in Table 1. Since only 10 subjects of Gr 1 and 3 subjects of Gr 2 successfully completed 10 min of the initial sustained hypoxia test, we present in Table 1 the data for 7 min only so that data of all subjects could be represented. Before IHT, resting heart rate and ventilatory frequency were lower in the fit subjects of Gr 1 compared to the less fit subjects of Gr 2. Seven minutes of hypoxia before IHT caused significant increases in heart rate and mean systemic arterial pressure in subjects of both Gr 1 and Gr 2. Minute ventilation rose during the 1st to 3rd minutes and then gradually decreased to the end of the test. During hypoxia, arterial O_2 saturation fell significantly in both groups, reaching 83.9 ± 1.2% in Gr 1 and 82.0 ± 0.7% in Gr 2 ($p > 0.05$) at 7 min. Arterial O_2 saturation values were significantly greater in Gr 1 subjects only at 3 and 5 min of hypoxia. During hypoxia before IHT, final 7-min values for heart rate, arterial pressure, and ventilatory frequency were less in Gr 1 subjects. Gr 1 values for heart rate and arterial pressure were also less at some other time intervals during hypoxia.

After IHT, hypoxia caused changes in cardiorespiratory values relative to the rest values that were similar to those observed before IHT (Table 1). For Gr 1, values at rest and during hypoxia after IHT were similar to respective values recorded before IHT. For Gr 2, values at 5 and 7 min during hypoxia for heart rate and arterial pressure were less after than before IHT, and arterial O_2 saturation was greater. Values for respective cardiorespiratory variables of Gr 1 and Gr 2 after IHT were similar except for heart rate at 2-min hypoxia, which was less in Gr 1.

Blood count data and biochemical indexes are presented in Table 2. Before IHT, no differences were observed between groups, except for leukocyte count, which was higher in Gr 2. IHT did not significantly akter any of

TABLE 1. CARDIORESPIRATORY PARAMETERS OF HEALTHY SENIOR MEN DURING SUSTAINED HYPOXIA TEST (12% O_2) BEFORE AND AFTER IHT

		Gr1			Gr2		
I	*II*	*III*	*IV*	*V*	*VI*	*VII*	*VIII*
Parameters	*Period of hypoxia (min)*	*Before IHT*	*After IHT*	*Statistical difference between III and IV*	*Before IHT*	*After IHT*	*Statistical difference between YI and VII*
HR min^{-1}	Rest	68.8 ± 2.6	68.0 ± 2.2	NS	74.9 ± 2.8[a]	73.2 ± 3.0	NS
	1	72.9 ± 3.7	71.5 ± 2.2	NS	77.3 ± 3.1	77.3 ± 3.1[b]	NS
	3	77.4 ± 3.4	75.5 ± 2.2[c]	NS	81.6 ± 3.2	78.8 ± 3.2	NS
	5	77.5 ± 3.6	75.5 ± 2.3[c]	NS	83.4 ± 2.8[a,c]	79.2 ± 3.3	<0.1 > 0.05
	7	78.7 ± 2.9[c]	76.5 ± 2.3[c]	NS	84.6 ± 2.9[a,c]	78.3 ± 3.2	0.05
SBP, mmHg	Rest	131 ± 3.2	130 ± 3.0	NS	134 ± 3.0	130 ± 3.3	NS
	1	136 ± 3.4	134 ± 3.9	NS	145 ± 3.7[a,c]	137 ± 3.2	NS
	3	137 ± 4.5	135 ± 4.1	NS	147 ± 3.9[a,c]	138 ± 4.2	<0.1 > 0.05
	5	139 ± 4.3[c]	135 ± 3.7	NS	149 ± 4.6[a,c]	138 ± 5.1	<0.05
	7	140 ± 5.4[c]	136 ± 4.0	NS	159 ± 4.2[a,c]	139 ± 4.8	<0.05
Sa_{O_2}, %	Rest	97.7 ± 0.3	97.6 ± 0.3	NS	97.3 ± 0.3[a,c]	97.4 ± 0.4	NS
	1	92.6 ± 0.7[d]	93.7 ± 0.8[d]	NS	91.4 ± 0.6[a,d]	92.7 ± 0.6[d]	NS
	3	88.0 ± 0.9[d]	88.1 ± 1.2[d]	NS	86.5 ± 0.5[a,d]	87.7 ± 0.6[d]	NS
	5	85.4 ± 1.0[d]	86.1 ± 1.3[d]	NS	83.3 ± 0.7[a,d]	86.1 ± 0.7[d]	<0.05
	7	83.9 ± 1.2[d]	84.4 ± 1.5[d]	NS	82.0 ± 0.7[a,d]	84.2 ± 1.0[d]	<0.05
f, min^{-1}	Rest	14.1 ± 0.8	14.9 ± 1.1	NS	16.6 ± 1.2[a,d]	16.3 ± 2.2	NS
	1	15.3 ± 1.1	15.9 ± 1.1	NS	16.5 ± 1.7	16.5 ± 2.0	NS
	3	15.4 ± 1.3	15.8 ± 1.1	NS	17.2 ± 1.7	18.0 ± 1.6	NS
	5	14.8 ± 1.2	14.6 ± 1.1	NS	16.0 ± 1.8	16.3 ± 1.8	NS
	7	15.3 ± 1.1	15.0 ± 1.1	NS	18.0 ± 1.5[a]	17.8 ± 2.0	NS
V_E, L/min	Rest	8.6 ± 0.7	8.1 ± 0.9	NS	7.8 ± 0.7	7.9 ± 0.8	NS
	1	10.9 ± 1.0[c]	10.6 ± 0.8[c]	NS	8.7 ± 0.6	8.2 ± 0.9	NS
	3	10.8 ± 1.3[c]	10.5 ± 0.7[c]	NS	9.5 ± 0.9[c]	9.0 ± 0.8	NS
	5	10.5 ± 1.2	10.2 ± 1.0[c]	NS	8.9 ± 0.7	8.9 ± 1.0	NS
	7	10.2 ± 1.1	9.8 ± 0.8	NS	9.0 ± 0.9	9.3 ± 1.0	NS

Values are means ± SD.
Gr 1: healthy old men with regular physical training (peak submaximal $\dot{V}_{O_2}$, 23.7 ± 1.0 mL/min/kg) (n = 14).
Gr 2: healthy untrained (peak submaximal $\dot{V}_{O_2}$, 18.2 ± 1.3 mL/min/kg) old men (n = 21).
[a]Statistical difference between Gr 1 and Gr 2 within columns III and VI, $p < 0.05$.
[b]Statistical difference between Gr 1 and Gr 2 within columns IV and VII, $p < 0.05$.
[c]Statistical difference between rest and hypoxia, $p < 0.05$.
[d]Statistical difference between rest and hypoxia, $p < 0.01$.
IHT, intermittant hypoxia training; HR, heart rate; SBP, systolic arterial blood pressure; Sa_{O_2}, blood arterial oxygen saturation; V_E, expired minute ventilation; NS, not significant; *f*, breathing frequency.

these parameters relative to respective pre-IHT values. After IHT, erythrocyte count was greater in Gr 1 subjects and leukocyte count was greater in Gr 2 subjects, consistent with their greater pre-IHT count.

Table 3 shows changes in physical work capacity and anaerobic threshold before and after IHT. Before IHT, all parameters of physical ability were significantly lower in Gr 2 compared to Gr 1. IHT did not affect either submaximal work capacity or anaerobic threshold in well-trained subjects of Gr 1, whereas in the untrained individuals of Gr 2 submaximal work capacity increased by 11.3%, and the ventilatory index of anaerobic threshold increased by 12.7%.

Before IHT, during both 25- and 55-W loads, HR, systolic arterial blood perssure (SBP), diastolic arterial blood pressure (DBP) and heart rate–blood pressure product rose much more substantially in Gr 2 than in Gr 1 (Table 4). IHT did not change cardiorespiratory responses to both loads in well-trained subjects, whereas in untrained individuals, a significant decrease in

TABLE 2. BLOOD ANALYSIS IN HEALTHY SENIOR MEN BEFORE AND AFTER IHT

	Gr 1			Gr 2		
I	II	III	IV	V	VI	VII
Parameters	Before IHT	After IHT	Statistical difference between II and III	Before IHT	After IHT	Statistical difference between V and VII
Erythrocytes, 10^{12}/L[a]	4.34 ± 0.1	4.4 ± 0.1	NS	4.3 ± 0.1	4.3 ± 0.1	NS
Hemoglobin, g/L	141 ± 3.5	142 ± 2.7	NS	137 ± 2.0	139 ± 1.6	NS
Leucocytes, 10^9/L[a]	4.9 ± 0.4	4.8 ± 0.4	NS	5.7 ± 0.3[b]	5.7 ± 0.3[a]	NS
Blood glucose, mmol/L	4.9 ± 0.8	4.8 ± 0.9	NS	5.1 ± 1.0	4.9 ± 0.7	NS
ALT, mmol/L	0.48 ± 0.1	0.45 ± 0.07	NS	0.44 ± 0.06	0.51 ± 0.08	NS
AST, mmol/L	0.38 ± 0.04	0.37 ± 0.05	NS	0.34 ± 0.03	0.36 ± 0.03	NS
Bilirubin, mkmol/L	11.1 ± 2.8	12.7 ± 3.5	NS	11.2 ± 1.8	11.8 ± 1.7	NS
Creatinine, mkmol/L	69.6 ± 5.1	66.3 ± 5.4	NS	72.3 ± 3.1	73.7 ± 2.5	NS
Urea, mmol/L	6.2 ± 0.5	6.1 ± 0.4	NS	6.14 ± 0.3	5.9 ± 0.2	NS
Albumin, g/L	68.2 ± 2.6	68.3 ± 2.9	NS	68.5 ± 1.1	70.1 ± 1.6	NS
Cholesterol, mmol/L	5.2 ± 0.7	4.7 ± 0.4	NS	5.6 ± 0.3	5.3 ± 0.2	NS

Values are means ± SE.
[a]Statistical difference between Gr 1 and Gr 2 within columns III and VI, $p < 0.05$.
[b]Statistical difference between Gr 1 and Gr 2 within columns II and V, $p < 0.05$.
For G1, G2, and IHT, see Table 1 notes.
NS, not significant.

heart rate, blood pressure, and heart rate–blood pressure product, as well as ventilation and a tendency for oxygen consumption to fall, were observed.

Results of the forearm cutaneous perfusion test are presented in Table 5. Before training there were no differences in microvascular reactivity between the groups, as could seen from basal perfusion, maximal perfusion during hyperemia, and time to recovery of baseline flow. IHT enhanced basal perfusion in Gr 1 by 0.06 ± 0.04 mL/min/100 g and in Gr 2 by 0.11 ± 0.04 mL/min/100 g. Maximal perfusion during hyperemia rose by 11.6% in Gr 2, with a tendency for this variable to increase this in Gr 1. Time of PORH recovery was augmented in both groups (by 14% in Gr I and 24.7% in Gr II).

TABLE 3. PHYSICAL WORKING CAPACITY AND ANAEROBIC THRESHOLDS IN HEALTHY SENIOR MEN BEFORE AND AFTER IHT

	Gr 1			Gr 2		
I	II	III	IV	V	VI	VII
Parameters	Before IHT	After IHT	Statistical difference between II and III	Before IHT	After IHT	Statistical difference between V and VII
Submaximal work load, W	94.0 ± 3.7	96.1 ± 3.2	NS	66.3 ± 3.1[a]	73.8 ± 3.3[b]	<0.05
Anaerobic threshold, L/min	1.45 ± 0.08	1.48 ± 0.07	NS	1.1 ± 0.05[a]	1.24 ± 0.06[b]	<0.05
Anaerobic threshold, W	73.8 ± 4.2	75.1 ± 3.8	NS	56.4 ± 1.4	62.9 ± 2.0[b]	<0.05

Values are means ± SD.
[a]Statistical difference between Gr 1 and Gr 2 within columns II and V, $p < 0.01$.
[b]Statistical difference between Gr 1 and Gr 2 within columns III and VI, $p < 0.01$.
For G1, G2, and IHT, see Table 1 notes.
NS, not significant.

TABLE 4. HEMODYNAMICS, LUNG VENTILATION AND OXYGEN UPTAKE IN HEALTHY SENIOR MEN DURING 25-W AND 50-W LOAD BEFORE AND AFTER IHT

		Gr1			Gr2		
I	II	III	IV	V	VI	VII	VIII
Parameters	Load (W)	Before IHT	After IHT	Statistical difference between III and IV	Before IHT	After IHT	Statistical difference between VI and VII
HR min^{-1}	Rest	71.3 ± 2.3	72.7 ± 2.6	NS	75.8 ± 2.7	74.8 ± 2.6	NS
	25	85.7 ± 2.6[a]	86.7 ± 2.7[a]	NS	97.9 ± 3.3[a,b]	92.0 ± 3.4[a,c]	<0.05
	55	100.0 ± 3.3[a]	101.5 ± 3.7[a]	NS	120.4 ± 3.7[a,b]	115.1 ± 3.1[a,c]	<0.05
SBP, mmHg	Rest	132.0 ± 2.8	130.4 ± 2.4	NS	135.5 ± 2.5	129.5 ± 3.1	<0.05
	25	149.3 ± 3.3[a]	145.2 ± 2.9[d]	NS	158.2 ± 3.9[a,e]	148.4 ± 3.0[a]	<0.05
	55	167.3 ± 3.4[a]	166.1 ± 2.9[a]	NS	182.1 ± 3.9[a,b]	171.6 ± 4.3[a]	<0.05
DBP, mmHg	Rest	81.5 ± 1.5	79.6 ± 1.3	NS	83.3 ± 1.1	80.0 ± 1.5	NS
	25	88.3 ± 1.5[a]	87.8 ± 1.7[a]	NS	91.4 ± 1.8[a]	90.4 ± 1.9[a]	NS
	55	92.5 ± 1.8[a]	93.2 ± 2.0[a]	NS	99.3 ± 2.5[a,e]	93.1 ± 2.9[a]	<0.05
SBP · HR/100, units	Rest	94.0 ± 3.6	94.1 ± 3.4	NS	103.1 ± 3.7[e]	97.2 ± 3.5	NS
	25	128.3 ± 5.4[a]	124.0 ± 4.3[a]	NS	155.5 ± 7.3[a,e]	137.3 ± 6.9[a,c]	<0.05
	55	168.5 ± 7.9[a]	167.5 ± 6.4[a]	NS	220.9 ± 11.7[a,e]	18.8 ± 9.5[a,c]	<0.05
V_E, L/min	Rest	11.9 ± 0.5	12.3 ± 0.6	NS	10.0 ± 0.5	10.1 ± 0.5	NS
	25	20.3 ± 0.9[a]	19.8 ± 0.7[a]	NS	19.1 ± 1.3[a]	17.7 ± 1.1[a,c]	NS
	55	28.1 ± 1.0[a]	28.5 ± 0.9[a]	NS	28.6 ± 1.9[a]	26.4 ± 1.6[a]	<0.05
V_{O_2}, mL/min	Rest	373.5 ± 13.4	369.9 ± 12.3	NS	298.3 ± 14.2[e]	289.3 ± 12.8	NS
	25	839 ± 35[a]	829 ± 28[a]	NS	758 ± 29[a,e]	708 ± 41[a,c]	NS
	55	1187 ± 42[a]	1189 ± 31[a]	NS	1126 ± 52[a]	1089 ± 56[a]	NS

Values are means ± SD.
[a]Statistical difference between rest and hypoxia, $p < 0.05$.
[b]Statistical difference between Gr I and Gr II within columns III and VI, $p < 0.01$.
[c]Statistical difference between Gr I and Gr II within columns IV and VII, $p < 0.05$.
[d]Statistical difference between rest and hypoxia, $p < 0.05$.
[e]Statistical difference between Gr 1 and Gr 2 within columns III and VI, $p < 0.05$.
HR, heart rate; SBP, systolic arterial blood pressure; DBP, diastolic arterial blood pressure; SBP · HR/100, heart rate–blood pressure product; V_E, expired minute ventilation; $\dot{V}_{O_2}$ minute oxygen consumption.
NS, not significant.
For IHT, Gr 1 and Gr 2, see Table 1 notes.

DISCUSSION

The purpose of this study was to elucidate the efficacy and safety of IHT application to healthy senior men of different physical activity. We confirmed that healthy men of 60 to 74 yr well tolerate IHT as performed in this investigation (i.e., hypoxic rebreathing until F_{iO_2} of 12% was reached, with subsequent maintenance at this level for 4 to 5 min, then 5-min normoxia, 4/day, with S_{aO_2} reduced to ~80%) without dangerous side effects. In general, the effects of IHT on hemodynamics, microvascular endothelial function, and work capacity were more pronounced in untrained subjects. However, IHT had little effect on respiratory indixes either during sustained hypoxia or during exercise.

One of the rare investigations reported in western literature of IHT applied to elderly patients is the work of Burtscher et al. (2004). They subjected middle-aged or elderly men (aged 50 to 70 yr), half of whom had prior myocardial infarction, to 5 cycles/day of breathing 10% O_2 for 5 min/cycle. According to these authors, "IH was well tolerated by the elderly with and without coronary artery disease." This is not so surprising, since IHT had already been used in Russia for treatment of patients with cardiac arrhythmia and exercise-induced angina due to coronary artery disease (Meerson et al., 1989; Ehrenburg, 1992; Meerson, 1993; Lyamina et al., 2001). IHT increased treadmill exercise tolerance and reduced arrhythmias in these patients. Thus, even patients with coronary artery

TABLE 5. PARAMETERS OF FOREARM CUTANEOUS PERFUSION TEST IN HEALTHY SENIOR MEN BEFORE AND AFTER IHT

I	Gr1			Gr2		
	II	III	IV	V	VI	VII
Parameters	*Before IHT*	*After IHT*	*Statistical difference between II and III*	*Before IHT*	*After IHT*	*Statistical difference between V and VI*
PORHb, mL/min · 100 g	1.10 ± 0.02	1.16 ± 0.03	NS	1.07 ± 0.03	1.18 ± 0.04	<0.05
PORHmax, mL/min · 100 g	5.85 ± 0.25	6.18 ± 0.29	NS	5.24 ± 0.36	5.85 ± 0.31	NS
PORHt, sec	109.0 ± 7.2	124.3 ± 9.6	$p < 0.05$	102.2 ± 7.4	127.4 ± 11.2	<0.05

Values are means ± SD.
PORHb, basal perfusion; PORHmax, maximal perfusion during hyperemia; PORHt, time of PORH recovery.
NS, not significant.
For IHT, G1, and G2, see Table 1 notes.

disease and a history of myocardial infarction tolerated hypoxia of the severity employed in the current investigation without dangerous side effects. On the other hand, there is not complete agreement about this question. Rapino et al. (2005) consider that intermittent hypoxia, followed by reoxygenation, increases the production of reactive oxygen species, which may lead to accelerated aging and the appearance of age-related diseases. The same opinion was expressed by Kolchinskaya et al. (1999). Considering the results of the current investigation, it appears that whether intermittent hypoxia is beneficial or not is most dependent on the hypoxia protocol.

Aging is associated with a loss in both muscle mass and the metabolic efficiency of skeletal muscle. A major part, but not all, of these changes is associated with an age-related decrease in physical activity and can be counteracted partially by increased exercise (Dela and Kjaer, 2006; Garcia-Mendoza et al., 2006). In addition, a sedentary lifestyle has been shown to be predictive of total mortality and cardiovascular mortality by a multivariate analysis adjusted for potential confounding variables. Other related predictors of total mortality were exercise time and inadequate hemodynamic responses, such as a small increase in pulse rate and systolic blood pressure from rest to peak exercise (Al-Khalili et al., 2007). Another opinion was expressed by Haseler et al. (2004): The maximal muscle oxidative rate of sedentary subjects, unlike their exercise-trained counterparts, is limited by mitochondrial capacity and not O_2 availability in normoxia.

Our current data demonstrate that IHT is particular effective in untrained senior individuals. One of the strongest markers of physical health identified in exercise testing is maximum exercise capacity. The second is heart rate–blood pressure product. Our investigation has shown the improvement of both indixes in untrained subjects. This was evidenced by attenuation of the cardiovascular responses both to hypoxia and during physical work in these subjects. Only in the untrained subjects did IHT produce an increase in submaximal work load and oxygen consumption at anaerobic threshold. It is interesting to note that Arai et al. (2006) found that in elderly subjects exercise produced responses similar to those produced by IHT in the current study. Since many elderly people cannot exercise, IHT may provide an alternative means of improving cardiorespiratory fitness. The mechanisms responsible for IHT-induced improvement of cardiorespiratory fitness are not known but, from the results of the current study, may involve improved control of heart rate and blood pressure, endothelial function, and enhanced activity of metabolic enzymes.

Before IHT, we did not reveal any differences in microvascular reactivity between the groups. IHT enhanced basal perfusion and maximal perfusion during hyperemia in sedentary subjects more distinctly than in well-trained senior men. Thus, we demonstrated

that IHT improved microvascular endothelial function in sedentary men. Physical training also improves microvascular endothelial function (Gill et al., 2004; Middlebrooke et al., 2005), and this fact may account for the lack of effect of IHT in the well-trained subjects of Gr 1. However, in contrast to the current findings, Heylen et al. (2005) reported that physical training was more effective in improving microvascular endothelial function of fit subjects compared to sedentary controls.

Since the primary objective of this investigation was to investigate and compare responses of the two fitness groups to IHT, we did not include placebo groups, that is, "sham" IHT. Data from such groups would be valuable in identifying directly the effects of intermittent hypoxia. However, in this regard we can cite the results of an earlier investigation (Ishchuk, 2007) in which 60 patients with ischemic heart disease were treated with IHT (similar protocol as in the current investigation; 40 patients) or sham IHT (20 patients). After IHT, clinical symptoms of the disease were essentially absent. Physical work capacity was increased significantly by 9.9%, and the duration of periods of myocardial ischemia (24-h Holter monitoring) was shortened significantly by 51.1%. Sham IHT caused only a slight decrease in clinical symptoms and produced no significant change in work capacity.

CONCLUSION

Healthy senior men well tolerate IHT as performed in this investigation. In untrained healthy, senior men, IHT had greater positive effects on hemodynamics, microvascular endothelial function, and work capacity.

REFERENCES

Al-Khalili F., Janszky I., Andersson A., Svane B., and Schenck-Gustafsson K. (2007). Physical activity and exercise performance predict long-term prognosis in middle-aged women surviving acute coronary syndrome. J. Intern. Med. 261:178–187.

Arai T., Obuchi S., Kojima M., Matumoto Y., and Inaba Y. (2006). The evaluation of the relationships between physical factors and effects of exercise intervention on physical functions in community-dwelling older people. Nippon Ronen. Igakkai. Zasshi. 43:781–788.

Balykin M.V., Vinogradov S.N., and Gening T.P. (2004). [Effect of normobaric hypoxia and physical load on the functional indixes of cardiorespiratory system in overweight people.] Vopr. Kurortol. Fizioter. Lech. Fiz. Kult. Jan.–Feb.:18–21.

Bernardi L., Passino C., Serebrovskaya Z., Serebrovskaya T., and Appenzeller O. (2001). Respiratory and cardiovascular adaptations to progressive hypoxia: effect of interval hypoxic training. Eur. Heart J. 22:879–886.

Burtscher M., Pachinger O., Ehrenbourg I., Mitterbauer G., Faulhaber M., Puhringer R., and Tkatchouk E. (2004). Intermittent hypoxia increases exercise tolerance in elderly men with and without coronary artery disease. Int. J. Cardiol. 96:247–254.

Dela F., and Kjaer M. (2006). Resistance training, insulin sensitivity and muscle function in the elderly. Essays Biochem. 42:75–88.

del Pilar Valle M., García-Godos F., Woolcott O.O., Marticorena J.M., Rodríguez V., Gutiérrez I., Fernández-Dávila L., Contreras A., Valdivia L., Robles J., and Marticorena E.A. (2006). Improvement of myocardial perfusion in coronary patients after intermittent hypobaric hypoxia. J. Nucl. Cardiol. 13:69–74.

Ehrenbourg I.V. (1992). The effect of intermittent normobaric hypoxia on physical working ability and oxygen homeostasis in ischemic heart disease. In: Intermittent Hypoxic Training, Effectiveness, Mechanisms of Action. Institute of Physical Culture. Kiev, Ukraine; pp. 93–95.

Garcia-Mendoza M., Valdes C., Ortega T., Rebollo P., and Ortega F. (2006). Differences in health-related quality of life between elderly and younger patients on hemodialysis. J. Nephrol. 19:808–818.

Gill J.M., Al-Mamari A., Ferrell W.R., Cleland S.J., Packard C.J., Sattar N., Petrie J.R., and Caslake M.J. (2004). Effects of prior moderate exercise on postprandial metabolism and vascular function in lean and centrally obese men. J. Am. Coll. Cardiol. 44:2375–2382.

Gippenreiter E., and West J.B. (1996). High altitude medicine and physiology in the former Soviet Union. Aviat. Space Environ. Med. 67:576–584.

Gurvich H.E., and Fainberg R.S. (1938). Increase of organism endurance to high-altitude flights. In: Physiology and Hygiene of High-Altitude Flights. F.G. Krotkov, ed. State Publishing House of the Biological and Medical Literature, Moscow–Leningrad; pp. 109–118.

Haseler L.J., Lin A.P., and Richardson R.S. (2004). Skeletal muscle oxidative metabolism in sedentary humans: 31P-MRS assessment of O2 supply and demand limitations. J. Appl. Physiol. 97:1077–1081.

Heylen E., Simon B., Guerrero F., Elkaim J.P., Saiag B., and Mansourati J. (2005). Reactive hyperaemia in the forearm skin of highly trained windsurfers. Int. J. Sports Med. 26:822–826.

Ishchuk V.I. (2007). Safety and efficacy of intermittent normobaric hypoxia training in elderly patients with ischemic heart disease. J. Ukrainian Acad. Med. Sci. 13:374–384.

Janssens J.P., Pache J.C., and Nicod L.P. (1999). Physiological changes in respiratory function associated with ageing. Eur. Respir. J. 13:197–205.

Klieman L., Hyde S., and Berra K. (2006). Cardiovascular disease risk reduction in older adults. J. Cardiovasc. Nurs. 21(5, Suppl. 1):S27–S39.

Kolchinskaya A.Z., Hatsukov B.H., and Zakusilo M.P. (1999). Oxygen Insufficiency: Destructive and Constructive Actions. Kabardino-Balkaria Scientific Center, Nalchik, Russia.

Kolesnikova E.E., and Serebrovskaya T.V. (2001). Age-related peculiarities of catecholamines exchange and ventilatory responses to hypoxia and hypercapnia under adaptation to intermittent hypoxia. Arkhiv Clin. Exper. Med. 10:165–166.

Korkusko O.V., Sarkisov K.G., and Frajfel'd V.E. (1982). Age-associated peculiarities of microcirculation system in skeletal muscles and their role in muscle work capacity in human aging. ZFA. 37:147–153.

Luckner G., Dunser M.W., Stadlbauer K.H., Mayr V.D., Jochberger S., Wenzel V., Ulmer H., Pajk W., Hasibeder W.R., Friesenecker B., and Knotzer H. (2006). Cutaneous vascular reactivity and flow motion response to vasopressin in advanced vasodilatory shock and severe postoperative multiple organ dysfunction syndrome. Crit. Care.10:135.

Lyamina N.P., Senchikhin V.N., Pokidyshev D.A., and Manukhina E.B. (2001). Disturbed NO production in patients with essential hypertension and a non-drug method of its correction. Kardiologiia. 41:17–21.

Meerson F.Z. (1993). Adaptation to intermittent hypoxia: mechanisms of protective effects. Hypoxia Med. J. 1:2–8.

Meerson F.Z., Tverdokhlib V.P., and Soev V.M. (1989). Adaptation to Periodic Hypoxia in Therapy and Prophylaxis, Nauka, Moscow.

Middlebrooke A.R., Armstrong N., Welsman J.R., Shore A.C., Clark P., and MacLeod K.M. (2005). Does aerobic fitness influence microvascular function in healthy adults at risk of developing Type 2 diabetes? Diabet. Med. Apr. 22:483–489.

Mukharliamov F.Iu., Smirnova M.I., Bedritskii S.A., and Liadov K.V. (2006). Interval hypoxic training in arterial hypertension. Vopr. Kurortol. Fizioter. Lech. Fiz. Kult. :5–6.

Neubauer J.A. (2001). Invited review: physiological and pathophysiological responses to intermittent hypoxia. J. Appl. Physiol. 90:1593–1599.

Rapino C., Bianchi G., Di Giulio C., Centurione L., Cacchio M., Antonucci A., and Cataldi A. (2005). HIF-1alpha cytoplasmic accumulation is associated with cell death in old rat cerebral cortex exposed to intermittent hypoxia. Aging Cell. 4:177–185.

Reeves S.R., and Gozal D. (2005). Developmental plasticity of respiratory control following intermittent hypoxia. Respir. Physiol. Neurobiol. 149:301–311.

Serebrovskaya T.V. (1995). Method for nonspecific body resistance increasing by means of intermittent hypoxic influences "Hypotron." Author's Certificate PA #32, 06 Dec.. Ukraine.

Serebrovskaya T.V. (2002). 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. 3:205–221.

Serebrovskaya T.V., Karaban I.N., Kolesnikova E.E., Mishunina T.M., Swanson R.J., Beloshitsky P.V., Ilyin V.N., Krasuk A.N., Safronova O.S., and Kuzminskaya L.A. (2000). Geriatric men at altitudes: hypoxic ventilatory sensitivity and blood dopamine changes. Respiration. 67:253–260.

Serebrovskaya T.V., Swanson R.J., and Kolesnikova E.E. (2003a). Intermittent hypoxia: mechanisms of action and some applications to bronchial asthma treatment. J. Physiol. Pharmacol. 54:35–41.

Serebrovskaya T.V., Kolesnikova E.E., and Karaban I.N. (2003b). Breathing regulation under intermittent hypoxic training in patients with Parkinson's disease. Fiziol. Zh. 49:95–103.

Sergeev A.A. (1962). Essays on the History of Airspace Medicine, Academy of Sciences of the USSR, Moscow.

Simonenko V.B., Ermolaev A.L., Poshievskaia V.I., and Stepaniants O.S. (2003). Effects of adaptation to intermittent normobaric hypoxia on the results of 24-hour monitoring of arterial pressure in hypertensive patients. Klin. Med. (Mosk.). 81:22–25.

Wasserman K. (1987). Determinants and detection of anaerobic threshold and consequences of exercise above it. Circulation. 76:V129–V139.

Zdolsek J.M., Droog E.J., Thorfinn J., and Lidman D. (2006). Laser Doppler perfusion imaging of the radial forearm flap: a clinical study. Scand. J. Plast. Reconstr. Surg. Hand Surg. 40:101–105.

Address reprint requests to:
Tatiana Serebrovskaya, PhD
Bogomoletz Institute of Physiology
4 Bogomoletz St.
Kiev 01601, Ukraine

E-mail: sereb@biph.kiev.ua

Received August 7, 2007; accepted in final form October 10, 2007.

Effects of intermittent hypoxic training performed at high hypoxia level on exercise performance in highly trained runners

- February 2018
- Journal of Sports Sciences 36(1):1-8

- DOI:
- 10.1080/02640414.2018.1434747

- Anthony M J Sanchez
- Fabio Borrani

Abstract

This study exanimated the effects of intermittent hypoxic training (IHT) conducted at a high level of hypoxia with recovery at ambient air on aerobic/anaerobic capacities at sea level and hematological variations. According to a double-blind randomized design, fifteen highly endurance-trained runners completed a 6-weeks regimented training with 3 sessions per week consisting of intermittent runs (6x work-rest ratio of 5′:5′) on a treadmill at 80–85% of maximal aerobic speed ( ). Nine athletes (hypoxic group, HG) performed the exercise bouts at FI02 = 10.6–11.4% while six athletes (normoxic group, NG) exercised at ambient air. Running time to exhaustion at a velocity corresponding to 95% significantly increased for HG while no effect was found for NG. Regarding , no significant effects were found in either training group. In addition, the decline of jumping performances over a 45s-continuous maximal vertical jump test (i.e. anaerobic capacity index) tended to be lower in HG compared to NG. The levels of the studied hematological variables, including erythropoietin and hematocrit, did not significantly change for either HG or NG. These results highlight that our IHT protocol may induce additional effects on aerobic performance without compromising the anaerobic capacity index in highly-trained athletes.

Intermittent Hypoxia–Hyperoxia Conditioning Improves Cardiorespiratory Fitness in Older Comorbid Cardiac Outpatients Without Hematological Changes: A Randomized Controlled Trial

Article in High altitude medicine & biology · September 2018

DOI: 10.1089/ham.2018.0014

CITATION
1

READS
158

4 authors, including:

Elena N Dudnik
I.M. Sechenov First Moscow State Medical University
47 PUBLICATIONS 87 CITATIONS
SEE PROFILE

Oleg Glazachev
I.M. Sechenov First Moscow State Medical University
87 PUBLICATIONS 133 CITATIONS
SEE PROFILE

Davide Susta
Dublin City University
46 PUBLICATIONS 551 CITATIONS
SEE PROFILE

HIGH ALTITUDE MEDICINE & BIOLOGY
Volume 00, Number 00, 2018

DOI: 10.1089/ham.2018.0014

Intermittent Hypoxia–Hyperoxia Conditioning Improves Cardiorespiratory Fitness in Older Comorbid Cardiac Outpatients Without Hematological Changes: A Randomized Controlled Trial

Elena Dudnik,[1] Elena Zagaynaya,[1] Oleg S. Glazachev,[1] and Davide Susta[1,2]

Abstract

Dudnik, Elena, Zagaynaya E, Glazachev OS, and Susta D. Intermittent Hypoxia–Hyperoxia Conditioning Improves Cardiorespiratory Fitness in Older Comorbid Cardiac Outpatients Without Hematological Changes: A Randomized Controlled Trial. *High Alt Med Biol* 00:000–000, 2018.

Aim: To compare a program based on intermittent hypoxia–hyperoxia training (IHHT) consisting of breathing hypoxic–hyperoxic gas mixtures while resting to a standard exercise-based rehabilitation program with respect to cardiorespiratory fitness (CRF) in older, comorbid cardiac outpatients.

Materials and Methods: Thirty-two cardiac patients with comorbidities were randomly allocated to IHHT and control (CTRL) groups. IHHT completed a 5-week program of exposure to hypoxia–hyperoxia while resting, CTRL completed an 8-week tailored exercise program, and participants in the CTRL were also exposed to sham hypoxia exposure. CRF and relevant hematological biomarkers were measured at baseline and after treatment in both groups.

Results: After intervention, CRF in the IHHT group was not significantly different ($n = 15$, 19.9 ± 6.1 mlO_2 $minutes^{-1}$ kg^{-1}) compared with the CTRL group ($n = 14$, 20.6 ± 4.9 mlO_2 $minutes^{-1}$ kg^{-1}). CRF in IHHT increased significantly from baseline (6.05 ± 1.6 mlO_2 $minutes^{-1}$ kg^{-1}), while no difference was found in CTRL. Systolic and diastolic blood pressures were not significantly different between groups after treatment. Hemoglobin content was not significantly different between groups. Erythrocytes and reticulocytes did not change pre/post interventions in both experimental groups.

Conclusions: IHHT is safe in patients with cardiac conditions and common comorbidities and it might be a suitable option for older patients who cannot exercise. A 5-week IHHT is as effective as an 8-week exercise program in improving CRF, without hematological changes. Further studies are needed to clarify the nonhematological adaptations to short, repeated exposure to normobaric hypoxia–hyperoxia.

Keywords: cardiorespiratory fitness; comorbid cardiac patients; normobaric hypoxia; simulated altitude

Introduction

PHYSICAL INACTIVITY IS one of the leading cardiovascular risk factors and people are less likely to regularly exercise as they age. Usually correlated to levels of physical activity, cardiorespiratory fitness (CRF) has been shown to be an independent predictor of cardiovascular health and it is inversely associated with cardiovascular mortality (DeFina et al., 2015; Myers et al., 2015).

Intermittent exposure to hypoxia has been proven effective in improving CRF in healthy senior men (Shatilo et al., 2008), in coronary disease (Burtscher et al., 2004), and heart failure patients (Saeed et al., 2012). Despite a considerable variety of the exposure patterns, there is growing evidence that simulating altitude by reducing the oxygen content of the inhaled air can provide humans with a stimulus potentially useful to help treating some chronic conditions, as recently reviewed by Lizamore and Hamlin (2017). Replacing normoxia with hyperoxia during intermittent exposure to hypoxia has been proven to be effective in preliminary studies focused on exercise performance in athletes with overtraining syndrome (Susta et al., 2017) and in coronary artery disease patients

[1]Department of Normal Physiology, I.M. Sechenov First Moscow State Medical University, Moscow, Russia.
[2]School of Health and Human Performance, Dublin City University Glasnevin Campus, Dublin, Ireland.

(Glazachev et al., 2017). This novel approach has been shown to trigger positive adaptations such as a better autonomic nervous system balance, with reduction of the sympathetic drive, an improved endothelial function (Lyamina et al., 2011), and a better total antioxidant capacity (Sazontova et al., 2012). In addition to these physiological adaptations, replacing normoxia with hyperoxia allows for a shorter recovery between bouts of hypoxic exposure, thus making it more convenient to patients and healthcare staff.

The aim of the present study is to investigate the effects of a novel intervention based on repeated, short, intermittent normobaric hypoxia–hyperoxia exposures, or intermittent hypoxia-hyperoxia training (IHHT), delivered 15 times over 5 weeks, on CRF in comorbid older patients and to compare IHHT with a traditional, physical, exercise-based, aerobic fitness program.

Materials and Methods

Thirty-two cardiology outpatients with comorbidities (such as hypertension, type 2 diabetes, chronic obstructive pulmonary disease, dyslipidemia, mild obesity) volunteered to our study and were randomly (sealed envelope) allocated to control (CTRL) or intervention (IHHT) groups. All participants were initially assessed by being exposed to 10 minutes of continuous hypoxia (11% O_2) to analyze individual responses to hypoxia to tailor individual hypoxia–hyperoxia conditioning according to previously published principles and protocols (Glazachev, 2013), and dependent variables' measurements were collected in all participants. The IHHT group completed a 5-week hypoxia (11%–12% O_2)—hyperoxia (30%–33% O_2) training: 3 sessions/week, 5–7 hypoxic periods of 4–6 minutes, 3-minute hyperoxic recovery, 15 sessions in total (ReOxy; AiMediq, Luxembourg). The CTRL group completed 8 weeks of a standard tailored cardiopulmonary exercise program according to the European Society of Cardiology suggestions and was exposed to 15 sessions of a sham hypoxic training over 8 weeks (breathing room air). Exercise tailoring was based on an incremental cardiopulmonary test at baseline, and exercise was planned to target heart rate corresponding to metabolic intensities as per guidelines ("at least 150 minutes a week at moderate intensities, i.e., Borg RPE between 12–13 and HR between 64 and 76% of HRmax, able to speak full sentences while walking/cycling/exercising," Corrà et al., 2010) depending on the availability to visit our laboratory. Group allocation concealment was not possible because CTRL group participants were asked to exercise, while IHHT were asked to "keep their physical activity habits" and not to participate in any structured exercise program during the 5 weeks of IHHT exposure. Sham or actual hypoxia–hyperoxia exposures were delivered as same duration sessions and by following very similar schedules (three times a week in IHHT group, two times a week in CTRL). Both groups were tested at baseline and again 9–10 weeks after the beginning of their respective interventions (i.e., 4 weeks after completing the hypoxia–hyperoxia exposure in the IHHT group and 1–2 weeks after completing the standard rehabilitation program in the CTRL group). The rationale for this time line was based on our previous study showing an improved CRF 1 month after completing an IHHT protocol (Glazachev et al., 2017) with the aim of being able to compare two treatments of different durations (Table 1).

During each session of both the IHHT and sham-IHHT treatments, all participants' pulse rate and SaO_2 were continuously monitored (without providing participants with feedback) by using a finger pulse oximeter connected to the ReOxy equipment and they were supervised by physicians and/or nurses.

Baseline and "after intervention" measurements included the following:

(1) CRF was measured by indirect calorimetry (Fitmate Med, Cosmed, Italy) as VO_{2peak} during an incremental cardiopulmonary test (Bruce and M-Bruce protocols).
(2) Hematological biomarkers were measured from blood samples collected at baseline and at the end of the study and analyzed using hospital blood biochemistry laboratory analyzers according to international standards.

All participants were asked to comply with their drugs therapies and any change in therapy was an exclusion criteria.

Statistical analysis was conducted using a two-way ANOVA (group × time) and a Tukey's multiple comparison test (Prism 6 Software; GraphPad). Significance was set at 0.05, the sample size being calculated (power of 80%) based on our previous study (Glazachev et al., 2017). Effect size (ES) was calculated using *Cohen's d* formula and the effect graded as "small" (ES <0.2), "moderate" (ES: 0.2–0.5), "large" (ES: 0.5–0.8), and "very large" (ES >0.8).

The study was conducted according to the World Medical Association Helsinki guidelines (Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects, Bulletin of World Health Organization 2001) and ethical approval was granted by the local university ethics committee.

Results

Only 29 of 32 participants were available to be assessed at baseline. Three participants left the study before being as-

Table 1. Study Time Line

	Week 1	*Week 2*	*Week 6*	*Week 9*	*Week 10*	*Week 11*
CTRL	Baseline tests CRF, hypoxic test, blood samples	Start of exercise+sham IHHT intervention	—	End of exercise+sham IHHT exposure	Posttest	Posttest
IHHT	Baseline tests CRF, hypoxic test, blood samples	Start of IHHT interventions	End of IHHT exposure	Posttest	Posttest	

CRF, cardiorespiratory fitness.

Table 2. Participants' Profile (Mean ± Standard Deviation) and Comorbidities

	IHHT (n = 15)	*CTRL (n = 14)*
Age (years)	66.7 ± 5.7	65.0 ± 6.2
BMI (kg/m^2)	27.7 ± 2.3	28.9 ± 2.0
Hypertension	12/15	10/14
Previous MI	5/15	6/14
Type 2 diabetes	7/15	6/14
COPD	2/15	2/14
Dyslipidemia	12/15	12/14
Obesity (BMI >30)	4/15	4/14

COPD, chronic obstructive pulmonary disease; CTRL, control; IHHT, intermittent hypoxia–hyperoxia training or intermittent normobaric hypoxia–hyperoxia exposures; MI, myocardial infarction.

sessed because of personal reasons. The IHHT and CTRL groups were balanced with respect to age, gender, and BMI. Table 2 shows participant profiles in each group.

After intervention, cardiorespiratory fitness, measured as VO_{2peak}, was similar in both groups (mean difference –0.66, 95% CI –4.9 to 3.6 mlO_2 minutes^{-1} kg^{-1}). In the IHHT group, the aerobic capacity was significantly higher (mean difference 6.05 mlO_2 minutes^{-1} kg^{-1}) compared with baseline, and likely to be clinically meaningful because of its large ES (Cohen's >1). The increase in aerobic capacity seen in IHHT is 1.72 METs (metabolic unit equivalent to 3.5 mlO_2/min), whereas the increase in CTRL is lower than one MET (0.76). In the CTRL group, the value of peak oxygen consumption was not significantly increased compared with values measured at baseline.

The interaction was not significant, please see Table 3 for a summary of time × group interaction, time effect, and ES (reported for IHHT group only).

Table 3. Interaction, Time Effect, and Effect Size (Intermittent Hypoxia–Hyperoxia Training Only) for Each Dependent Variable

	Interaction	*Time*	*Effect size*
HR rest	$F(1,54) = 0.005$ $p = 0.94$	$F(1,54) = 0.34$ $p = 0.94$	0.12
SBP	$F(1,54) = 3.42$ $p = 0.07$	$F(1,54) = 0.34$ $p = 0.56$	0.74
DBP	$F(1,54) = 4.96$ **$p = 0.03$**	$F(1,54) = 0.42$ $p = 0.52$	0.70
VO_{2peak}	$F(1,54) = 2.21$ $p = 0.14$	$F(1,54) = 14.65$ **$p = 0.0003$**	1.10
RBC	$F(1,54) = 0.007$ $p = 0.93$	$F(1,54) = 0.018$ $p = 0.89$	0.01
Hemoglobin	$F(1,54) = 0.052$ $p = 0.82$	$F(1,54) = 0.078$ $p = 0.78$	0.01
Reticulocytes	$F(1,54) = 0.74$ $p = 0.39$	$F(1,54) = 0.027$ $p = 0.87$	0.23
WBC	$F(1,54) = 0.77$ $p = 0.38$	$F(1,54) = 0.47$ $p = 0.50$	0.47
Platelets	$F(1,54) = 2.56$ $p = 0.12$	$F(1,54) = 0.69$ $p = 0.41$	0.61

Bold indicates significant changes.

Red blood cells (RBCs) were significantly lower in IHHT compared with CTRL at baseline (due to random allocation of participants). At the end of the interventions, RBCs did not increase in both groups (Tables 3 and 4).

Hemoglobin was significantly lower in IHHT compared with CTRL at baseline (due to random allocation of participants). IHHT and CTRL hemoglobin values were still different after intervention and the interventions did not change hemoglobin values within each group (Tables 3 and 4).

After intervention, reticulocytes were significantly higher in the IHHT group compared with CTRL. Since reticulocytes in the IHHT group did not significantly increase after intervention and reticulocytes in CTRL decreased (although not significantly) after intervention, this finding has to be interpreted cautiously (Tables 3 and 4).

White blood cells and platelets did not change after hypoxia–hyperoxia exposure in IHHT group as well as after intervention in CTRL group; there were no differences between IHHT and CTRL groups after intervention (Tables 3 and 4).

Heart rate at rest as well as systolic blood pressure (SBP) and diastolic blood pressure (DBP) did not change after intervention. The interaction between time and group was significant in DBP (Tables 3 and 4).

Discussion

Our study shows that cardiopulmonary fitness was significantly improved after repeated, intermittent exposures to normobaric hypoxia–hyperoxia as the values of VO_{2peak} in IHHT group were higher than those measured at baseline. These values are similar to the ones measured in the CTRL group chronic outpatients involved in rehabilitation based on tailored exercise prescription and lifestyle advice, thus showing that IHHT is equally effective compared with a traditional exercise-based rehabilitation program among chronic outpatients. Indeed, after treatment, the level of fitness was similar in both groups, thus showing that improving cardiopulmonary fitness without exercising is feasible in patients with low baseline values and comorbidities usually affecting noncommunicable disease chronic patients. Our findings confirm the efficacy of intermittent hypoxia exposure to improve exercise tolerance in coronary artery disease patients (Burtscher et al., 2004; Korkushko et al., 2010) and provide additional evidence that short, repeated, intermittent exposures to hypoxia can play a role as therapeutic option in patients suffering from a variety of chronic conditions (Burtscher et al., 2010; Duennwald et al., 2013). Interestingly, our results suggest that such improved cardiorespiratory fitness is likely to be independent of hematological adaptations since hemoglobin, RBC counts, and reticulocytes did not change after exposure to hypoxia–hyperoxia in the IHHT group and this result is aligned with our previous findings in a population of young athletes with overtraining syndrome (Susta et al., 2017). Thus, IHHT seems to be effective and efficient (the number of sessions and each session duration are reduced compared with usual hypoxia–normoxia intermittent exposure) in improving the overall aerobic capacity of older, comorbid patients, whose margins to improve are usually reduced. It is well accepted that adaptations to hypoxia are dependent on the hypoxic exposure patterns and it has been suggested that the therapeutic potential and the effects of hypoxia exposure are dose dependent (Navarrete-Opazo and Mitchell, 2014). Our results suggest that using

TABLE 4. SUMMARY OF RESULTS (MEAN ± STANDARD DEVIATION)

	IHHT (n = 15)		*CTRL (n = 14)*	
	Baseline	*After*	*Baseline*	*After*
HR rest (beat/min)	70.9 ± 13.2	69.6 ± 8.3	67.6 ± 8.0	65.9 ± 9.2
SBP (mmHg)	140.5 ± 14.1	131.3 ± 9.5	136.4 ± 14.8	135.1 ± 18.1
DBP (mmHg)	82.1 ± 11.1	74.7 ± 8.9	77.9 ± 9.7	82.0 ± 9.3
VO_{2peak} (mlO_2 $minutes^{-1}$ kg^{-1})	13.9 ± 2.5	19.9 ± 6.1*	17.9 ± 2.8	20.6 ± 4.9
RBC ($\times 10^{12}$/L)	4.38 ± 0.33^	4.38 ± 0.30^	4.77 ± 0.42	4.79 ± 0.28
Hemoglobin (g/dL)	13.6 ± 0.8^	13.6 ± 1.1	14.5 ± 1.1	14.3 ± 1.1
Reticulocytes (%)	0.9 ± 0.6	1.1 ± 0.5^	0.6 ± 0.4	0.6 ± 0.3
WBC ($\times 10^9$/L)	6.12 ± 1.05	5.49 ± 1.58	6.55 ± 1.71	6.63 ± 1.76
Platelets ($\times 10^9$/L)	215.5 ± 30.0	251.6 ± 74.8	227.2 ± 51.8	215.8 ± 59.9

*Significantly different compared with baseline values in the same group. Tukey's multiple comparisons tests ($p < 0.05$).
^Significantly different compared with other group values at the same time. Tukey's multiple comparisons tests ($p < 0.05$).
DBP, diastolic blood pressure; HR, heart rate; RBC, red blood cell, SBP, systolic blood pressure; WBC, white blood cell.

exposure to hypoxia–hyperoxia can generate adaptations similar to the ones measured in patients after completing a higher number of intermittent hypoxia–normoxia exposures. As speculation, cellular and molecular adaptations known, from animal studies, to be triggered by hypoxia–hyperoxia exposure could explain our results (Sazontova et al., 2012). Furthermore, based on our results, normobaric hypoxia–hyperoxia seems even more applicable than normobaric hypoxia–normoxia because of its convenience: shorter hyperoxic recovery times (typically 3 minutes) between bouts of hypoxia (O_2 at 11%–12%) allow for more exposures during each session and this exposure pattern helps reducing the number of sessions per week (to three 1-hour sessions a week in our intervention protocol), a schedule likely to be associated with higher compliance among the outpatient populations. Also, being exposed to hyperoxia (O_2 at 30%) immediately after being exposed to hypoxia (O_2 at 11%–12%) seems to minimize symptoms, such as headache, commonly experienced by patients during the first hypoxia–normoxia exposures. In fact, our study participants did not experience any "side effects" and each session was well tolerated by all of them.

In relation to SBP and DBP, our results are not aligned with our previous findings on a similar population where IHHT was associated with reduced SBP and DBP (Glazachev et al., 2017). It it worth noting here that the interaction between group and time was significant in DBP behavior.

Finally, three potential limitations to our study are to be mentioned here. First, our participants' baseline differences may have limited our study ability to identify potential hematological mechanisms of adaptations following IHHT, but this limitation cannot affect our findings if cautiously and accurately interpreted. Second, participants' follow-up at 3 and 6 months or longer is needed to better know the long-term effects of exposure to hypoxia–hyperoxia on parameters relevant to the patients and to verify the IHHT applicability of exercise replacing therapy. Third, we could not monitor CTRL group levels of physical activity during the study. In the future, studies are needed for a better understanding of the effects of IHHT as a therapeutic tool for patients, classified according to their chronic disease profile. Moreover, a larger, more homogeneous sample would allow for a more accurate patient stratification and levels of physical activity should be monitored during the study.

Conclusion

Intermittent hypoxia–hyperoxia exposure is well tolerated by older, comorbid patients and provides them with an alternative way to improve their cardiorespiratory fitness without exercising. Further studies are needed to better understand the role of nonhematological mechanisms likely to explain such adaptations and to explore the potential for this novel therapeutic option to treat older people as preventive strategy and to be offered to noncommunicable chronic disease patients, often struggling to exercise on a regular basis for clinical and personal reasons.

Acknowledgments

The study was partially supported by the Russian Foundation for Basic Research (Department for Humanities), Grant 17-06-00784 "Quality of life in elderly patients with cardiovascular disease: the impact of adaptation to intermittent hypoxia–hyperoxia." The authors acknowledge all the outpatients who made themselves available to participate in this trial. Also, they thank AiMediq S.A. Company, Luxembourg, for supplying at cost the ReOxy equipment for hypoxic testing and hypoxic–hyperoxic training.

Author Disclosure Statement

Oleg S. Glazachev provided consultancy to AiMediq to develop ReOxy equipment's software.

Davide Susta, Elena Dudnik, and Elena Zagaynaya have nothing to declare.

References

Burtscher M, Gatterer H, Szubski C, Pierantozzi, Faulhaber M. (2010). Effects of interval hypoxia on exercise tolerance: Special focus on patients with CAD or COPD. Sleep Breath 14:209–220.

Burtscher M, Pachinger O, Ehrenbourg I, Mitterbauer G, Faulhaber M, Puringer R, and Tkatchouk E. (2004). Intermittent hypoxia increases exercise tolerance in elderly men with and without coronary artery disease. Int J Cardiol 96: 247–254.

Corrà U, Piepoli MF, Carré F, Heuschmann P, Hoffmann U, Verschuren M, Halcox J, Giannuzzi P, Saner H, Wood D, Benzer W, Bjarnason-Wehrens B, Dendale P, Gaita D,

McGee H, Mendes M, Niebauer J, Olsen Zwisler A-D, and Schmid J-P. (2010). Secondary prevention through cardiac rehabilitation: Physical activity counselling and exercise training: Key components of the position paper from the Cardiac Rehabilitation Section of the European Association of Cardiovascular Prevention and Rehabilitation. Eur Heart J 31:1967–1974.

DeFina LF, Haskell WL, Willis BL, Barlow CE, Finley CE, Levine BD, and Cooper KH. (2015). Physical activity versus cardiorespiratory fitness: Two (partly) distinct components of cardiovascular health? Prog Cardiovasc Dis 57:324–329.

Duennwald T, Gatterer H, Groop P-H, Burtscher M, and Bernardi L. (2013). Effects of a single bout of interval hypoxia on cardiorespiratory control in patients with type 1 diabetes. Diabetes 62:4220–4227.

Glazachev O, Kopylov P, Susta D, Dudnik E, and Zagaynaya E. (2017) Adaptations following an intermittent hypoxia-hyperoxia training in coronary artery disease patients: A controlled study. Clin Cardiol 40:370–376.

Glazachev OS. Optimization of clinical application of interval hypoxic training. 2013. Biomed Eng 47:134–137. [translated from Meditsinskaya Tekhnika, Vol. 47, No. 3, May-June, 2013, pp. 21–24].

Korkushko OV, Shatilo VB, and Ishchuk VA. (2010). Effectiveness of intermittent normobaric hypoxic training in elderly patients with coronary artery disease. Adv Gerontol 23:476–482.

Lizamore CA, and Hamlin MJ. (2017). The use of simulated altitude techniques for beneficial cardiovascular health outcomes in nonathletic, sedentary, and clinical populations: A literature review. High Alt Med Biol 18:305–321.

Lyamina NP, Lyamina SV, Senchiknin VN, Mallet RT, Downey HF, and Manukhina EB. (2011). Normobaric hypoxia conditioning reduces blood pressure and normalizes nitric oxide synthesis in patients with arterial hypertension. J Hypertens 29:2265–2272.

Myers J, McAuley P, Lavie CJ, Despres J-P, Arena R, and Kokkinos P. (2015). Physical activity and cardiorespiratory fitness as major markers of cardiovascular risk: Their independent and interwoven importance to health status. Prog Cardiovasc Dis 57:306–314.

Navarrete-Opazo A, and Mitchell GS. (2014). Therapeutic potential of intermittent hypoxia: A matter of dose. Am J Physiol Regul Integr Comp Physiol 307:R1181–R1197.

Saeed O, Bhatia V, Formica P, Browne A, Aldrich TK, Shin J, and Maybaum S. (2012). Improved exercise performance and skeletal muscle strength after simulated altitude exposure: A novel approach for patients with chronic heart failure. J Card Fail 18:387–391.

Sazontova T, Glazachev O, and Bolotova A. (2012). Adaptation to hypoxia and hyperoxia improves physical endurance: The role of reactive oxygen species and redox-signaling. Russ J Physiol 98:793–806.

Shatilo VB, Korkushko OV, Ischuk VA, Downey HF, and Serebrovskaya TV. (2008). Effects of intermittent hypoxic training on exercise performance, haemodynamics, and ventilation in healthy senior men. High Alt Med Biol 9:43–52.

Susta D, Dudnik E, and Glazachev OS. (2017). A programme based on repeated hypoxia–hyperoxia exposure and light exercise enhances performance in athletes with overtraining syndrome: A pilot study. Clin Physiol Funct Imaging 37:276–281.

Address correspondence to:
Davide Susta, MD
School of Health and Human Performance
Dublin City University
DCU Glasnevin Campus
Collins Avenue
Dublin D9
Ireland

E-mail: davide.susta@dcu.ie

Received February 8, 2018;
accepted in final form July 4, 2018.

Doppelblind randomisiert
Placebo kontrolliert

Intermittent hypoxia increases exercise tolerance in elderly men with and without coronary artery disease

Article *in* International Journal of Cardiology · September 2004

DOI: 10.1016/j.ijcard.2003.07.021 · Source: PubMed

CITATIONS
56

READS
54

7 authors, including:

Burtscher Martin
University of Innsbruck
286 PUBLICATIONS **2,557** CITATIONS
SEE PROFILE

Igor Ehrenburg
Pirogov Russian National Research Medical U...
9 PUBLICATIONS **179** CITATIONS
SEE PROFILE

Martin Faulhaber
University of Innsbruck
78 PUBLICATIONS **796** CITATIONS
SEE PROFILE

ELSEVIER

International Journal of Cardiology 96 (2004) 247–254

International Journal of Cardiology

www.elsevier.com/locate/ijcard

Intermittent hypoxia increases exercise tolerance in elderly men with and without coronary artery disease

Martin Burtscher[a,*], Otmar Pachinger[b], Igor Ehrenbourg[c], Günther Mitterbauer[a], Martin Faulhaber[a], Reinhard Pühringer[a], Elena Tkatchouk[c]

[a] *Department of Sport Science, Medical Section, University of Innsbruck, Fürstenweg 185, 6020 Innsbruck, Austria*
[b] *Division of Cardiology, Internal Medicine, University of Innsbruck, Anichstrasse 35, 6020 Innsbruck, Austria*
[c] *Clinical Research Laboratory, Hypoxia Medical Academy, 3, Ivankovskoye shosse, 123367 Moscow, Russia*

Received 24 February 2003; received in revised form 22 July 2003; accepted 25 July 2003

Abstract

Background: Intermittent hypoxia has been suggested to increase exercise tolerance by enhancing stress resistance and improving oxygen delivery. Because the improvement of exercise tolerance reduces mortality in the elderly with and without coronary artery disease intermittent hypoxia might be a valuable preventive and therapeutic tool. However, controlled studies are lacking. *Methods and results:* Sixteen males (50–70 years, 8 with and 8 without prior myocardial infarction) were randomly assigned in a double-blind fashion to receive 15 sessions of passive intermittent hypoxia (hypoxia group) or normoxia (control group) within 3 weeks. For the hypoxia group each session consisted of three to five hypoxic (14–10% oxygen) periods (3–5 min) with 3-min normoxic intervals. Controls inhaled only normoxic air in the same way. Exercise tests were performed before and after the 3-week breathing program. After 3 weeks of intermittent hypoxia peak oxygen consumption had increased compared to normoxic conditions (+6.2% vs. −3%, $p<0.001$). This improvement was closely related to the enhanced arterial oxygen content after hypoxia ($r=0.9$, $p<0.001$). Both higher haemoglobin concentration and less arterial oxygen desaturation during exercise contributed to the increase in arterial oxygen content. During sub-maximal exercise (cycling at 1 W/kg) heart rate, systolic blood pressure, blood lactate concentration, and the rating of perceived exertion were diminished after intermittent hypoxia compared to control conditions (all $p<0.05$). Changes in responses to exercise after intermittent hypoxia were similar in subjects with and without prior myocardial infarction. *Conclusions:* Three weeks of passive short-term intermittent hypoxic exposures increased aerobic capacity and exercise tolerance in elderly men with and without coronary artery disease.

Keywords: Intermittent hypoxia; Exercise tolerance; Aerobic capacity; Elderly; Coronary artery disease

1. Introduction

Intermittent hypoxia is defined as repeated episodes of hypoxia interspersed with normoxic periods [1]. Hypoxic episodes are created by exposure to natural high altitude, sojourns in hypobaric chambers or by breathing hypoxic gas mixtures in normobaric conditions. Intermittent hypoxia has been suggested to improve exercise performance, to acclimatize before going to high altitude or for prevention and treatment of various illnesses [2–7]. On the one hand, the main rationale for the clinical use of intermittent hypoxia is based on the potential cross-protective value of adaptations to one stress, which then provides resistance to another stress [8–10]. On the other hand, as is the case with acclimatization to chronic hypoxia, intermittent hypoxia is characterised by a progressive increase in ventilation, adaptations of the haematopoetic and cardio-circulatory systems to enhance oxygen delivery to the tissues, and alterations on the tissue level to optimise the utilisation of oxygen [11–13]. Both enhanced stress resistance and improved oxygen delivery are basic preconditions for increased exercise tolerance. Because the improvement of exercise tolerance reduces mortality in the elderly, in particular in patients with coronary artery disease [14,15], intermittent hypoxia might be considered to be a valuable preventive and therapeutic tool. However, beneficial and adverse effects of intermittent

* Corresponding author. Prof. Martin Burtscher, Dept. of Sport Science, Medical Section, University of Innsbruck, Fürstenweg 185, 6020 Innsbruck, Austria.
E-mail address: Martin.Burtscher@uibk.ac.at (M. Burtscher).

0167-5273/$ - see front matter © 2003 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ijcard.2003.07.021

hypoxia may vary markedly depending on the timing of hypoxic cycling, the cycle length, the degree of hypoxia and various co-stimuli like hypo- and hypercapnia, acidosis or alkalosis [1,13]. From among a broad variety of protocols, experimentally repeated short-term hypoxia with normoxic intervals with a cycle length of about 5 min, also known as interval hypoxic training, has been clinically used by Russian physicians since many years [7,16,17]. They report these passive short-term hypoxic exposures to be beneficial and well tolerated by the healthy elderly and patients with various diseases as well. However, the exclusion of control groups has been a common feature of studies employing the intermittent hypoxia protocol in the healthy and diseased elderly. Therefore, we conducted a randomised, double blind, placebo-controlled trial to investigate the effects of repeated short-term hypoxia on exercise tolerance in elderly men with and without coronary artery disease.

2. Methods

2.1. Subjects

Normally physically active men (age 50–70 years; NYHA class I and II) with or without prior myocardial infarction, living in or near Innsbruck (600 m; Austria), were invited to participate in the study. Volunteers had to undergo a routine physical examination. Subjects were excluded if they could not perform cycle exercise, or had recent myocardial infarction and/or revascularisation (<8 weeks prior to inclusion in the study), episode of instable angina, decompensated heart failure, life-threatening arrhythmias, known symptomatic aortic outflow obstruction, severe hypertension (>180/100 mm Hg) or any other severe systemic non-cardiac disease. The first 16 subjects meeting the inclusion criteria (8 with and 8 without prior myocardial infarction) comprised the study population. Finally, after stratification for prior myocardial infarction, subjects were randomly assigned in a double-blind fashion to the hypoxia group or the control group. Baseline characteristics of the study groups are shown in Table 1. Study participants were advised not to change medications, nutrition and levels and pattern of physical activity during the entire study period. The study was approved by the local ethics committee. The investigation was carried out in conformity with the ethical standards laid down in the 1964 Declaration of Helsinki. All persons gave their informed consent prior to their participation in the study.

2.2. Study protocol

Initial examination before exercise testing included medical history, data on physical activity, blood determinations (red and white blood cell count, haemoglobin concentration, haematocrite, concentrations of blood glucose, total cholesterol and HDL, triglycerides, uric acid, and blood gas analyses), electrocardiography, echocardiography, blood pressure measurements and basic pulmonary function testing.

Table 1
Baseline characteristics of the hypoxia and the control group

	Hypoxia group ($n=8$)	Control group ($n=8$)
Age (years)	59.3 (5.4)	61.3 (5.0)
Height (cm)	172.1 (3.1)	177.0 (3.3)
Body mass (kg)	77.8 (12.9)	76.1 (4.4)
Heart rate (bpm)	67.4 (6.8)	63.3 (9.7)
Systolic blood pressure (mm Hg)	144.3 (13.9)	140.8 (12.7)
Diastolic blood pressure (mm Hg)	84.0 (13.3)	82.5 (8.9)
Arterial oxygen saturation (%)	95.9 (1.3)	96.0 (1.5)
FEVC (l)	5.0 (0.8)	5.2 (0.6)
FEV_1 (%)	76.3 (7.0)	77.5 (3.9)
MVV (l/min)	153.6 (28.1)	161.4 (20.9)
Total cholesterol (mg/dl)	259.1 (41.0)	210.9 (30.5)
VO_2 peak (ml/min/kg)	30.1 (6.4)	36.9 (9.5)
Physical activity (h/week)	6.4 (4.8)	6.3 (6.5)
Current smokers, n (%)	1 (13)	2 (25)
Ejection fraction (%)	54.9 (8.3)	50.8 (14.8)
Hypertension, n (%)	3 (38)	3 (38)
Hypercholesterolaemia, n (%)	3 (38)	3 (38)
Diabetes, n (%)	0 (0)	1 (13)
Previous MI, n (%)	4 (50)	4 (50)
Medications, n (%)		
Aspirin	2 (25)	3 (38)
β-blockers	2 (25)	1 (13)
ACE inhibitors	0 (0)	2 (25)
Calcium channel blockers	1 (13)	1 (13)
Anticoagulants	1 (13)	2 (25)
Statins	2 (25)	2 (25)
Diuretics	0 (0)	2 (25)
Nitrates	1 (13)	1 (13)

Data represent means (SD) or frequencies.
Abbreviations: Forced Expiratory Vital Capacity (FEVC), Forced Expiratory Volume (FEV_1), Maximal Voluntary Ventilation (MVV), Peak Oxygen Uptake (VO_2peak), Angiotensin-Converting-Enzyme-Inhibitors (ACE-inhibitors); myocardial infarction (MI).

2.2.1. Exercise tests

Incremental symptom-limited spiro-ergometric pre-tests were performed in the week preceding the breathing program in the late morning not earlier than 2 h after breakfast. No intense physical activity was permitted during 3 days prior to the tests. Venous blood samples were taken before exercise testing. Resting respiratory and cardiovascular parameters were measured during a 5-min period in a sitting position on the cycle ergometer (Ergoline 900, Schiller, Switzerland). The starting workload was 0.5 W/kg body mass, which was increased by 0.5 W/kg every 3 min until subjects were unable to continue because of fatigue or dyspnoea. The following criteria for termination were ap-

Table 2
The 3-week breathing program

Hypoxia Group									
Days 1–5									
Duration of breathing periods (min)	3	3	3	3	3				
Fraction of oxygen (%)	14	21	14	21	14				
Days 8–12									
Duration of breathing periods (min)	4	3	4	3	4	3	4		
Fraction of oxygen (%)	12	21	12	21	12	21	12		
Days 15–19									
Duration of breathing periods (min)	5	3	5	3	5	3	5	3	5
Fraction of oxygen (%)	10	21	10	21	10	21	10	21	10

Control Group

Performed the same program breathing only normoxic air (21% of inspired oxygen fraction).

plied: angina, signs of cerebral or peripheral hypoperfusion (pallor, cyanosis, faintness, nausea), horizontal or downsloping ST-segment depression >2 mV, ST-segment elevation >2 mV (except in dyskinetic segments after infarction), onset of second- or third-degree AV block, ventricular extrasystoles >Lown 4b, complex supraventricular arrhythmias, increase in blood pressure >230 mm Hg systolic or 120 mm Hg diastolic, decrease in systolic blood pressure below the baseline value or no increase in heart rate.

Gas exchange was measured by an open spirometric system (Oxycon Alpha, Jaeger, Germany). A six-lead electrocardiogram and arterial oxygen saturation (by finger pulseoximetry) were recorded continuously. Blood lactate concentrations from the hyperaemized ear lobe, systolic blood pressure, and ratings of perceived intensity of exertion according to the "Borg scale" [18] were determined at the end of each workload.

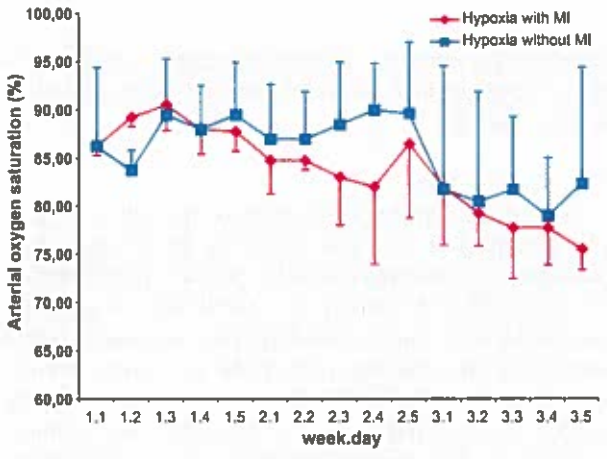


Fig. 1. Arterial oxygen saturation during the last hypoxic period of each day in subjects with ($n=4$) and without ($n=4$) prior myocardial infarction (MI) of the hypoxia group. Data represent means (SD).

Table 3
Haematological parameters of the hypoxia and the control group before and after the 3 week breathing program

	Hypoxia group ($n=8$)		Control group ($n=8$)		p-value
	Before	After	Before	After	
RBC (10^6/ml)	4.89 (0.24)	5.08 (0.19)	4.94 (0.41)	4.77 (0.41)	0.02
Hb (g/dl)	14.4 (0.8)	15.0 (0.7)	14.6 (0.9)	14.6 (1.0)	0.04
Hct (%)	44.1 (2.5)	44.3 (3.0)	45.0 (4.1)	43.8 (3.8)	0.38
MCV (fl)	90.3 (2.6)	87.3 (6.5)	91.2 (4.9)	92.0 (4.8)	0.22
MCH (pg)	29.4 (0.9)	29.5 (1.6)	29.6 (1.8)	30.7 (1.3)	0.73
MCHC (g/dl)	32.6 (1.0)	33.9 (1.1)	32.5 (2.1)	33.4 (1.6)	0.59

Data represent means (SD). p-values for differences in changes between groups.
Abbreviations: Red Blood Cell Count (RBC), Haemoglobin (Hb), Haematocrit (Hct), Mean Cell Volume (MCV), Mean Cell Haemoglobin (MCH), Mean Cell Haemoglobin Concentration (MCHC).

2.2.2. Breathing program

After completion of the pre-tests, the 3-week breathing program (Table 2), consisting of five session per week, took place. For the hypoxia group, each session consisted of three to five hypoxic (14–10% inspired fraction of oxygen; HypoxyComplex HypO2, HypoMed, Moscow) periods, each lasting 3–5 min with 3-min normoxic intervals. Hypoxic and normoxic air was inhaled via face mask in a sitting position. The control group performed the program (inhaling only normoxic air) in the same way. The breathing protocol was adapted to that proposed by the Clinical Research Laboratory of the Hypoxia Medical Academy in

Table 4
Cardiovascular and ventilatory responses to sub-maximal exercise (1 W/kg) of the hypoxia and the control group before and after the 3-week breathing program

	Hypoxia group ($n=8$)		Control group ($n=8$)		p-value
	Before	After	Before	After	
Heart rate (bpm)	112 (18.5)	103 (16.9)	96 (11.9)	94 (11.3)	0.03
Systolic blood pressure (mm Hg)	165 (36.9)	156 (33.3)	163 (16.9)	164 (11.0)	0.02
Rate pressure product	18,986 (6593)	16,380 (5419)	15,746 (3033)	15,443 (2386)	0.02
Oxygen consumption (ml/min/kg)	15.6 (1.3)	15.4 (1.4)	16.2 (0.7)	15.5 (1.2)	0.35
Respiratory exchange ratio	0.84 (0.08)	0.85 (0.07)	0.83 (0.07)	0.82 (0.06)	0.60
Minute ventilation (l/min)	35.8 (7.6)	36.6 (7.2)	35.7 (3.5)	32.8 (2.9)	0.06
Arterial oxygen saturation (%)	95.4 (1.4)	97.0 (0.9)	96.8 (1.3)	97.0 (1.3)	<0.01
Arterial oxygen content (ml/l)	186.3 (11.0)	197.6 (10.3)	191.8 (11.1)	192.4 (13.8)	<0.01
Blood lactate concentration (mmol/l)	2.8 (0.6)	2.3 (0.5)	2.3 (0.5)	2.4 (0.6)	<0.01
Perceived exertion	12.4 (1.2)	11.0 (1.2)	11.6 (1.2)	11.8 (1.3)	<0.01

Data represent means (SD). p-values for differences in changes between groups.

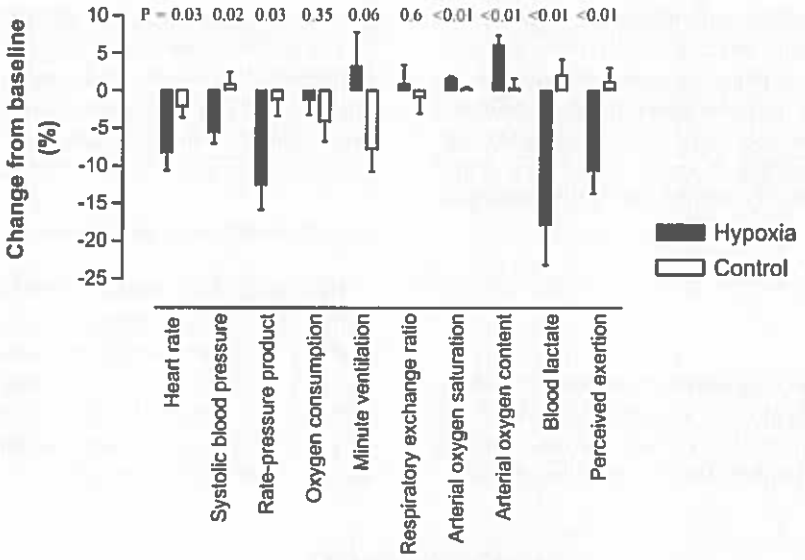


Fig. 2. Changes (in percentages) from baseline of cardiorespiratory responses at sub-maximal workload (1 W/kg) after the 3-week breathing program of the hypoxia ($n=8$) and the control group ($n=8$). Data represent means (SEM). p-values for differences in changes between groups.

Moscow [7]. The breathing program was carried out at the Department of Sports Science (Medical Section) of the University Innsbruck and the entire program was under the supervision of two physicians. Start and termination of breathing periods were announced and controlled by instructors. Arterial oxygen saturation and heart rate were monitored continuously by a pulseoximeter attached to a finger tip, which, however, was invisible for the study subjects themselves. Incremental spiro-ergometric tests were repeated 3 days after completion of the breathing program in the same way as the pre-tests.

Table 5
Cardiovascular and ventilatory responses at maximal exercise of the hypoxia and the control group before and after the 3-week breathing program

	Hypoxia group ($n=8$)		Control group ($n=8$)		p-value
	Before	After	Before	After	
Exercise time (min)	9.3 (2.4)	9.7 (2.5)	10.6 (2.6)	10.7 (2.7)	0.40
Workload (W)	189 (57.1)	209 (53.6)	224 (53.7)	224 (56.7)	0.07
Heart rate (bpm)	162 (16.5)	162 (12.1)	147 (15.5)	146 (16.2)	0.71
Systolic blood pressure (mm Hg)	213 (36.2)	211 (24.5)	218 (32.1)	218 (39.6)	0.73
Rate pressure product	34,661 (7939)	33,994 (4399)	32,161 (7037)	31,961 (8576)	0.78
Oxygen consumption (ml/min)	2330 (586)	2475 (546)	2813 (747)	2729 (765)	<0.001
Minute ventilation (l/min)	88.0 (14.5)	102.3 (13.3)	100.1 (19.7)	102.2 (22.8)	0.03
Arterial oxygen saturation (%)	94.9 (1.9)	96.6 (1.3)	94.5 (1.2)	94.9 (0.6)	<0.01
Arterial oxygen content (ml/l)	185.3 (10.6)	196.8 (9.6)	187.2 (9.6)	188.2 (13.2)	<0.01
Blood lactate (mmol/l)	8.4 (1.8)	6.6 (2.0)	7.8 (1.5)	7.3 (1.8)	0.04

Data represent means (SD). p-values for differences in changes between groups.

2.3. Statistics

The calculated power of the study, based on the observations of our recent study [5] for the chosen sample size, amounted to 85% (Alpha = 0.05). Data are presented as means (SD or SEM) or frequencies as appropriate. Differences in haematological changes and

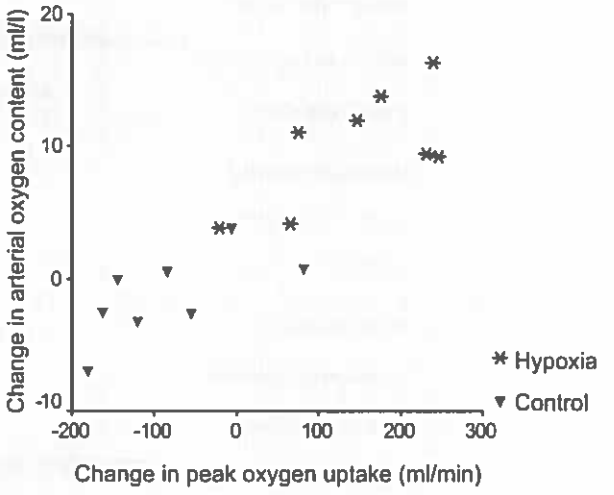


Fig. 3. Relationship between the changes in peak oxygen consumption and the arterial oxygen content in the hypoxia and control group after the 3-week breathing program. $R^2=0.8$, $p<0.001$.

changes in cardiorespiratory and metabolic responses to exercise between groups were evaluated by repeated-measures ANOVA. Correlation analyses (Pearson) were applied to examine the relation between two continuous variables. A p-value of less than 0.05 (two-tailed) was considered to indicate statistical significance. Data analyses were conducted with the use of the SPSS statistical-software package.

3. Results

All study participants completed the 3-week breathing program. Intermittent hypoxia was well tolerated by the elderly with and without coronary artery disease. Inhaling hypoxic air resulted in slightly lower arterial oxygen saturation in subjects with prior myocardial infarction (Fig. 1). ECG recordings, performed when arterial oxygen saturation fell below 85% for the first time, did not reveal any ST-segment or T-wave changes. Besides dizziness and sleepiness during the breathing sessions (in the hypoxia and the placebo group as well), no side effects occurred.

3.1. Haematological parameters

Red blood cell count (+3.9%) and haemoglobin concentration (+4.2%) increased during 3 weeks of intermittent hypoxia when compared to the control group (−3.4% and 0.0%) ($p=0.02$ and $p=0.04$) (Table 3). Changes regarding haematocrite, mean cell volume, mean cell haemoglobin and mean cell haemoglobin concentration during the 3 weeks did not differ between groups.

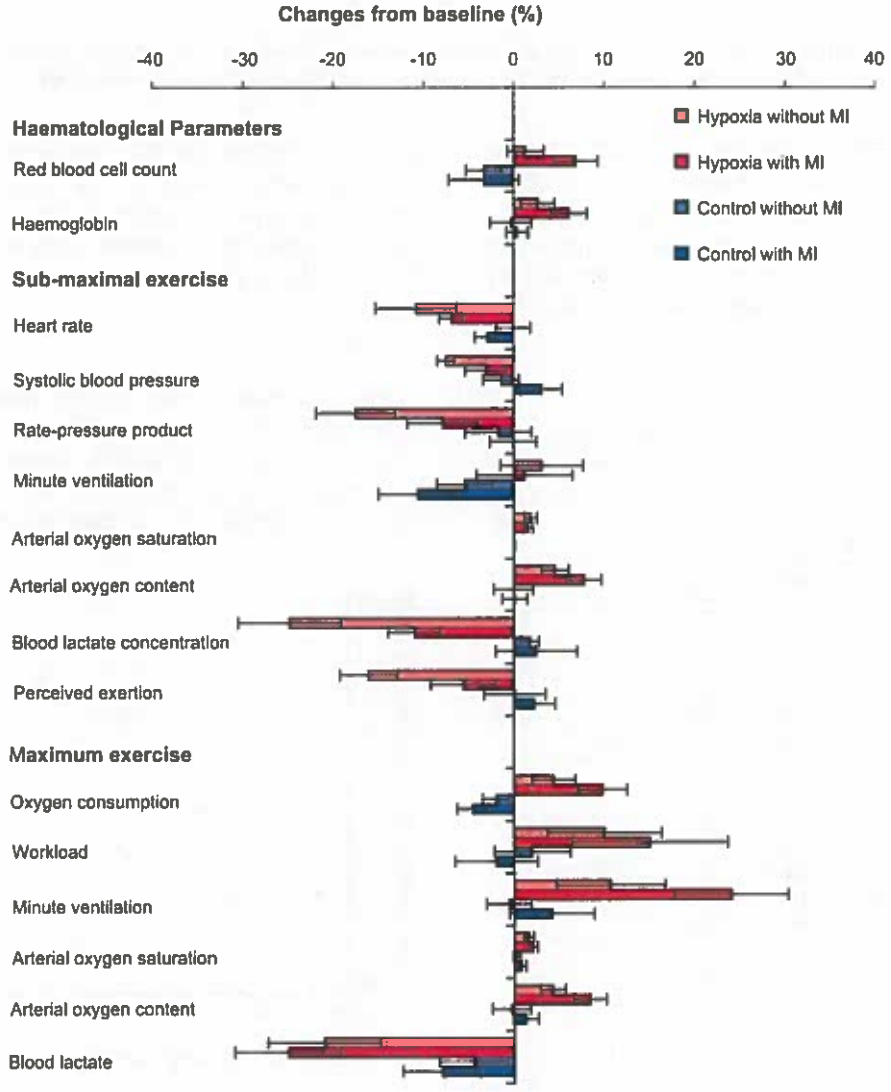


Fig. 4. Changes (in percentages) from baseline for sub-groups with ($n=4$) and without ($n=4$) prior myocardial infarction (MI) of the hypoxia and the control group. All variables with p-values < 0.1 for differences in changes between the hypoxia and the control group are shown. Data represent means (SEM).

3.2. Sub-maximal exercise

Sub-maximal exercise responses were clearly influenced by 3 weeks of intermittent hypoxia (Table 4, Fig. 2). The mean values of heart rate (−8.3%), systolic blood pressure (−5.5%), rate pressure product (−13.7%), blood lactate concentration (−17.9%) and rate of perceived exertion (−11.3%) were diminished at the workload of 1 watt/kg in subjects who were exposed to intermittent hypoxia when compared to the control group (heart rate: −2.4%, systolic blood pressure: +0.6%, rate pressure product: −1.9%, blood lactate: +4.3%, rate of perceived exertion: +1.7%) (all $p<0.05$). Arterial oxygen saturation (+1.7%) and arterial oxygen content (=exercising arterial oxygen saturation times resting haemoglobin concentration times 1.36) (+6.1%) were increased after intermittent hypoxia compared to controls (+0.4%, +0.3%) ($p<0.01$). Correlation analyses revealed a significant relation between the heart-rate decrease and the arterial oxygen-content increase after intermittent hypoxia ($r=-0.7$, $p<0.05$).

3.3. Maximum exercise

None of the exercise tests (pre- and re-tests) had to be terminated prematurely because of ischaemic events, severe arrhythmias or high blood pressure values. General fatigue, leg pain and dyspnoea were the reasons for termination of exercise testing. Dyspnoea was the cause of exercise termination in three subjects of the hypoxia group and two of the control group during the pre-tests and in none of the hypoxia group and again in two of the control group at the re-tests. Changes in exercise responses at peak workload after the 3-week breathing program are shown in Table 5. Whereas the peak workload (+10.6%) tended to be enhanced after 3 weeks of intermittent hypoxia compared to the control group (0.0%) ($p=0.07$) peak oxygen uptake had also increased (+6.2% vs. −3.0%) ($p<0.001$). Additionally, minute ventilation (+16.3%), arterial oxygen saturation (+1.8%) and arterial oxygen content (+6.2%) at the peak workload had increased compared to control conditions (minute ventilation: +1.1%, arterial oxygen saturation: +0.4%, arterial oxygen content: +0.5%) (all $p<0.05$). Maximal blood lactate concentration (−21.4%) remained lower in the hypoxia group when compared to the control group (−6.4%) ($p=0.04$). Correlation analyses revealed a close relationship between the changes in peak oxygen consumption and those in arterial oxygen content after hypoxia ($r=0.9$, $p<0.01$) (Fig. 3). Besides, less oxygen desaturation during exercise after intermittent hypoxia was related to increased minute ventilation ($r=-0.8$, $p<0.05$).

3.4. Responses of sub-groups

For variables with a p-value <0.1 for differences in changes between the hypoxia and the control group, changes from baseline are shown separately for subjects with and without prior myocardial infarction (Fig. 4). Because of the small sub-sample sizes we did not statistically evaluate differences between sub-groups. It can be seen clearly that each of the two sub-groups responded in a similar fashion to hypoxia or placebo. Nevertheless, a tendency towards more pronounced changes with regard to haematological parameters and responses to maximum exercise after hypoxia could be observed in subjects with prior myocardial infarction. Changes with regard to responses to sub-maximal exercise tended to be less pronounced in these subjects, particularly in those taking beta-blockers.

4. Discussion

4.1. Haematological parameters

The 3-week intermittent hypoxia effected a small but significant increase in red blood cell count and haemoglobin concentrations, indicating improved oxygen-carrying capacity. These results may be surprising because single hypoxic exposures up to 60 min were shown not to stimulate erythropoietin production [19]. On the other hand, Gulyaeva et al. demonstrated that the erythropoietin response also depends on the repetition of hypoxic exposure [20]. Using a similar intermittent hypoxia protocol as we did, they found a marked erythropoietin response after the 4th hypoxic session. Applying a similar protocol for 2 weeks also Bernardi et al. reported haematological changes comparable to those of the presented study [21]. The fact that haematocrite did not increase with haemoglobin concentration may be considered as a favourable effect that avoids an increase of blood viscosity. The slightly increased hypoxic stimulus in subjects with prior myocardial infarction (Fig. 1) could well explain the tendency of an enhanced erythropoietic response observed in this sub-group (Fig. 4).

4.2. Sub-maximal exercise

Responses to sub-maximal exercise after 3 weeks of intermittent hypoxia are characterized by diminished values of heart rate, systolic blood pressure, blood lactate and rate of perceived exertion and increases in arterial oxygen saturation and arterial oxygen content. Minute ventilation and oxygen uptake at the workload of 1 W/kg did not change. Because of the close relationship between arterial systemic oxygen delivery (arterial oxygen content times cardiac output) and oxygen uptake, limb blood flow and cardiac output will decline when arterial oxygen content rises at the same oxygen uptake [22,23]. Thus, the decreased exercising heart rate after intermittent hypoxia could well be explained by the increased arterial oxygen content as indicated by the relation between the heart rate decrease and arterial oxygen content increase after intermittent hypoxia.

The reduction in heart rate dependent on the arterial oxygen content may be mediated by a decline in the relative sympathetic tone. Both the reduced vagal withdrawal and decreased sensitivity of beta-adrenoceptors were reported after intermittent hypoxia [21,24]. These effects seem to be less marked in subjects with prior myocardial infarction, especially in those taking beta-blockers. Reduced heart rate and also systolic blood pressure values caused lower rate pressure products after intermittent hypoxia at similar submaximal workloads, indicating a decrease in myocardial oxygen consumption [25]. Because both the healthy and the diseased showed similar changes after intermittent hypoxia, and furthermore, maximum systolic blood pressure did not change, a negative adaptation, secondary to compromised left-ventricular function or decreased myocardial blood flow in patients with coronary artery disease, is unlikely.

Because the rate of lactate appearance in the blood was shown to be closely correlated to sympatho-adrenergic activity in normoxia and hypoxia [26–28], lower blood lactate levels after intermittent hypoxia may be partly attributed to a lesser beta-adrenergic stimulation of glycogenolysis [29,30]. Although the mechanisms of adaptation remain speculative, all these changes observed after intermittent hypoxia indicate improved aerobic capacity and tolerance to sub-maximal exercise. This is also supported by the fact of the lower rate of perceived exertion after intermittent hypoxia. These results are comparable with those shown after more prolonged daily hypobaric hypoxia (3–5 h/day for 17 days), suggesting that shorter total hypoxic exposures effect similar adaptations when applied progressively in alternating hypoxic and normoxic intervals [3].

4.3. Maximum exercise

Peak oxygen uptake increased after intermittent hypoxia accompanied by a rise of the haemoglobin concentration and maximal minute ventilation with lower arterial oxygen desaturation during exercise. The peak workload, however, showed only a tendency to increase. Enhanced oxygen consumption by both respiratory and leg muscles may have contributed to the improvement of peak oxygen uptake [31]. Peak oxygen consumption incline was repeatedly shown to be due to increases in arterial oxygen content by raising the haemoglobin concentration and/or preventing arterial oxygen desaturation [32–35]. In fact, correlation analyses between the observed changes in peak oxygen uptake and arterial oxygen content after intermittent hypoxia revealed an excellent fit (Fig. 3). Thus, 81% of the variation in changes of the peak oxygen uptake can be explained by the changes in the arterial oxygen content. The higher haemoglobin concentration may result from the hypoxia-related stimulation of erythropoiesis [20]. Thus, the slightly lower arterial oxygen saturation during intermittent hypoxia may have been responsible for the somewhat higher haemoglobin concentration and accompanying peak oxygen consumption in the sub-group with prior myocardial infarction. The diminished arterial oxygen desaturation during exercise is closely related to the increased ventilation after intermittent hypoxia as also demonstrated in previous studies [36]. Despite the higher peak workloads heart rate, systolic blood pressure and the rate pressure product did not change, indicating slower inclines of these parameters with workload. An even diminished maximum rate pressure product despite higher workloads was reported in healthy men after intermittent hypoxia with exercise [12]. The authors considered a hypoxia-related positive adaptation with potentially cardio-protective implications. The question remains whether exercise under hypoxic conditions would be more effectively than passive hypoxia. It is interesting to note that maximal blood lactate concentrations remained lower despite the somewhat higher peak workloads. This phenomenon, described as the lactate paradox, is known to occur after acclimatization to hypoxia [37]. Although retests were performed only 3 days after terminating the breathing program our previous study indicate that the hypoxia-related adaptations may be preserved for about 1 month without repeating hypoxic exposures [5].

In conclusion, aerobic capacity and exercise tolerance had increased after 3 weeks of passive intermittent hypoxia. The perceived rating of exertion, blood lactate accumulation and myocardial oxygen consumption, as indicated by the diminished rate-pressure product, were reduced during submaximal exercise, and peak oxygen uptake had increased after intermittent hypoxia. These changes in aerobic capacity and responses to exercise seem to be closely related to the hypoxia-induced rise in the arterial oxygen content and the consequently reduced sympathetic activation by exercise stress. Thus, intermittent hypoxia may be a valuable and safe tool to increase aerobic capacity and exercise tolerance in elderly men with and without coronary artery disease.

References

[1] Neubauer JA. Physiological and pathophysiological responses to intermittent hypoxia. J Appl Physiol 2001;90:1593–9.
[2] Casas M, Casas H, Pages T, et al. Intermittent hypobaric hypoxia induces altitude acclimation and improves the lactate threshold. Aviat Space Environ Med 2000;71:125–30.
[3] Rodriguez FA, Casas H, Casas M, et al. Intermittent hypobaric hypoxia stimulates erythropoiesis and improves aerobic capacity. Med Sci Sports Exerc 1999;31:264–8.
[4] Zhuang J, Zhou Z. Protective effects of intermittent hypoxic adaptation on myocardium and its mechanisms. Biol Signals Recept 1999; 8:316–22.
[5] Burtscher M, Tsvetkova AM, Tkatchouk EN, et al. Beneficial effects of short term hypopxia. Hypoxia into the Next Millennium. In: Roach RC, Wagner PD, Hackett PH, editors. Advances in Experimental Medicine and Biology, vol. 474; 1999. p. 371–2.
[6] Aleshin IA, Tinkov AN, Kots YI, et al. Treatment of cardiovascular diseases by means of adaptation to periodic hypoxia in pressure chamber. Ter Arkh 1997;69:54–8.
[7] Tkatchouk EN, Gorbatchenkov AA, Kolchinskaya AZ, et al. Adapta-

tion to interval hypoxia with the purpose of prophylaxis and treatment. Hypoxia Med J 1994;11:308–28.
[8] Banasiaka KJ, Xiab Y, Haddad GG. Mechanisms underlying hypoxia-induced neuronal apoptosis. Prog Neurobiol 2000;62:215–49.
[9] Meerson F, Pozharov V, Minyailenko T. Superresistance against hypoxia after preliminary adaptation to repeated stress. J Appl Physiol 1994;76:1856–61.
[10] Meerson FZ, Malyshev YI, Zamotrinsky AV. Differences in adaptive stabilisation of structures in response to stress and hypoxia relate with the accumulation of hsp70 isoforms. Mol Cell Biochem 1992;111:87–95.
[11] Bisgard GE, Neubauer JA. Peripheral and central effects of hypoxia on the control of ventilation. In: Dempsey JA, Pack A, editors. Regulation of Breathing. 2nd ed. New York, NY: Marcel Dekker; 1995. p. 617–68.
[12] Bailey DM, Davies B, Baker J. Training in hypoxia: modulation of metabolic and cardiovascular risk factors in men. Med Sci Sports Exerc 2000;32:1058–66.
[13] Clanton TL, Klawitter PF. Adaptive responses of skeletal muscle to intermittent hypoxia: the known and the unknown. J Appl Physiol 2001;90:2476–87.
[14] Gordon DJ, Ekelund LG, Karon JM, et al. Predictive value of the exercise tolerance test for mortality in North American men: the lipid research clinics mortality follow-up study. Circulation 1986;74:252–61.
[15] Bijnen FC, Feskens EJ, Caspersen CJ, et al. Baseline and previous physical activity in relation to mortality in elderly men: the Zutphen elderly study. Am J Epidemiol 1999;150:1289–96.
[16] Meerson FZ, Ustinova EE, Orlova EH. Prevention and elimination of heart arrhythmias by adaptation to intermittent high altitude hypoxia. Clin Cardiol 1987;10:783–9.
[17] Ustinova EE, Saltykova VA, Didenko VV, et al. Effect of adaptations to periodic and continuous hypoxia in disorders of electrical stability of the heart in postinfarction cardiosclerosis. Bull Exp Biol Med 1988;105:533–5.
[18] Borg G. Psychophysical bases of perceived exertion. Med Sci Sports Exerc 1982;14:377–81.
[19] Knaupp W, Khilnani S, Sherwood J, et al. Erythropoietin response to acute normobaric hypoxia in humans. J Appl Physiol 1992;73:837–40.
[20] Gulyaeva NV, Tkatchouk EN. Effects of normobaric hypoxic training on immunoreactive erythropoietin and transferrin levels in blood serum of healthy volunteers. Hypoxia Med J 1998;6:13–7.
[21] Bernardi L, Passino C, Serebrovskaya Z, et al. Respiratory and cardiovascular adaptations to progressive hypoxia. Effect of interval hypoxic training. Eur Heart J 2000;22:879–87.
[22] Ferretti G, Kayser B, Schena F, et al. Regulation of perfusive O_2 transport during exercise in humans: effects of changes in haemoglobin concentration. J Physiol 1992;455:679–88.
[23] Roach RC, Koskolou M, Calbert J, et al. Arterial O_2 content and tension in regulation of cardiac output and leg blood flow during exercise in humans. Am J Physiol 1999;276:H438–45.
[24] Meerson FZ, Kopylov IN, Baldenkov GN. Increase of alpha 1-adrenoreactivity of the rat heart in adaptation to periodic hypoxia. Bull Exp Biol Med 1991;111:570–2.
[25] Raven PB, Potts JT. Cardiovascular responses to exercise and training. In: Harries M, Williams C, Stanish WD, et al, editors. Oxford Textbook of Sports Medicine. Oxford: University Press; 1998. p. 32–45.
[26] Mazzeo RS, Bender PR, Brooks GA, et al. Arterial catecholamine response during exercise with acute and chronic high altitude exposure. Am J Physiol 1991;261:E419–24.
[27] Reeves JT, Wolfel EE, Green HJ, et al. Oxygen transport during exercise at altitude and the lactate paradox: lessons from operation Everest II and Pikes peak. Exerc Sport Sci Rev 1992;20:275–96.
[28] Brooks GA, Wolfel EE, Groves BM, et al. Muscle accounts for glucose disposal but not blood lactate appearance during exercise after acclimatization to 4.300 m. J Appl Physiol 1992;72:2435–45.
[29] Green H, Sutton J, Wolfel E, et al. Altitude acclimatization and energy metabolic adaptations in skeletal muscle during exercise. J Appl Physiol 1992;73:2701–8.
[30] Brooks GA, Butterfield GE, Wolfe RR, et al. Decreased reliance on lactate during exercise after acclimatization to 4.300 m. J Appl Physiol 1991;71:333–41.
[31] Harms CA, Dempsey JA. Cardiovascular consequences of exercise hyperpnea. Exerc Sport Sci Rev 1999;27:37–62.
[32] Ekblom B, Goldberg A, Gullbring B. Response to exercise after blood loss and reinfusion. J Appl Physiol 1972;33:175–80.
[33] Thomson JM, Stone JA, Girsburg A, et al. O_2 transport during exercise following blood reinfusion. J Appl Physiol 1982;53:1213–9.
[34] Knight DR, Schaffartzik W, Poole DC, et al. Effects of hyperoxia on maximal leg O_2 supply and utilisation in man. J Appl Physiol 1993;75:2586–94.
[35] Harms CA, McClaran SR, Nickele GA, et al. Exercise-induced arterial hypoxaemia in healthy young women. J Physiol 1998;507(2):619–28.
[36] Ricart A, Casas H, Casas M, Pages T, et al. Acclimatization near home? Early respiratory changes after short-term intermittent exposure to simulated altitude. Wilderness Environ Med 2000;11:84–8.
[37] Hochachka PW. The lactate paradox: analysis of underlying mechanisms. Ann Sports Med 1989;11:184–8.

HIGH ALTITUDE MEDICINE & BIOLOGY
Volume 9, Number 1, 2008

DOI: 10.1089/ham.2008.1053

Effects of Intermittent Hypoxia Training on Exercise Performance, Hemodynamics, and Ventilation in Healthy Senior Men

VALERIY B. SHATILO,[1] OLEG V. KORKUSHKO,[1] VADIM A. ISCHUK,[1] H. FRED DOWNEY,[2] and TATIANA V. SEREBROVSKAYA[3]

ABSTRACT

Shatilo, Valeriy B., Oleg V. Korkushko, Vadim A. Ischuk, H. Fred Downey, and Tatiana V. Serebrovskaya. Effects of intermittent hypoxia training on exercise performance, hemodynamics, and ventilation in healthy senior men. *High Alt. Med. Biol.* 9:43–52, 2008.—The efficacy and safety of intermittent hypoxia training (IHT) were investigated in healthy, 60- to 74-yr-old men. Fourteen men (Gr 1) who routinely exercised daily for 20 to 30 min were compared with 21 (Gr 2) who avoided exercise. Their submaximal work-load power values before the IHT training were 94 ± 3.7 and 66 ± 3.1, respectively. Before and after 10 days of IHT, the ventilatory response to sustained hypoxia (SH; 12% O_2 for 10 min), work capacity (bicycle ergometer), and forearm cutaneous perfusion (laser Doppler) were determined. During SH, no negative electrocardiogram (ECG) changes were observed in either group, and the ventilatory response to SH was unaltered by IHT. In Gr 1, IHT (normobaric rebreathing for 5 min, final Sa_{O_2} = 85% to 86%, followed by 5 min normoxia, 4/day) produced no changes in hemodynamic indixes and work capacity. In Gr 2, IHT decreased blood pressure (BP) by 7.9 ± 3.1 mmHg ($p < 0.05$) and increased submaximal work by 11.3% ($p < 0.05$) and anaerobic threshold by 12.7% ($p < 0.05$). The increase in HR and BP caused by a 55 W-work load was reduced by 5% and 6.5%, respectively ($p < 0.05$). Cutaneous perfusion increased by 0.06 ± 0.04 mL/min/100 g in Gr 1 and by 0.11 ± 0.04 mL/min/100 g in Gr 2 ($p < 0.05$). Hyperemia recovery time increased significantly by 15.3 ± 4.6 sec in Gr 1 and by 25.2 ± 11.2 sec in Gr 2. Thus, healthy senior men well tolerate IHT as performed in this investigation. In untrained, healthy senior men, IHT had greater positive effects on hemodynamics, microvascular endothelial function, and work capacity.

Key Words: intermittent hypoxia; old age; ventilation; hemodynamics; exercise performance

INTRODUCTION

Aging is associated with loss of muscle mass, decrease of muscle blood flow, dilatation of alveoli, enlargement of air spaces, reduction of hypoxic ventilatory sensitivity, and other changes that limit physical activity (Korkusko et al., 1982; Janssens et al., 1999; Serebrovskaya et al., 2000; Dela and Kjaer, 2006). Luckner et al. (2006) proposed that age-

[1]Institute of Gerontology, Kiev, Ukraine.
[2]University of North Texas Health Science Center, Fort Worth, Texas, USA.
[3]Bogomoletz Institute of Physiology, Kiev, Ukraine.

related disturbances in microcirculatory homeostasis play a key role in the pathophysiology of multiple organ dysfunction syndromes. Today is well known that physical activity reduces cardiovascular disease risk in older adults (Klieman et al., 2006). Multivariate analysis demonstrated that a sedentary lifestyle associated with aging is related to mortality (Al-Khalili et al., 2007). Conforming to the laws of nature, the vigor of adult maturity is replaced by the increasing fragility of old age, but elderly individuals desire the same full and active life as younger adults in spite of biologically inescapable decreases in physiological processes and reserves.

Intermittent hypoxia training (IHT) has been demonstrated to enhance the physical performance of athletes (see reviews, Sergeev, 1962; Gippenreiter and West, 1996; Serebrovskaya, 2002) and older individuals (Kolesnikova and Serebrovskaya, 2001), even patients with heart disease (Burtscher et al., 2004). Although the first use of IHT for training of pilots and climbers was described more than 70 years ago (Gurvich and Fainberg, 1938), in the last decade of the 20th century, interest in IHT has been revived, mainly in Russia and other eastern European countries. Recently, IHT has been advocated for the prevention and treatment of some diseases, such as bronchial asthma (Serebrovskaya et al., 2003a), coronary heart disease (del Pilar Valle et al., 2006), myocardial infarction (Burtscher et al., 2004), essential hypertension (Simonenko et al., 2003; Mukharliamov et al., 2006), Parkinson's disease (Serebrovskaya et al., 2003b), and obesity (Balykin et al., 2004).

Various mechanisms for the beneficial effects of IHT have been hypothesized (Bernardi et al., 2001; Serebrovskaya, 2002). It has been shown that by enhancing stress resistance and improving oxygen delivery, IHT is an effective stimulus for evoking respiratory, cardiovascular, and metabolic adaptations, which increase exercise tolerance (Neubauer, 2001; Burtscher, 2004). Reeves and Gozal (2005) have shown that intermittent hypoxia induces alterations in respiratory control that reflect various types of ventilatory plasticity. Thus, it is likely that IHT would also be a particularly beneficial therapy to slow or reverse the effects of aging. Therefore, the purpose of this study was to evaluate the safety of IHT in healthy senior men and, more specifically, to test the hypothesis that IHT improves indixes of ventilation, hemodynamics, and exercise performance in exercise-trained and untrained subjects.

METHODS

This work was officially approved and authorized by the Ethics Committee for Human Experiments of the Institute of Gerontology.

Subjects

The efficacy and safety of IHT were investigated in two groups of aged, healthy volunteers with different levels of physical activity, who gave their informed consent. All subjects were sea-level residents and nonsmokers. Most subjects consumed one to three alcoholic drinks weekly. The subjects were in good health with no evidence of cardiovascular or pulmonary disease. Group 1 (Gr 1) consisted of 14 healthy men (age 67.4 ± 2.0 yr; weight 64.5 ± 3.1 kg; height 171 ± 2 cm; body mass index 22.2 ± 0.9) in good physical condition. These subjects exercised daily for 20 to 30 min at an average energy cost of 500 kcal and had submaximal $\dot{V}_{O_2}$ of 23.7 ± 1.0 mL/kg^{-1}/min^{-1}. Group 2 (Gr 2) consisted initially of 22 healthy but sedentary men (age 61.0 ± 1.5 yr; weight 69 ± 3 kg; height 169 ± 2 cm; body mass index 24.2 ± 1.0) who, unlike their exercise-trained counterparts, avoided exercise and had peak $\dot{V}_{O_2}$ of 18.2 ± 0.3 mL/kg^{-1}/min^{-1} ($p < 0.05$). One subject of this group could not pass the first hypoxia test and was excluded from subsequent investigation, so for the remainder of the investigation Gr 2 was comprised of 21 sedentary men.

Experimental protocol

Initially, a sustained hypoxia test was administered to all subjects. Those who performed satisfactorily on this test (see Results) continued in the study and received 10 days of IHT. A sustained hypoxia test was again administered after 10 days of IHT. In addition, these subjects underwent tests for hematology assessment, exercise capacity, and forearm microvascular reactivity during the next 2 days

after the hypoxic test, before initiation of IHT, and on the days following 10 days of IHT. The tests were performed during the early morning with the subjects fasting. First, venous blood was drawn from the median antecubital vein to provide hematology assessment. Then anaerobic threshold was determined. On the next day the forearm cutaneous perfusion test was provided and, after that, physical work capacity was evaluated. The same protocol was realized after 10 days of IHT course.

Intermittent hypoxia training (IHT)

IHT was performed in the morning, from 10 till 12 AM, 2 h after a light breakfast. With the subjects in a sitting position, normobaric, isocapnic hypoxia was administered for 5 min 4 times/day for 10 days with a Hypotron (modified closed spirometer with CO_2 absorption) (Serebrovskaya, 1995). The four periods of hypoxia were separated by three 5-min periods of room-air inspiration. Initial inspired gas composition (F_i) was 20.9% O_2 and 79.1% N_2. Partial pressure of expiratory carbon dioxide (P_{ETCO_2}) was continuously monitored at the mouth with a medical mass spectrometer (MX62-03, Ukraine), which was calibrated before and after each test with standardized gases that had been assayed by the Scholander technique. During the first 1 to 1.5 min of rebreathing, F_{iO_2} fell progressively with body utilization of O_2 until it reached 12%. During the remaining 3.5 to 4 min of IHT, O_2 and CO_2 were added gradually as needed to maintain F_{iO_2} at 12% and P_{ETCO_2} at its prehypoxia value. S_{aO_2} at conclusion of IHT was 85% to 86%. P_{ETCO_2} was maintained at the initial pretest pressure for each subject, typically 38 to 40 mmHg, throughout the training period. Subjects easily endured the hypoxia periods without any distress or side effects. ECG and ventilation were continuously monitored during IHT, and arterial pressure was measured at 2-min intervals.

Analytical procedures

Sustained hypoxia test. After a 30-min rest, the subject in a sitting position inspired a hypoxic gas mixture (12% O_2, 88% N_2). Before and during the test, ventilation, arterial pressure (BP), heart rate (HR), S_{aO_2} (pulsoximeter), and ECG were recorded. The test lasted 10 min or was interrupted if one of the following disturbances was observed: (1) dizziness, nausea, precordial chest pain, or other negative subjective feelings, (2) an increase in HR of more than 30%, (3) a decrease in S_{aO_2} to lower than 80%, (4) a rise of systolic BP of more than 30%, (5) ECG signs of ischemia or frequent extrasystoles (more than 6/min), or AV conduction defects (see Results).

Blood analysis. Blood was sampled from a finger puncture for routine hematology assessment of erythrocyte and leukocyte count, blood hemoglobin and glucose concentration, and content of alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, creatinine, urea, albumin, and total cholesterol.

Forearm cutaneous perfusion test. Forearm cutaneous perfusion was measured using a BLF 21 D laser instrument (Transonic Systems, Inc., USA) at room temperature (22°C) with the subject in a sitting position and after resting in that position for at least 30 min. Microvascular reactivity (MVR) was evaluated from the maximal postocclusive reactive hyperemia (PORH) following 3-min forearm ischemia produced by cuff inflation. The time required for forearm flow to return to normal was also measured. Similar procedures have been used by other investigators (e.g., Luckner et al., 2006; Zdolsek et al., 2006).

Exercise tests. A bicycle ergometer test was used to evaluate anaerobic threshold and physical work capacity. Anaerobic threshold was estimated from ventilatory gas exchange indixes during continuously accelerated load (the increase by 12.5 W every minute up to pulse rate [HR = 200 − age] was reached). HR was monitored continuously from the ECG, and arm BP was measured intermittently by sphygmomanometry, with a microphone placed over the brachial artery to detect Korotkoff sounds. V_{O_2} and lung ventilation parameters were monitored with the Oxycon-4 System (Mijnhardt, the Netherlands). All recordings were made by the same technicians, and the spirometric values were corrected for body temperature, atmospheric pressure, and humidity. Anaerobic threshold was calculated as Wasserman (1987) has described. Physical work capacity

was determined the next day. Subjects completed 5 min of work at 25 W. The load was then increased every 5 min by15 W until the individual's maximum tolerable level was reached (i.e., to volitional exhaustion). Peak V_{O_2} was determined, using an oxygen analyzer, the Oxycon-4 System, as the highest value of O_2 consumption during maximum effort.

Statistical analyses. All values are expressed as means ± SE. Treatment means were compared statistically with the ANOVA test. Correlations were identified by the least-squares method and expressed as linear regression slopes. Differences were considered significant for $p < 0.05$.

RESULTS

To ensure that the senior subjects could safely tolerate IHT, each first underwent the sustained hypoxia test to assess individual tolerance of hypoxia. None of the subjects showed changes in ECG during or after this sustained hypoxic test. In some patients, single extrasystoles were observed, but this was not considered a reason for stopping the test or excluding the subjects from the investigation. During first administration of the sustained hypoxia test, three subjects of Gr 1 (21%) and 15 subjects of Gr 2 (68%) could not pass the test completely because Sa_{O_2} fell lower than 80% before 10 min of breathing 12% O_2 had elapsed. For these subjects, the duration of the test was 8.7 ± 0.4 min. One subject of Gr 1 and 3 subjects of Gr 2 complained of shortness of breath, weakness, or dizziness at 7 or more min of the procedure, and the test was then stopped. One subject of Gr 2 revealed an increase in blood pressure above 30% during the 3rd to 5th min, and this patient was excluded from further exposure to hypoxia. For the remaining subjects who completed the 10-min test, their final S_{aO_2} was 81.0 ± 0.6%. After this initial sustained hypoxia test, 14 subjects in Gr 1 and 21 subjects in Gr 2 received IHT.

During IHT, most subjects felt no distress. Three of the 35 subjects complained of tinnitus, dizziness, or mild chest discomfort on days 1 and 2 of IHT. However, measured variables (arterial pressure, heart rate, pulmonary ventilation indexes, blood S_{aO_2}, ECG) did not reflect any substantial changes, and these subjects continued in the investigation. After completion of IHT, no changes in ECG were observed.

Cardiorespiratory data measured during sustained hypoxia tests are presented in Table 1. Since only 10 subjects of Gr 1 and 3 subjects of Gr 2 successfully completed 10 min of the initial sustained hypoxia test, we present in Table 1 the data for 7 min only so that data of all subjects could be represented. Before IHT, resting heart rate and ventilatory frequency were lower in the fit subjects of Gr 1 compared to the less fit subjects of Gr 2. Seven minutes of hypoxia before IHT caused significant increases in heart rate and mean systemic arterial pressure in subjects of both Gr 1 and Gr 2. Minute ventilation rose during the 1st to 3rd minutes and then gradually decreased to the end of the test. During hypoxia, arterial O_2 saturation fell significantly in both groups, reaching 83.9 ± 1.2% in Gr 1 and 82.0 ± 0.7% in Gr 2 ($p > 0.05$) at 7 min. Arterial O_2 saturation values were significantly greater in Gr 1 subjects only at 3 and 5 min of hypoxia. During hypoxia before IHT, final 7-min values for heart rate, arterial pressure, and ventilatory frequency were less in Gr 1 subjects. Gr 1 values for heart rate and arterial pressure were also less at some other time intervals during hypoxia.

After IHT, hypoxia caused changes in cardiorespiratory values relative to the rest values that were similar to those observed before IHT (Table 1). For Gr 1, values at rest and during hypoxia after IHT were similar to respective values recorded before IHT. For Gr 2, values at 5 and 7 min during hypoxia for heart rate and arterial pressure were less after than before IHT, and arterial O_2 saturation was greater. Values for respective cardiorespiratory variables of Gr 1 and Gr 2 after IHT were similar except for heart rate at 2-min hypoxia, which was less in Gr 1.

Blood count data and biochemical indexes are presented in Table 2. Before IHT, no differences were observed between groups, except for leukocyte count, which was higher in Gr 2. IHT did not significantly akter any of

TABLE 1. CARDIORESPIRATORY PARAMETERS OF HEALTHY SENIOR MEN DURING SUSTAINED HYPOXIA TEST (12% O_2) BEFORE AND AFTER IHT

		Gr1			Gr2		
I	II	III	IV	V	VI	VII	VIII
Parameters	Period of hypoxia (min)	Before IHT	After IHT	Statistical difference between III and IV	Before IHT	After IHT	Statistical difference between VI and VII
HR min^{-1}	Rest	68.8 ± 2.6	68.0 ± 2.2	NS	74.9 ± 2.8[a]	73.2 ± 3.0	NS
	1	72.9 ± 3.7	71.5 ± 2.2	NS	77.3 ± 3.1	77.3 ± 3.1[b]	NS
	3	77.4 ± 3.4	75.5 ± 2.2[c]	NS	81.6 ± 3.2	78.8 ± 3.2	NS
	5	77.5 ± 3.6	75.5 ± 2.3[c]	NS	83.4 ± 2.8[a,c]	79.2 ± 3.3	<0.1 > 0.05
	7	78.7 ± 2.9[c]	76.5 ± 2.3[c]	NS	84.6 ± 2.9[a,c]	78.3 ± 3.2	0.05
SBP, mmHg	Rest	131 ± 3.2	130 ± 3.0	NS	134 ± 3.0	130 ± 3.3	NS
	1	136 ± 3.4	134 ± 3.9	NS	145 ± 3.7[a,c]	137 ± 3.2	NS
	3	137 ± 4.5	135 ± 4.1	NS	147 ± 3.9[a,c]	138 ± 4.2	<0.1 > 0.05
	5	139 ± 4.3[c]	135 ± 3.7	NS	149 ± 4.6[a,c]	138 ± 5.1	<0.05
	7	140 ± 5.4[c]	136 ± 4.0	NS	159 ± 4.2[a,c]	139 ± 4.8	<0.05
Sa_{O_2}, %	Rest	97.7 ± 0.3	97.6 ± 0.3	NS	97.3 ± 0.3[a,c]	97.4 ± 0.4	NS
	1	92.6 ± 0.7[d]	93.7 ± 0.8[d]	NS	91.4 ± 0.6[a,d]	92.7 ± 0.6[d]	NS
	3	88.0 ± 0.9[d]	88.1 ± 1.2[d]	NS	86.5 ± 0.5[a,d]	87.7 ± 0.6[d]	NS
	5	85.4 ± 1.0[d]	86.1 ± 1.3[d]	NS	83.3 ± 0.7[a,d]	86.1 ± 0.7[d]	<0.05
	7	83.9 ± 1.2[d]	84.4 ± 1.5[d]	NS	82.0 ± 0.7[a,d]	84.2 ± 1.0[d]	<0.05
f, min^{-1}	Rest	14.1 ± 0.8	14.9 ± 1.1	NS	16.6 ± 1.2[a,d]	16.3 ± 2.2	NS
	1	15.3 ± 1.1	15.9 ± 1.1	NS	16.5 ± 1.7	16.5 ± 2.0	NS
	3	15.4 ± 1.3	15.8 ± 1.1	NS	17.2 ± 1.7	18.0 ± 1.6	NS
	5	14.8 ± 1.2	14.6 ± 1.1	NS	16.0 ± 1.8	16.3 ± 1.8	NS
	7	15.3 ± 1.1	15.0 ± 1.1	NS	18.0 ± 1.5[a]	17.8 ± 2.0	NS
V_E, L/min	Rest	8.6 ± 0.7	8.1 ± 0.9	NS	7.8 ± 0.7	7.9 ± 0.8	NS
	1	10.9 ± 1.0[c]	10.6 ± 0.8[c]	NS	8.7 ± 0.6	8.2 ± 0.9	NS
	3	10.8 ± 1.3[c]	10.5 ± 0.7[c]	NS	9.5 ± 0.9[c]	9.0 ± 0.8	NS
	5	10.5 ± 1.2	10.2 ± 1.0[c]	NS	8.9 ± 0.7	8.9 ± 1.0	NS
	7	10.2 ± 1.1	9.8 ± 0.8	NS	9.0 ± 0.9	9.3 ± 1.0	NS

Values are means ± SD.
Gr 1: healthy old men with regular physical training (peak submaximal $\dot{V}_{O_2}$, 23.7 ± 1.0 mL/min/kg) (n = 14).
Gr 2: healthy untrained (peak submaximal $\dot{V}_{O_2}$, 18.2 ± 1.3 mL/min/kg) old men (n = 21).
[a]Statistical difference between Gr 1 and Gr 2 within columns III and VI, $p < 0.05$.
[b]Statistical difference between Gr 1 and Gr 2 within columns IV and VII, $p < 0.05$.
[c]Statistical difference between rest and hypoxia, $p < 0.05$.
[d]Statistical difference between rest and hypoxia, $p < 0.01$.
IHT, intermittant hypoxia training; HR, heart rate; SBP, systolic arterial blood pressure; Sa_{O_2}, blood arterial oxygen saturation; V_E, expired minute ventilation; NS, not significant; f, breathing frequency.

these parameters relative to respective pre-IHT values. After IHT, erythrocyte count was greater in Gr 1 subjects and leukocyte count was greater in Gr 2 subjects, consistent with their greater pre-IHT count.

Table 3 shows changes in physical work capacity and anaerobic threshold before and after IHT. Before IHT, all parameters of physical ability were significantly lower in Gr 2 compared to Gr 1. IHT did not affect either submaximal work capacity or anaerobic threshold in well-trained subjects of Gr 1, whereas in the untrained individuals of Gr 2 submaximal work capacity increased by 11.3%, and the ventilatory index of anaerobic threshold increased by 12.7%.

Before IHT, during both 25- and 55-W loads, HR, systolic arterial blood perssure (SBP), diastolic arterial blood pressure (DBP) and heart rate–blood pressure product rose much more substantially in Gr 2 than in Gr 1 (Table 4). IHT did not change cardiorespiratory responses to both loads in well-trained subjects, whereas in untrained individuals, a significant decrease in

TABLE 2. BLOOD ANALYSIS IN HEALTHY SENIOR MEN BEFORE AND AFTER IHT

	Gr 1			Gr 2		
I	*II*	*III*	*IV*	*V*	*VI*	*VII*
Parameters	*Before IHT*	*After IHT*	*Statistical difference between II and III*	*Before IHT*	*After IHT*	*Statistical difference between V and VII*
Erythrocytes, 10^{12}/L[a]	4.34 ± 0.1	4.4 ± 0.1	NS	4.3 ± 0.1	4.3 ± 0.1	NS
Hemoglobin, g/L	141 ± 3.5	142 ± 2.7	NS	137 ± 2.0	139 ± 1.6	NS
Leucocytes, 10^9/L[a]	4.9 ± 0.4	4.8 ± 0.4	NS	5.7 ± 0.3[b]	5.7 ± 0.3[a]	NS
Blood glucose, mmol/L	4.9 ± 0.8	4.8 ± 0.9	NS	5.1 ± 1.0	4.9 ± 0.7	NS
ALT, mmol/L	0.48 ± 0.1	0.45 ± 0.07	NS	0.44 ± 0.06	0.51 ± 0.08	NS
AST, mmol/L	0.38 ± 0.04	0.37 ± 0.05	NS	0.34 ± 0.03	0.36 ± 0.03	NS
Bilirubin, mkmol/L	11.1 ± 2.8	12.7 ± 3.5	NS	11.2 ± 1.8	11.8 ± 1.7	NS
Creatinine, mkmol/L	69.6 ± 5.1	66.3 ± 5.4	NS	72.3 ± 3.1	73.7 ± 2.5	NS
Urea, mmol/L	6.2 ± 0.5	6.1 ± 0.4	NS	6.14 ± 0.3	5.9 ± 0.2	NS
Albumin, g/L	68.2 ± 2.6	68.3 ± 2.9	NS	68.5 ± 1.1	70.1 ± 1.6	NS
Cholesterol, mmol/L	5.2 ± 0.7	4.7 ± 0.4	NS	5.6 ± 0.3	5.3 ± 0.2	NS

Values are means ± SE.
[a]Statistical difference between Gr 1 and Gr 2 within columns III and VI, $p < 0.05$.
[b]Statistical difference between Gr 1 and Gr 2 within columns II and V, $p < 0.05$.
For G1, G2, and IHT, see Table 1 notes.
NS, not significant.

heart rate, blood pressure, and heart rate–blood pressure product, as well as ventilation and a tendency for oxygen consumption to fall, were observed.

Results of the forearm cutaneous perfusion test are presented in Table 5. Before training there were no differences in microvascular reactivity between the groups, as could seen from basal perfusion, maximal perfusion during hyperemia, and time to recovery of baseline flow. IHT enhanced basal perfusion in Gr 1 by 0.06 ± 0.04 mL/min/100 g and in Gr 2 by 0.11 ± 0.04 mL/min/100 g. Maximal perfusion during hyperemia rose by 11.6% in Gr 2, with a tendency for this variable to increase this in Gr 1. Time of PORH recovery was augmented in both groups (by 14% in Gr I and 24.7% in Gr II).

TABLE 3. PHYSICAL WORKING CAPACITY AND ANAEROBIC THRESHOLDS IN HEALTHY SENIOR MEN BEFORE AND AFTER IHT

	Gr 1			Gr 2		
I	*II*	*III*	*IV*	*V*	*VI*	*VII*
Parameters	*Before IHT*	*After IHT*	*Statistical difference between II and III*	*Before IHT*	*After IHT*	*Statistical difference between V and VII*
Submaximal work load, W	94.0 ± 3.7	96.1 ± 3.2	NS	66.3 ± 3.1[a]	73.8 ± 3.3[b]	<0.05
Anaerobic threshold, L/min	1.45 ± 0.08	1.48 ± 0.07	NS	1.1 ± 0.05[a]	1.24 ± 0.06[b]	<0.05
Anaerobic threshold, W	73.8 ± 4.2	75.1 ± 3.8	NS	56.4 ± 1.4	62.9 ± 2.0[b]	<0.05

Values are means ± SD.
[a]Statistical difference between Gr 1 and Gr 2 within columns II and V, $p < 0.01$.
[b]Statistical difference between Gr 1 and Gr 2 within columns III and VI, $p < 0.01$.
For G1, G2, and IHT, see Table 1 notes.
NS, not significant.

TABLE 4. HEMODYNAMICS, LUNG VENTILATION AND OXYGEN UPTAKE IN HEALTHY SENIOR MEN DURING 25-W AND 50-W LOAD BEFORE AND AFTER IHT

		Gr1			Gr2		
I	II	III	IV	V	VI	VII	VIII
Parameters	Load (W)	Before IHT	After IHT	Statistical difference between III and IV	Before IHT	After IHT	Statistical difference between YI and VII
HR min^{-1}	Rest	71.3 ± 2.3	72.7 ± 2.6	NS	75.8 ± 2.7	74.8 ± 2.6	NS
	25	85.7 ± 2.6[a]	86.7 ± 2.7[a]	NS	97.9 ± 3.3[a,b]	92.0 ± 3.4[a,c]	<0.05
	55	100.0 ± 3.3[a]	101.5 ± 3.7[a]	NS	120.4 ± 3.7[a,b]	115.1 ± 3.1[a,c]	<0.05
SBP, mmHg	Rest	132.0 ± 2.8	130.4 ± 2.4	NS	135.5 ± 2.5	129.5 ± 3.1	<0.05
	25	149.3 ± 3.3[a]	145.2 ± 2.9[d]	NS	158.2 ± 3.9[a,e]	148.4 ± 3.0[a]	<0.05
	55	167.3 ± 3.4[a]	166.1 ± 2.9[a]	NS	182.1 ± 3.9[a,b]	171.6 ± 4.3[a]	<0.05
DBP, mmHg	Rest	81.5 ± 1.5	79.6 ± 1.3	NS	83.3 ± 1.1	80.0 ± 1.5	NS
	25	88.3 ± 1.5[a]	87.8 ± 1.7[a]	NS	91.4 ± 1.8[a]	90.4 ± 1.9[a]	NS
	55	92.5 ± 1.8[a]	93.2 ± 2.0[a]	NS	99.3 ± 2.5[a,e]	93.1 ± 2.9[a]	<0.05
SBP · HR/100, units	Rest	94.0 ± 3.6	94.1 ± 3.4	NS	103.1 ± 3.7[e]	97.2 ± 3.5	NS
	25	128.3 ± 5.4[a]	124.0 ± 4.3[a]	NS	155.5 ± 7.3[a,c]	137.3 ± 6.9[a,c]	<0.05
	55	168.5 ± 7.9[a]	167.5 ± 6.4[a]	NS	220.9 ± 11.7[a,e]	18.8 ± 9.5[a,c]	<0.05
V_E, L/min	Rest	11.9 ± 0.5	12.3 ± 0.6	NS	10.0 ± 0.5	10.1 ± 0.5	NS
	25	20.3 ± 0.9[a]	19.8 ± 0.7[a]	NS	19.1 ± 1.3[a]	17.7 ± 1.1[a,c]	NS
	55	28.1 ± 1.0[a]	28.5 ± 0.9[a]	NS	28.6 ± 1.9[a]	26.4 ± 1.6[a]	<0.05
V_{O_2}, mL/min	Rest	373.5 ± 13.4	369.9 ± 12.3	NS	298.3 ± 14.2[e]	289.3 ± 12.8	NS
	25	839 ± 35[a]	829 ± 28[a]	NS	758 ± 29[a,e]	708 ± 41[a,c]	NS
	55	1187 ± 42[a]	1189 ± 31[a]	NS	1126 ± 52[a]	1089 ± 56[a]	NS

Values are means ± SD.
[a]Statistical difference between rest and hypoxia, $p < 0.05$.
[b]Statistical difference between Gr I and Gr II within columns III and VI, $p < 0.01$.
[c]Statistical difference between Gr 1 and Gr II within columns IV and VII, $p < 0.05$.
[d]Statistical difference between rest and hypoxia, $p < 0.05$.
[e]Statistical difference between Gr 1 and Gr 2 within columns III and VI, $p < 0.05$.
HR, heart rate; SBP, systolic arterial blood pressure; DBP, diastolic arterial blood pressure; SBP · HR/100, heart rate–blood pressure product; V_E, expired minute ventilation; $\dot{V}_{O_2}$ minute oxygen consumption.
NS, not significant.
For IHT, Gr 1 and Gr 2, see Table 1 notes.

DISCUSSION

The purpose of this study was to elucidate the efficacy and safety of IHT application to healthy senior men of different physical activity. We confirmed that healthy men of 60 to 74 yr well tolerate IHT as performed in this investigation (i.e., hypoxic rebreathing until F_{iO_2} of 12% was reached, with subsequent maintenance at this level for 4 to 5 min, then 5-min normoxia, 4/day, with S_{aO_2} reduced to ~80%) without dangerous side effects. In general, the effects of IHT on hemodynamics, microvascular endothelial function, and work capacity were more pronounced in untrained subjects. However, IHT had little effect on respiratory indixes either during sustained hypoxia or during exercise.

One of the rare investigations reported in western literature of IHT applied to elderly patients is the work of Burtscher et al. (2004). They subjected middle-aged or elderly men (aged 50 to 70 yr), half of whom had prior myocardial infarction, to 5 cycles/day of breathing 10% O_2 for 5 min/cycle. According to these authors, "IH was well tolerated by the elderly with and without coronary artery disease." This is not so surprising, since IHT had already been used in Russia for treatment of patients with cardiac arrhythmia and exercise-induced angina due to coronary artery disease (Meerson et al., 1989; Ehrenburg, 1992; Meerson, 1993; Lyamina et al., 2001). IHT increased treadmill exercise tolerance and reduced arrhythmias in these patients. Thus, even patients with coronary artery

TABLE 5. PARAMETERS OF FOREARM CUTANEOUS PERFUSION TEST IN HEALTHY SENIOR MEN BEFORE AND AFTER IHT

	Gr1			Gr2		
I	II	III	IV	V	VI	VII
Parameters	Before IHT	After IHT	Statistical difference between II and III	Before IHT	After IHT	Statistical difference between V and VI
PORHb, mL/min · 100 g	1.10 ± 0.02	1.16 ± 0.03	NS	1.07 ± 0.03	1.18 ± 0.04	<0.05
PORHmax, mL/min · 100 g	5.85 ± 0.25	6.18 ± 0.29	NS	5.24 ± 0.36	5.85 ± 0.31	NS
PORHt, sec	109.0 ± 7.2	124.3 ± 9.6	$p < 0.05$	102.2 ± 7.4	127.4 ± 11.2	<0.05

Values are means ± SD.
PORHb, basal perfusion; PORHmax, maximal perfusion during hyperemia; PORHt, time of PORH recovery.
NS, not significant.
For IHT, G1, and G2, see Table 1 notes.

disease and a history of myocardial infarction tolerated hypoxia of the severity employed in the current investigation without dangerous side effects. On the other hand, there is not complete agreement about this question. Rapino et al. (2005) consider that intermittent hypoxia, followed by reoxygenation, increases the production of reactive oxygen species, which may lead to accelerated aging and the appearance of age-related diseases. The same opinion was expressed by Kolchinskaya et al. (1999). Considering the results of the current investigation, it appears that whether intermittent hypoxia is beneficial or not is most dependent on the hypoxia protocol.

Aging is associated with a loss in both muscle mass and the metabolic efficiency of skeletal muscle. A major part, but not all, of these changes is associated with an age-related decrease in physical activity and can be counteracted partially by increased exercise (Dela and Kjaer, 2006; Garcia-Mendoza et al., 2006). In addition, a sedentary lifestyle has been shown to be predictive of total mortality and cardiovascular mortality by a multivariate analysis adjusted for potential confounding variables. Other related predictors of total mortality were exercise time and inadequate hemodynamic responses, such as a small increase in pulse rate and systolic blood pressure from rest to peak exercise (Al-Khalili et al., 2007). Another opinion was expressed by Haseler et al. (2004): The maximal muscle oxidative rate of sedentary subjects, unlike their exercise-trained counterparts, is limited by mitochondrial capacity and not O_2 availability in normoxia.

Our current data demonstrate that IHT is particular effective in untrained senior individuals. One of the strongest markers of physical health identified in exercise testing is maximum exercise capacity. The second is heart rate–blood pressure product. Our investigation has shown the improvement of both indixes in untrained subjects. This was evidenced by attenuation of the cardiovascular responses both to hypoxia and during physical work in these subjects. Only in the untrained subjects did IHT produce an increase in submaximal work load and oxygen consumption at anaerobic threshold. It is interesting to note that Arai et al. (2006) found that in elderly subjects exercise produced responses similar to those produced by IHT in the current study. Since many elderly people cannot exercise, IHT may provide an alternative means of improving cardiorespiratory fitness. The mechanisms responsible for IHT-induced improvement of cardiorespiratory fitness are not known but, from the results of the current study, may involve improved control of heart rate and blood pressure, endothelial function, and enhanced activity of metabolic enzymes.

Before IHT, we did not reveal any differences in microvascular reactivity between the groups. IHT enhanced basal perfusion and maximal perfusion during hyperemia in sedentary subjects more distinctly than in well-trained senior men. Thus, we demonstrated

that IHT improved microvascular endothelial function in sedentary men. Physical training also improves microvascular endothelial function (Gill et al., 2004; Middlebrooke et al., 2005), and this fact may account for the lack of effect of IHT in the well-trained subjects of Gr 1. However, in contrast to the current findings, Heylen et al. (2005) reported that physical training was more effective in improving microvascular endothelial function of fit subjects compared to sedentary controls.

Since the primary objective of this investigation was to investigate and compare responses of the two fitness groups to IHT, we did not include placebo groups, that is, "sham" IHT. Data from such groups would be valuable in identifying directly the effects of intermittent hypoxia. However, in this regard we can cite the results of an earlier investigation (Ishchuk, 2007) in which 60 patients with ischemic heart disease were treated with IHT (similar protocol as in the current investigation; 40 patients) or sham IHT (20 patients). After IHT, clinical symptoms of the disease were essentially absent. Physical work capacity was increased significantly by 9.9%, and the duration of periods of myocardial ischemia (24-h Holter monitoring) was shortened significantly by 51.1%. Sham IHT caused only a slight decrease in clinical symptoms and produced no significant change in work capacity.

CONCLUSION

Healthy senior men well tolerate IHT as performed in this investigation. In untrained healthy, senior men, IHT had greater positive effects on hemodynamics, microvascular endothelial function, and work capacity.

REFERENCES

Al-Khalili F., Janszky I., Andersson A., Svane B., and Schenck-Gustafsson K. (2007). Physical activity and exercise performance predict long-term prognosis in middle-aged women surviving acute coronary syndrome. J. Intern. Med. 261:178–187.

Arai T., Obuchi S., Kojima M., Matumoto Y., and Inaba Y. (2006). The evaluation of the relationships between physical factors and effects of exercise intervention on physical functions in community-dwelling older people. Nippon Ronen. Igakkai. Zasshi. 43:781–788.

Balykin M.V., Vinogradov S.N., and Gening T.P. (2004). [Effect of normobaric hypoxia and physical load on the functional indixes of cardiorespiratory system in overweight people.] Vopr. Kurortol. Fizioter. Lech. Fiz. Kult. Jan.–Feb.:18–21.

Bernardi L., Passino C., Serebrovskaya Z., Serebrovskaya T., and Appenzeller O. (2001). Respiratory and cardiovascular adaptations to progressive hypoxia: effect of interval hypoxic training. Eur. Heart J. 22:879–886.

Burtscher M., Pachinger O., Ehrenbourg I., Mitterbauer G., Faulhaber M., Puhringer R., and Tkatchouk E. (2004). Intermittent hypoxia increases exercise tolerance in elderly men with and without coronary artery disease. Int. J. Cardiol. 96:247–254.

Dela F., and Kjaer M. (2006). Resistance training, insulin sensitivity and muscle function in the elderly. Essays Biochem. 42:75–88.

del Pilar Valle M., García-Godos F., Woolcott O.O., Marticorena J.M., Rodríguez V., Gutiérrez I., Fernández-Dávila L., Contreras A., Valdivia L., Robles J., and Marticorena E.A. (2006). Improvement of myocardial perfusion in coronary patients after intermittent hypobaric hypoxia. J. Nucl. Cardiol. 13:69–74.

Ehrenbourg I.V. (1992). The effect of intermittent normobaric hypoxia on physical working ability and oxygen homeostasis in ischemic heart disease. In: Intermittent Hypoxic Training, Effectiveness, Mechanisms of Action. Institute of Physical Culture. Kiev, Ukraine; pp. 93–95.

Garcia-Mendoza M., Valdes C., Ortega T., Rebollo P., and Ortega F. (2006). Differences in health-related quality of life between elderly and younger patients on hemodialysis. J. Nephrol. 19:808–818.

Gill J.M., Al-Mamari A., Ferrell W.R., Cleland S.J., Packard C.J., Sattar N., Petrie J.R., and Caslake M.J. (2004). Effects of prior moderate exercise on postprandial metabolism and vascular function in lean and centrally obese men. J. Am. Coll. Cardiol. 44:2375–2382.

Gippenreiter E., and West J.B. (1996). High altitude medicine and physiology in the former Soviet Union. Aviat. Space Environ. Med. 67:576–584.

Gurvich H.E., and Fainberg R.S. (1938). Increase of organism endurance to high-altitude flights. In: Physiology and Hygiene of High-Altitude Flights. F.G. Krotkov, ed. State Publishing House of the Biological and Medical Literature, Moscow–Leningrad; pp. 109–118.

Haseler L.J., Lin A.P., and Richardson R.S. (2004). Skeletal muscle oxidative metabolism in sedentary humans: 31P-MRS assessment of O2 supply and demand limitations. J. Appl. Physiol. 97:1077–1081.

Heylen E., Simon B., Guerrero F., Elkaim J.P., Saiag B., and Mansourati J. (2005). Reactive hyperaemia in the forearm skin of highly trained windsurfers. Int. J. Sports Med. 26:822–826.

Ishchuk V.I. (2007). Safety and efficacy of intermittent normobaric hypoxia training in elderly patients with ischemic heart disease. J. Ukrainian Acad. Med. Sci. 13:374–384.

Janssens J.P., Pache J.C., and Nicod L.P. (1999). Physiological changes in respiratory function associated with ageing. Eur. Respir. J. 13:197–205.

Klieman L., Hyde S., and Berra K. (2006). Cardiovascular disease risk reduction in older adults. J. Cardiovasc. Nurs. 21(5, Suppl. 1):S27–S39.

Kolchinskaya A.Z., Hatsukov B.H., and Zakusilo M.P. (1999). Oxygen Insufficiency: Destructive and Constructive Actions. Kabardino-Balkaria Scientific Center, Nalchik, Russia.

Kolesnikova E.E., and Serebrovskaya T.V. (2001). Age-related peculiarities of catecholamines exchange and ventilatory responses to hypoxia and hypercapnia under adaptation to intermittent hypoxia. Arkhiv Clin. Exper. Med. 10:165–166.

Korkusko O.V., Sarkisov K.G., and Frajfel'd V.E. (1982). Age-associated peculiarities of microcirculation system in skeletal muscles and their role in muscle work capacity in human aging. ZFA. 37:147–153.

Luckner G., Dunser M.W., Stadlbauer K.H., Mayr V.D., Jochberger S., Wenzel V., Ulmer H., Pajk W., Hasibeder W.R., Friesenecker B., and Knotzer H. (2006). Cutaneous vascular reactivity and flow motion response to vasopressin in advanced vasodilatory shock and severe postoperative multiple organ dysfunction syndrome. Crit. Care.10:135.

Lyamina N.P., Senchikhin V.N., Pokidyshev D.A., and Manukhina E.B. (2001). Disturbed NO production in patients with essential hypertension and a non-drug method of its correction. Kardiologiia. 41:17–21.

Meerson F.Z. (1993). Adaptation to intermittent hypoxia: mechanisms of protective effects. Hypoxia Med. J. 1:2–8.

Meerson F.Z., Tverdokhlib V.P., and Soev V.M. (1989). Adaptation to Periodic Hypoxia in Therapy and Prophylaxis, Nauka, Moscow.

Middlebrooke A.R., Armstrong N., Welsman J.R., Shore A.C., Clark P., and MacLeod K.M. (2005). Does aerobic fitness influence microvascular function in healthy adults at risk of developing Type 2 diabetes? Diabet. Med. Apr. 22:483–489.

Mukharliamov F.Iu., Smirnova M.I., Bedritskii S.A., and Liadov K.V. (2006). Interval hypoxic training in arterial hypertension. Vopr. Kurortol. Fizioter. Lech. Fiz. Kult. :5–6.

Neubauer J.A. (2001). Invited review: physiological and pathophysiological responses to intermittent hypoxia. J. Appl. Physiol. 90:1593–1599.

Rapino C., Bianchi G., Di Giulio C., Centurione L., Cacchio M., Antonucci A., and Cataldi A. (2005). HIF-1alpha cytoplasmic accumulation is associated with cell death in old rat cerebral cortex exposed to intermittent hypoxia. Aging Cell. 4:177–185.

Reeves S.R., and Gozal D. (2005). Developmental plasticity of respiratory control following intermittent hypoxia. Respir. Physiol. Neurobiol. 149:301–311.

Serebrovskaya T.V. (1995). Method for nonspecific body resistance increasing by means of intermittent hypoxic influences "Hypotron." Author's Certificate PA #32, 06 Dec.. Ukraine.

Serebrovskaya T.V. (2002). 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. 3:205–221.

Serebrovskaya T.V., Karaban I.N., Kolesnikova E.E., Mishunina T.M., Swanson R.J., Beloshitsky P.V., Ilyin V.N., Krasuk A.N., Safronova O.S., and Kuzminskaya L.A. (2000). Geriatric men at altitudes: hypoxic ventilatory sensitivity and blood dopamine changes. Respiration. 67:253–260.

Serebrovskaya T.V., Swanson R.J., and Kolesnikova E.E. (2003a). Intermittent hypoxia: mechanisms of action and some applications to bronchial asthma treatment. J. Physiol. Pharmacol. 54:35–41.

Serebrovskaya T.V., Kolesnikova E.E., and Karaban I.N. (2003b). Breathing regulation under intermittent hypoxic training in patients with Parkinson's disease. Fiziol. Zh. 49:95–103.

Sergeev A.A. (1962). Essays on the History of Airspace Medicine, Academy of Sciences of the USSR, Moscow.

Simonenko V.B., Ermolaev A.L., Poshievskaia V.I., and Stepaniants O.S. (2003). Effects of adaptation to intermittent normobaric hypoxia on the results of 24-hour monitoring of arterial pressure in hypertensive patients. Klin. Med. (Mosk.). 81:22–25.

Wasserman K. (1987). Determinants and detection of anaerobic threshold and consequences of exercise above it. Circulation. 76:V129–V139.

Zdolsek J.M., Droog E.J., Thorfinn J., and Lidman D. (2006). Laser Doppler perfusion imaging of the radial forearm flap: a clinical study. Scand. J. Plast. Reconstr. Surg. Hand Surg. 40:101–105.

Address reprint requests to:
Tatiana Serebrovskaya, PhD
Bogomoletz Institute of Physiology
4 Bogomoletz St.
Kiev 01601, Ukraine

E-mail: sereb@biph.kiev.ua

Received August 7, 2007; accepted in final form October 10, 2007.

Randomisierte kontrollierte Humane Studie

Adaptation to Intermittent Hypoxia–Hyperoxia in the Rehabilitation of Patients With Ischemic Heart Disease: Exercise Tolerance and Quality of Life

Article in Kardiologiia · May 2017

DOI: 10.18565/cardio.2017.5.10-16

6 authors, including:

Oleg Glazachev
I.M. Sechenov First Moscow State Medical University
87 PUBLICATIONS 134 CITATIONS
SEE PROFILE

Philipp Kopylov
I.M. Sechenov First Moscow State Medical University
72 PUBLICATIONS 94 CITATIONS
SEE PROFILE

Elena N Dudnik
I.M. Sechenov First Moscow State Medical University
47 PUBLICATIONS 88 CITATIONS
SEE PROFILE

D. S. Tuter
I.M. Sechenov First Moscow State Medical University
8 PUBLICATIONS 7 CITATIONS
SEE PROFILE

Адаптация к интервальной гипоксии-гипероксии в реабилитации пациентов с ишемической болезнью сердца: переносимость физических нагрузок и качество жизни

DOI: https://doi.org/10.18565/cardio.2017.5.10-16

А.Л. СЫРКИН, О.С. ГЛАЗАЧЕВ, Ф.Ю. КОПЫЛОВ, Е.Н. ДУДНИК, Е.Э. ЗАГАЙНАЯ, Д.С. ТУТЕР

ФГБОУ ВО Первый Московский государственный медицинский университет им. И.М. Сеченова Минздрава РФ, Москва

Контактная информация: Глазачев О.С. E-mail: glazachev@mail.ru

Цель исследования. Оценка эффективности и безопасности нового метода — интервальных гипоксических-гипероксических тренировок (ИГГТ) в отношении переносимости физических нагрузок (ПФН) и качества жизни (КЖ) больных ишемической болезнью сердца, получающих оптимальную медикаментозную терапию. ***Материал и методы.*** В исследование включены 46 пациентов (18 мужчин) со стабильной стенокардией напряжения II—III функционального класса, рандомизированных на 2 группы в соотношении 1:1,5: ИГГТ проводились 27 пациентам (15 процедур в течение 3 нед), 19 больных составили группу плацебо (имитация ИГГТ). Обследования пациентов выполнены до, после и через 1 мес после окончания курса процедур. ПФН оценивали при проведении кардиопульмонального нагрузочного тестирования с регистрацией пикового потребления кислорода (VO_2peak, VO_2peak/кг), % от должных значений VO_2peak, потребления кислорода на уровне анаэробного порога (VO_2АП). Анализ КЖ проводили с использованием опросников MOS SF-36, SAQ, HADS. ***Результаты.*** После курса ИГГТ у пациентов достоверно повысилась ПФН: увеличились VO_2peak/кг ($p=0,03$), которые оставались достоверно повышенными в течение последующего месяца ($p=0,036$). Отмечено улучшение субъективного восприятия КЖ по характеристикам физического функционирования, психологического состояния; статистически значимый прирост оценок по всем шкалам опросника SAQ, снижение уровня депрессии и тревоги по динамике оценок по шкалам HADS. Выявленные эффекты были стабильны и сохранялись через 1 мес после курса ИГГТ. Установлены безопасность и хорошая переносимость процедур ИГГТ с минимальными побочными эффектами в виде легкого головокружения, чувства нехватки воздуха. ***Заключение.*** Получено клиническое подтверждение безопасности и эффективности курса ИГГТ у пациентов со стабильной стенокардией напряжения на фоне медикаментозной терапии: достоверно улучшаются ПФН, КЖ, снижается количество ангинозных приступов. ИГГТ обладают значительным потенциалом в комплексной терапии и реабилитации больных стабильной стенокардией напряжения.

Ключевые слова: интервальные гипоксические-гипероксические тренировки, ишемическая болезнь сердца, переносимость физических нагрузок, качество жизни.

Adaptation to Intermittent Hypoxia-Hyperoxia in the Rehabilitation of Patients With Ischemic Heart Disease: Exercise Tolerance and Quality of Life

DOI: https://doi.org/10.18565/cardio.2017.5.10-16

A.L. SYRKIN, O.S. GLAZACHEV, F.Yu. KOPYLOV, E.N. DUDNIK, E.E. ZAGAYNAYA, D.S. TUTER

I.M. Sechenov First Moscow State Medical University, Moscow, Russia

Contact information: Glazachev O.S. E-mail: glazachev@mail.ru

Aim: to assess effect of interval hypoxic-hyperoxic training (IHHT) on exercise tolerance and quality of life of patients with ischemic heart disease (IHD) receiving optimal medical therapy, as well as the safety of IHHT use. ***Methods.*** Patients with stable IHD with functional class II and III angina ($n=46$) were randomized into two groups: IHHT ($n=27$, 15 treatments in 3 weeks), and IHHT imitation ($n=19$). Cardiopulmonary stress test was performed to evaluate the following parameters of exercise tolerance: peak oxygen consumption (VO_2peak, VO_2peak/kg), % of predicted peak oxygen consumption (%VO_2 peak) and anaerobic threshold (VO2AT). MOS SF-36, SAQ, HADS questionnaires were used for assessment of quality of life (QL). Results. Exercise tolerance (VO_2peak/kg) after course of IHHT significantly increased ($p=0.03$) and remained significantly elevated during subsequent month ($p=0.036$). Marked improvement was also observed in patient's subjective perception of QL. This was evidenced by dynamics of characteristics of physical functioning as well as of psychological state, significant increase of values on all scales of disease-specific questionnaire SAQ, reduction of depression and anxiety according to dynamics of HADS scores. These effects persisted in 1 month after IHHT. IHHT was safe and well tolerated. Side effects were minimal (transient slight dizziness, feeling of shortage of air) and did not require IHHT termination. ***Conclusion.*** We received clinical confirmation of safety and effectiveness in of IHHT in medically treated patients with stable angina. IHHT was associated with significant improvement of exercise tolerance, subjective perception of QL, reduction of number of angina attacks. Thus, IHHT has significant potential as component of complex treatment and rehabilitation of patients with stable angina.

Key words: interval hypoxic-hyperoxic training; preconditioning; coronary artery disease; exercise tolerance; quality of life.

В реабилитации и комплексном лечении пациентов с ишемической болезнью сердца (ИБС) наиболее актуальными являются 2 основные задачи: 1) улучшение прогноза; 2) уменьшение частоты и интенсивности приступов стенокардии, улучшение качества жизни (КЖ) [1, 2].

По данным отечественных и зарубежных обзоров, рациональное применение реабилитационных программ приводит к достоверному снижению смертности от всех причин на 20—25% и от сердечно-сосудистых заболеваний на 26—30% [2].

Kardiologiia 2017; 5: 10—16

В последние годы структура методов кардиореабилитации расширяется за счет сочетанного применения (наряду с индивидуально дозированными физическими нагрузками) новых высокотехнологичных инструментальных методик. Одним из перспективных подходов является применение повторных многократных эпизодов адаптации к гипоксии — интервальные гипоксические тренировки (ИГТ). ИГТ — метод немедикаментозного лечения и профилактики хронических неинфекционных заболеваний, повышения физической работоспособности человека на основе многократной периодической стимуляции механизмов транспорта и утилизации кислорода путем дыхания газовыми смесями со сниженным содержанием кислорода.

Экспериментально и клинически доказано, что высокогорная адаптация или моделирование условий среднегорья в гипо- или нормобарическом вариантах, а также короткие повторяющиеся эпизоды нормобарической гипоксии с нормоксическими «паузами» активируют каскад прямых и перекрестных адаптационных эффектов, повышая устойчивость организма как к гипоксическим состояниям, так и другим стрессорам, патогенным факторам, посредством запуска гематологических (увеличение содержания эритропоэтина, гемоглобина, кислородной емкости крови) и негематологических (ангиогенез, активация гликолитической активности, утилизации липидов, систем антиоксидантной защиты, повышение буферной емкости мышц, их толерантности к повышению концентрации лактата, биоэнергетической эффективности митохондриальной дыхательной цепи, транспорта глюкозы в мышцах, хеморецепторной чувствительности, снижение симпатико-адреналовой реактивности и др.) механизмов [3—6].

Клинически значимые эффекты ИГТ во многом сходны с эффектами основного компонента «традиционных» программ кардиореабилитации — физических тренировок: повышение переносимости физических нагрузок (ПФН), улучшение сократительной функции миокарда, коронарной перфузии, снижение уровня фибриногена и агрегации тромбоцитов, позитивные изменения липидного состава плазмы крови, повышение чувствительности к инсулину, описанные как феномен ишемического прекондиционирования (чередование ишемии и последующей реперфузии), запускающего механизмы кардиопротекции и метаболической адаптации к умеренной ишемии, что актуально для пациентов со сниженным коронарным резервом [3, 7]. Поскольку при ИГТ воздействующим фактором является гипоксическая гипоксия с последующей реоксигенацией, то можно говорить об отсроченных эффектах повторяющегося, или хронического, гипоксического прекондиционирования, при котором происходит накопление веществ — триггеров множественных адаптивных сдвигов: опиоидов, норадреналина, аденозина, серотонина, ацетилхолина, ионов кальция, NO, цитокинов (интерлейкины 1В, 2), фактора некроза опухоли-α (TNF-α), ядерного фактора κВ (NF-κB), фактор, индуцируемый гипоксией (HIF-1α, HIF-2α), и др. [7]. Результатом такой активации являются открытие $K_{АТФ}$-каналов сарколеммы и митохондрий кардиомиоцитов, стабилизация мембран, ослабление внутриклеточной кальциевой перегрузки, оптимизация синтеза АТФ, снижение сократимости миокарда и потребности его в энергии, уменьшение выраженности окислительного стресса, изменение метаболизма жирных кислот [8].

Установлено, что эффективность ИГТ можно повысить путем замещения нормоксических пауз (реоксигенации) подачей пациенту гипероксической газовой смеси — методом интервальных гипоксически-гипероксических тренировок (ИГГТ) [9]. В период создаваемой гипероксии происходит более выраженная, чем при нормоксической реоксигенации, индукция активных форм кислорода, необходимая для запуска каскада редокс-сигнального пути, что приводит к усиленному синтезу защитных внутриклеточных белковых молекул, главным образом, с антиоксидантной функцией (ферменты антиоксидантной защиты, железосвязывающие белки, белки теплового шока) [4, 9, 10]. В экспериментальных исследованиях продемонстрированы более выраженные мембран-стабилизирующие эффекты, существенное повышение стрессорной и гипоксической устойчивости миокарда и мозга, уровня антиоксидантной защиты, ПФН в результате проведения адаптации к ИГГТ по сравнению с ИГТ [9—14].

Метод ИГГТ эмпирически обоснован на этапе санаторно-курортного лечения детей с бронхиальной астмой при сочетанном применении ИГТ и энтеральной оксигенотерапии (кислородные коктейли) [11], апробирован в пилотных исследованиях пациентов с метаболическим синдромом, ИБС, квалифицированных спортсменов с синдромом перетренированности [10, 12—14].

Цель настоящего клинического плацебо-контролируемого исследования — комплексный анализ возможности применения и эффективности метода ИГГТ у больных ИБС, получающих оптимально подобранную медикаментозную терапию, на этапе поликлинического наблюдения, с особым вниманием к оценке динамики показателей ПФН и КЖ.

Материал и методы

В исследование были включены 46 пациентов со стабильной стенокардией напряжения II и III функционального класса (ФК), среди которых 18 мужчин и 28 женщин в возрасте от 45 до 83 лет. Диагноз хронической ИБС и ФК устанавливали в соответствии с Национальными клиническими рекомендациями ВНОК (2009), согласно действующей классификации Канадской ассоциации кардиологов. Общая характеристика пациентов представлена в табл. 1.

Достоверные различия по клинико-демографическим признакам наблюдались по 2 характеристикам: в контрольной группе пациентов со стенокардией напряжения III ФК и с сахарным диабетом 2-го типа было несколько больше, чем в основной (p=0,04). Отбор пациентов в исследование осуществляли при условии наличия постоянной оптимально подобранной медикаментозной терапии, соответствующей национальным и европейским рекомендациям.

Достоверных различий по медикаментозной терапии среди пациентов группы ИГГТ и контрольной группы не наблюдалось. В группе ИГГТ на фоне лечения частота сердечных сокращений (ЧСС) в покое составляла 63±7 уд/мин, систолическое артериальное давление (АД) в покое — 125,8±20,2 мм рт.ст., диастолическое АД — 72,2±14,7 мм рт.ст., в группе контроля — 62±10 уд/мин, 125,8±21,2 мм рт.ст. и 76,4±8,6 мм рт.ст. соответственно.

Протокол исследований был сформирован в соответствии с положениями «Биоэтических правил проведения исследований на человеке» и одобрен биоэтической комиссией Университета, от всех пациентов до начала работы было получено письменное информированное согласие.

Таблица 1. **Клинико-демографическая характеристика обследованных пациентов**

Характеристика	Основная группа (n=27)	Контрольная группа (n=19)	p
Пол, мужчины	9 (33)	9 (47)	НД
Возраст, годы	63,9±8,6	63,2±7,9	НД
Курение	5 (18,5)	4 (18,5)	НД
ГБ	22 (81,5)	17 (89,5)	НД
СД 2-го типа	8 (29,6)	3 (15,8)	0,04
Стенокардия напряжения			
II ФК	20 (74,1)	17 (89,5)	НД
III ФК	7 (25,9)	2 (10,5)	0,04
Постинфарктный кардиосклероз	8 (29,6)	8 (42,1)	НД
Пароксизмальная ФП	5 (18,5)	2 (10,5)	НД
ХОБЛ/БА без дыхательной недостаточности	2 (7,4)	2 (10,5)	НД
Медикаментозная терапия, абс. число больных (% от максимальной суточной дозы*)			
β-адреноблокаторы	27 (52)	19 (49)	0,9
блокаторы кальциевых каналов	10 (68)	6 (75)	0,9
ингибиторы АПФ	13 (73)	14 (56)	0,8
БРА	10 (80)	4 (50)	0,1
антитромботические препараты:			
АСК	26 (58)	19 (59)	0,5
клопидогрел	1 (100)	—	—
статины	27 (32)	19 (34)	0,2
пролонгированные нитраты	17 (35)	8 (25)	0,09
молсидомин	8 (35)	11 (33)	0,1

Примечание. Данные представлены в виде абсолютного числа больных (%) возраст - $M\pm\sigma$. ГБ — гипертоническая болезнь; СД — сахарный диабет; ФК — функциональный класс; ФП — фибрилляция предсердий; ХОБЛ — хроническая обструктивная болезнь легких; БА — бронхиальная астма; АПФ — ангиотензинпревращающий фермент; БРА — блокаторы рецепторов ангиотензина II; АСК — ацетилсалициловая кислота; НД — недостоверно (p>0,05). * — максимальные суточные дозы для лечения стабильной стенокардии: β-адреноблокаторов — метопролол 400 мг, бисопролол 10 мг, небиволол 10 мг; блокаторов кальциевых каналов — амлодипин 10 мг, нифедипин 40 мг; ингибиторов АПФ — периндоприл 10 мг, эналаприл 40 мг; БРА — лозартан 100 мг; антитромботических препаратов — АСК 150 мг, клопидогрел 75 мг/сут; статинов — аторвастатин 80 мг, розувастатин 40 мг; пролонгированных нитратов — изосорбида динитрат 120 мг, изосорбида-5-мононитрат 120 мг; молсидомина 12 мг (Основные лекарственные препараты для лечения стабильной стенокардии напряжения. Национальные клинические рекомендации. М., 2009).

После исходного обследования пациенты случайным порядком были разделены на 2 группы в соотношении 1,5:1 — основная группа (n=27) и контрольная (n=19). Пациентам в основной группе проводили ИГГТ в течение 3 нед по 5 дней с перерывами 2 дня (15 тренировок) по одной процедуре в день. В исследовании использовали нормобарическую установку для получения гипоксических и гипероксических газовых смесей на основе обратной связи ReOxy Cardio (S.A. Aimediq, Luxembourg) [15].

Перед началом курса процедур определяли индивидуальную чувствительность пациентов к гипоксии путем проведения 10-минутного гипоксического теста (ГТ) — дыхание через маску газовой смесью с 12% содержанием O_2, с ежеминутным мониторированием ЧСС и насыщения гемоглобина артериальной крови кислородом (S_aO_2).

При отпуске процедур ИГГТ длительность подачи газовой гипоксической (11—12% O_2) и гипероксической (35% O_2) смесей регулировали с учетом результатов ГТ по принципу биологической обратной связи автоматически на основе мониторирования индивидуальных значений S_aO_2 и ЧСС [15]. Длительность одной процедуры составляла 45—50 мин, каждого гипоксического периода — в среднем 4—6 мин, гипероксического периода — 1—2 мин в зависимости от скорости восстановления S_aO_2 у пациента. После каждой тренировки вносили отметку в дневник наблюдения, где указывали дату проведения процедуры, оценку пациентом переносимости процедуры, все возможные изменения состояния во время тренировки и в период между ними. До и после тренировки измеряли АД, ЧСС. После курса ИГГТ в течение 1 мес пациенты вели дневник самоконтроля, в котором указывали наличие загрудинных, головных болей, оценку общего самочувствия по шкале 1—5 баллов, прием препаратов, результаты измерения АД, ЧСС утром и вечером. Пациенты контрольной группы прошли курс плацебо-тренировок, имитирующих ИГГТ, получая через маску того же аппарата атмосферный воздух.

Всем пациентам проводили обследование до и после курса ИГГТ или плацебо-тренировок. В группе ИГГТ было выполнено дополнительное обследование через 1 мес после тренировок для оценки длительности сохранения эффектов, возникших в результате курса ИГГТ. В силу ограниченности ресурсов исследование отдаленных эффектов в контрольной группе не проводили.

Обследование включало опрос и осмотр пациента, регистрацию АД, ЧСС, электрокардиографию в покое, оценку ПФН путем проведения кардиопульмонального нагрузочного тестирования. Нагрузочное тестирование с газовым анализом проведено с применением комплекса CARDIOVIT CS-200, система с использованием беговой дорожки. Выбор протокола нагрузочного тестирования (BRUCE или M-BRUCE) осуществляли в соответствии с тяжестью патологии сердца, ПФН, наличием сопутствующей патологии, возрастом пациента [16]. Критерии прекращения нагрузочного теста соответствовали рекомендациям (цит. по [17]). КЖ больных до, после ИГГТ и через 1 мес изучено при помощи вопросника MOS 36-Item Short-Form Health Survey (SF-36). Использовали официальный русскоязычный аналог вопросника [18]. По результатам анкетирования проводили расчет 8 параметров: физической активности (ФА), роли физических проблем ограничении жизнедеятельности (РФ), боли, жизнеспособности (ЖС), социальной активности (СА), роли эмоциональных проблем в ограничении жизнедеятельности (РЭ), психического здоровья (ПЗ) и общего здоровья (ОЗ). Каждый показатель вычисляли в соответствии со шкалой от 0 до 100 баллов: чем ниже балл, тем хуже КЖ.

Дополнительно проводили тестирование пациентов с применением Сиэтловского опросника стенокардии (SAQ) [19] и Госпитального опросника тревоги и депрессии (HADS). Среди разработанных специализированных опросников для стенокардии SAQ считается наиболее чувствительным и воспроизводимым, удобным в использовании самостоятельным клиническим психодиагностическим инструментом [20, 21].

Статистический анализ данных проводили с помощью программы Statistica 6.0. При описании показателей, представленных в виде альтернативных переменных, приведены число наблюдений и доля пациентов (в процентах). Для описания показателей, представленных в виде количественных перемен-

ных, использовали среднее значение ± стандартное отклонение ($M\pm\sigma$). Для оценки достоверности внутри- и межгрупповых различий показателей в динамике использовали одновыборочный критерий *t*, критерий Вилкоксона (для внутригрупповых сравнений) и критерий Манна—Уитни (для межгрупповых сравнений). Различия считали статистически значимыми при $p<0,05$.

Результаты

В табл. 2 отображена сравнительная характеристика параметров, отражающих ПФН у пациентов в группе ИГГТ и в группе контроля. После курса ИГГТ у пациентов отмечен статистически значимый прирост исходно сниженной по отношению к возрастным нормативам ПФН, что проявлялось в достоверном приросте времени физической нагрузки (протокол BRUCE), пикового потребления кислорода ($p=0,03$), его процентной доли от должных величин, а также потребления кислорода на уровне анаэробного порога (АП). После курса тренировок АП достоверно увеличился с 12,5 до 13,4 мл/кг/мин ($p=0,002$), а через 1 мес по их окончании — до 13,6 мл/кг/мин ($p=0,0005$). В группе плацебо-процедур достоверной динамики значений анализируемых показателей не отмечено.

Кроме того, в группе ИГГТ отмечалось снижение частоты возникновения ангинозных приступов во время повторных проведений нагрузочного теста на 50% сразу после процедур ИГГТ и на 75% через 1 мес после ИГГТ по сравнению с исходными значениями.

Повышение уровня ПФН у пациентов, прошедших курс ИГГТ, сопровождалось существенным улучшением субъективно оцениваемого КЖ по ряду шкал психодиагностических опросников (табл. 3). Так, по динамике показателей специфического Сиэтловского опросника стенокардии установлено статистически значимое улучшение по шкалам ограничения физических нагрузок ($p=0,0006$), стабильности приступов ($p=0,001$) и частоты приступов ($p=0,00004$). Отмеченные позитивные сдвиги сохранялись и через 1 мес после курса процедур. Важной представляется также позитивная динамика по шкалам психологического отношения к болезни ($p=0,0005$) и общей удовлетворенности лечением ($p=0,00008$). В группе пациентов, которым проводились плацебо-процедуры, достоверных изменений по шкалам теста SAQ не наблюдалось.

Достоверное улучшение в опытной группе было отмечено и при анализе данных опросника SF-36, причем позитивная динамика наблюдалась в оценках по шкалам, характеризующих физическую составляющую общей субъективной оценки здоровья: физическое функционирование, ролевая деятельность и жизнеспособность. Достигнутые субъективно оцениваемые улучшения состояния КЖ пациентов отмечались и через 1 мес после ИГГТ. По шкале «психическое здоровье» достоверный прирост показателя отмечен лишь через 1 мес после окончания курса ИГГТ — с 59,2±4,1 до 67,2±2,9 ($p=0,02$).

При анализе результатов применения опросника HADS в группе ИГГТ отмечалось достоверное снижение оценок по шкале «депрессия» после тренировок с 6,5±2,9 до 5,1±2,8 балла ($p=0,02$) и через 1 мес — до 4,9±2,5 балла ($p=0,002$). По шкале «тревога» в группе ИГГТ отмечалось достоверное снижение оценки с 8,6±2,3 до 6,2±3,1 балла ($p=0,08$) после тренировок и до 3,8±2,1 балла ($p=0,02$) через 1 мес. В группе контроля достоверных изменений оценок по шкалам опросников SAQ и HADS также не наблюдалось.

Полученные результаты позволили пересмотреть и провести анализ динамики клинической оценки ФК стенокардии напряжения у пациентов в группе ИГГТ. Отмечено сокращение числа пациентов с III ФК с 26 до 7% (такая динамика сохранялась через 1 мес после курса ИГГТ), прежде всего за счет перехода отдельных пациентов в I ФК. Однако выявленная динамика была нестабильной — через 1 мес после процедур число пациентов с I ФК сократилось. Стоит отметить, что в контрольной группе (пациенты аналогично получали оптимальную медикаментозную терапию) также отмечалось формирование группы пациентов с I ФК стенокардии (11%), однако число пациентов с III ФК в этой группе оставалось неизменным (11%).

Приобретенный опыт применения метода ИГГТ позволяет характеризовать метод как безопасный и хорошо переносимый пациентами. За время проведения плацебо- или гипоксических-гипероксических процедур (общее число ИГГТ составило 690), несмотря на существенную нагрузку — дыхание гипок-

Таблица 2. **Динамика показателей ПФН в курсе ИГГТ**

Показатель	До проведения курса тренировок		После проведения курса тренировок		Через 1 мес после проведения курса ИГГТ, 5 ($n=27$)
	основная группа, 1 ($n=27$)	контрольная группа, 2 ($n=19$)	основная группа, 3 ($n=27$)	контрольная группа, 4 ($n=19$)	
Время работы, с					
M-BRUCE*	354±194	280±92	373±141	323±64	375±130
BRUCE*	280±126	335±121	295±79	355±96	332±113 $p_{1-5}=0,011$
Ангинозный приступ во время нагрузочного теста, абс. число больных (%)	12 (44,4%)	4 (21,1)	6 (22,2) $p<0,05$	6 (31,6)	3 (11,1) $p<0,05$
Пиковое потребление кислорода, VO_2/кг	14,3±2,9	15,01±3,9	14,5±4,1 $p_{1-3}=0,03$	15,5±3,6	14,8±2,4 $p_{1-5}=0,036$
% от должного пикового потребления кислорода	73,0±12,6	73,2±16,9	79,3±13,6 $p_{1-3}=0,009$	75,2±18,3	76,3±10,7 $p_{1-5}=0,02$
Потребление кислорода на уровне АП, VO_2/кг	12,5±2,4	12,8±2,8	13,4±2,7 $p_{1-3}=0,002$	13,1±2,9	13,6±2,8 $p_{1-5}=0,0005$

Примечание. Здесь и в табл. 3 данные представлены в виде $M\pm\sigma$. * — число пациентов, выполнявших нагрузочное тестирование по протоколу M-BRUCE в группе ИГГТ — 12, в группе контроля — 5. ПФН — переносимость физической нагрузки; ИГГТ — интервальные гипоксические-гипероксические тренировки; АП — анаэробный порог.

Таблица 3. **Динамика показателей КЖ в курсе ИГТ, баллы**

Показатель	До проведения курса тренировок		После проведения курса тренировок		Через 1 мес после проведения курса ИГТ, 5 (n=27)
	основная группа, 1 (n=27)	контрольная группа, 2 (n=19)	основная группа, 3 (n=27)	контрольная группа, 4 (n=19)	
Шкала ограничения физических нагрузок (PL, SAQ)	43,3±17,7	51,6±17,8	51,6±13,1 p_{1-3}=0,0006	49,4±18,6	53,8±17,8 p_{1-5}=0,0008
Шкала стабильности приступов (AS, SAQ)	56,5±27,4	69,7±27,1	78,3±23,3 p_{1-3}=0,001	72,4±20,2	79,6±22,7 p_{1-5}=0,0003
Шкала частоты приступов (AF, SAQ)	59,6±27,7	69,5±32,7	81,1±17,9 p_{1-3}=0,00004	75,3±26,9	80,9±18,2 p_{1-5}=0,00006
Шкала удовлетворенности лечением (TS, SAQ)	60,7±16,2	77,7±19,6	77,4±16,8 p_{1-3}=0,00008	78,6±19,8	80,5±17,7 p_{1-5}=0,0001
Шкала отношения к болезни (DP, SAQ)	47,2±18,9	50,9±24,2	60,8±17,9 p_{1-3}=0,0005	56,1±24,5	63,4±17,4 p_{1-5}=0,0002
Общее здоровье (ОЗ, SF-36)	45,8±2,9	43,9±12,6	49,9±3,3	47,5±13,5	50,1±2,9
Физическое функционирование (ФА, SF-36)	49,5±4,6	52,3±21,7	60,5±4,5 p_{1-3}=0,003	50,5±22,9	58,8±4,6 p_{1-5}=0,007
Ролевая деятельность (РД, SF-36)	22,6±8,3	25,0±39,3	48,8±9,4 p_{1-3}=0,02	27,3±42,2	57,1±7,7 p_{1-5}=0,006
Эмоциональная деятельность (РЭ, SF-36)	41,4±9,99	42,5±47,34	52,6±9,1	44,0±48,6	63,8±7,2
Социальное функционирование (СА, SF-36)	47,9±2,8	50,2±13,5	47,2±1,9	46,3±11,8	47,7±1,05
Телесная боль (РФ, SF-36)	50,6±4,2	50,2±18,9	56,7±3,9	51,4±21,1	60,2±3,4
Жизнеспособность (ЖС, SF-36)	51,7±3,8	50,9±21,02	58,3±2,9 p_{1-3}=0,03	51,5±17,9	60,9±3,2 p_{1-5}=0,003
Психическое здоровье (ПЗ, SF-36)	59,2±4,1	57,8±20,01	62,0±3,1	61,4±16,5	67,2±2,9 p_{1-5}=0,02

сической смесью, что сопровождалось снижением индивидуальных значений S_aO_2 до 80—84%, — наблюдались единичные побочные эффекты, при которых не требовалось прекращение процедур. Умеренное чувство нехватки воздуха, учащенное сердцебиение либо легкое головокружение наблюдались у 5 (19%) больных в группе ИГТ. Все побочные явления проходили к 4—5-й процедурам. Число пациентов, отметивших побочные явления, в сравниваемых группах статистически значимо не различалось. Большинство пациентов отмечали релаксирующее, сомногенное действие процедур ИГТ, а периоды гипероксии были оценены ими как «освежающие», быстро снимающие некоторые неприятные ощущения и умеренно выраженную одышку в гипоксические фазы тренировки.

Обсуждение

Расширение средств реабилитации и вторичной профилактики, повышение КЖ пациентов с ИБС имеет большое медико-социальное значение. К числу таких перспективных технологий можно отнести методы адаптации к гипоксическим газовым смесям в различных режимах [3, 14]. Проведено несколько исследований, подтверждающих позитивные эффекты длительных гипоксических тренировок в интервальном режиме в повышении ПФН и коррекции факторов риска развития сердечно-сосудистых осложнений у кардиологических больных [10, 22], в частности у пациентов со стабильной стенокардией напряжения [3, 23]. Проведение ИГТ в режиме цикличного чередования периодов дозированной гипоксии и гипероксии является принципиально новой технологией повышения неспецифических адаптационных возможностей организма пациентов с ИБС.

В проведенном рандомизированном плацебо-контролируемом исследовании выявлено, что курс процедур ИГТ на фоне оптимальной медикаментозной терапии статистически значимо повышает ПФН пациентов со стабильной стенокардией напряжения II—III ФК, что объективизировано проведением кардиопульмонального нагрузочного тестирования с газовым анализом (достоверно возросли значения пикового потребления кислорода, АП). Важно, что достигнутый результат сохранялся и через 1 мес после окончания курса ИГТ, что ранее не было предметом специального анализа в сходных клинических исследованиях эффектов ИГТ [10].

Принципиально важным представляется одновременное улучшение практически у всех пациентов субъективного восприятия КЖ, что продемонстрировано в динамике оценок по шкалам специфического опросника стенокардии SAQ, а также по шкалам опросника SF-36, характеризующих субъективную оценку здоровья: «физическое функционирование», «ролевая деятельность» и «жизнеспособность». Показано [20, 21], что КЖ пациентов с ИБС существенно снижено, причем по мере увеличения ФК стенокардии физическое функционирование больных нарушается в большей степени, чем психологическое. В проведенном исследовании установлено, что после завершения курса ИГТ у пациентов не только улучшается физическое функционирование (по опроснику SF-36), но и отмечается улучшение клинической картины заболевания, что выражается снижением ФК стенокардии, а также уменьшением количества ангинозных приступов и кратности приема нитратов короткого действия.

В качестве позитивного эффекта следует также отметить повышение после курса ИГТ самооценок пациентов своего психологического состояния, а также удовлетворенности лечением, что можно рассматривать как повышение мотивации больных и их приверженности к рекомендуемому лечению.

Особое внимание в работе было уделено оценке безопасности применения технологии ИГТ в лечении больных выбранной категории. Полученные результаты минимальных побочных

эффектов при проведении процедур ИГГТ в целом подтверждают безопасность метода и более комфортную переносимость процедур по сравнению с традиционными протоколами гипоксически-нормоксического прекондиционирования, отмеченные в наших предыдущих работах [12, 13, 24]. Установленные нами и другими авторами оптимизирующие эффекты гипоксических тренировок в отношении модифицируемых факторов риска развития кардиометаболических нарушений открывают перспективы применения ИГГТ в качестве дополнительного метода лечения и реабилитации больных стабильной стенокардией напряжения.

Выводы

Получено клиническое подтверждение эффективности интервальных гипоксических-гипероксических тренировок у пациентов со стабильной стенокардией напряжения на фоне оптимальной медикаментозной терапии: применение курса интервальных гипоксических-гипероксических тренировок у пациентов с ишемической болезнью сердца повышает переносимость физических нагрузок, устойчивость к эпизодам гипоксии, а также сопровождается повышением качества жизни, снижением количества ангинозных приступов, сокращением кратности приема нитроглицерина.

Установлены безопасность и удовлетворительная переносимость процедур интервальных гипоксических-гипероксических тренировок с минимальными побочными эффектами в виде преходящих легкого головокружения, чувства нехватки воздуха, что не требовало прекращения проведения процедур. Таким образом, режим интервальных гипоксических-гипероксических тренировок хорошо переносится пациентами.

Ограничения исследования. В рамках исследования эффективности и безопасности метода ИГГТ по организационно-методическим соображениям не проведен сравнительный анализ эффектов ИГГТ и гипоксического прекондиционирования в режиме ИГТ, что потребовало бы обследования еще одной группы пациентов. Пациенты группы контроля получали плацебо-процедуры, дыша через маску прибора увлажненным атмосферным воздухом и не испытывая каких-либо затруднений, что потенциально могло ими не восприниматься как «медицинская процедура». Оптимальная медикаментозная терапия оценивалась со слов пациентов без проверки концентраций лекарственных средств в крови пациентов, что не позволяет исключить эффект повышения приверженности к проводимому лечению у пациентов в 2 группах пациентов.

Благодарности. *Авторы выражают благодарность компании AiMediqS.A. (Люксембург) за предоставленный опытный образец прибора ReOxy для проведения гипоксических-гипероксических тренировок пациентов.*

Информация о конфликте интересов/финансировании.

Конфликт интересов не заявляется.

Авторы подтверждают отсутствие спонсоров работы.

Аппарат REOXY (производство «AIMediq S.A.», Люксембург) предоставлен компанией-производителем безвозмездно. Компания и ее представители не участвовали в дизайне исследования, сборе, анализе и интерпретации данных, в подготовке публикации.

Исследование выполнено при частичной поддержке Российского гуманитарного научного фонда, грант №17-06-00784 «Качество жизни пожилых больных с сердечно-сосудистой патологией: влияние процедур адаптации к интервальной гипоксии-гипероксии».

Сведения об авторах:

ФГБОУ ВО Первый Московский государственный медицинский университет им. И.М. Сеченова Минздрава РФ, Москва

Глазачев О.С. – д.м.н., проф. кафедры нормальной физиологии, зав. лабораторией «Здоровье и качество жизни студентов» НИЦ.

Дудник Е.Н. – доцент кафедры нормальной физиологии.

Загайная Е.Э. – н.с. лаборатории «Здоровье и качество жизни студентов» НИЦ.

Кафедра профилактической и неотложной кардиологии ИПО

Сыркин А.Л. – д.м.н., проф., зав. кафедрой.

Копылов Ф.Ю. – д.м.н., проф. кафедры.

Тутер Д.С. – аспирант, ст. лаборант кафедры.

E-mail: glazachev@mail.ru

Information about the author:

I.M. Sechenov First Moscow State Medical University, Moscow, Russia

Oleg S. Glazachev – MD, professor.

E-mail: glazachev@mail.ru

Литература/REFERENCES

1. Drapkina O.V. Quality of Life in Patients with Coronary Artery Disease. Difficult Patient 2014;7:12–16. Russian (Драпкина О.В. Качество жизни у больных ИБС. Трудный пациент 2014;7:12–16).
2. Montalescot G., Sechtem U., Ashenbah S. et al. ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J 2013;34 (38):2949–3003.
3. Serebrovskaja T.V., Shatilo V.B. Experience of using interval hypoxia in prevention and treatment of cardiovascular diseases: Review. Circulation and haemostasis 2014;1–2:16–33. Russian (Серебровская Т.В., Шатило В.Б. Опыт использования интервальной гипоксии для предупреждения и лечения заболеваний сердечно-сосудистой системы. Обзор. Кровообращение и гемостаз 2014;1–2:16–33).
4. Arkhipenko Yu.V., Sazontova T.G., Tkatchouk E.N., Meerson F.Z.

Adaptation to continuous and intermittent hypoxia: role of the active oxygen-dependent system. «Adaptation Biology and Medicine (Vol.1 Sub-cellular Basis)» (Eds. B.K. Sharma et al.) New Dehli, Narosa Publishing House 1997;251–259.

5. Anderson J.D., Honigman B. The effect of altitude-induced hypoxia on heart disease: do acute, intermittent, and chronic exposures provide cardio-protection? High Alt Med Biol 2011;12(1):45–55.
6. Navarrete-Opazo A., Mitchell G.S. Therapeutic potential of intermittent hypoxia: a matter of dose. Am J Physiol Regul Integr Comp Physiol 2014;307:1181–1197, http://dx.doi.org/10.1152/ajpregu.00208.2014.
7. Maslov L.N., Lishmanov Ju.B., Emel'janova T.V., Prut D.A. Hypoxic preconditioning as a new approach to the prevention of ischemic and reperfusion injury of the brain and heart. Angiology and vascular surgery 2011;17(3):27–36. Russian (Маслов Л.Н., Лишманов Ю.Б., Емельянова Т.В., Прут Д.А. Гипоксическое прекондиционирование как новый подход к профилактике ишемических и реперфузионных повреждений головного мозга и сердца. Ангиология и сосудистая хирургия 2011;17(3):27–36).
8. Shljahto E.V., Nifontov E.M., Galagudza M.M. Pre- and postconditioning as methods of cardio cytoprotection: pathophysiological and clinical aspects. Heart Failure 2008;1:4–10. Russian (Шляхто Е.В., Нифонтов Е.М., Галагудза М.М. Пре- и посткондиционирование как способы кардиоцитопротекции: патофизиологические и клинические аспекты. Сердечная недостаточность 2008;1:4–10).
9. Sazontova T.G., Bolotova A.V., Glazachev O.S., et al. Adaptation to hypoxia and hyperoxia increases physical endurance: the role of reactive oxygen species and redox signaling (experimentally-applied research). Russian Journal of Physiology 2012;98(6):793–807. Russian (Сазонтова Т.Г., Болотова А.В., Глазачев О.С., и др. Адаптация к гипоксии и гипероксии повышает физическую выносливость: роль активных форм кислорода и редокс-сигнализации (экспериментально-прикладное исследование). Российский физиологический журнал 2012,98(6):793–807).
10. Glazachev O.S., Pozdnjakov Ju.M., Urinskij A.M., Zabashta S.P. Hypoxia-hyperoxia adaptation and increased exercise capacity in patients with coronary heart disease. Cardiovascular Therapy and prevention 2014;13(1):16–21. Russian (Глазачев О.С., Поздняков Ю.М., Уринский А.М., Забашта С.П. Повышение толерантности к физическим нагрузкам у пациентов с ишемической болезнью сердца путем адаптации к гипоксии-гипероксии. Кардиоваскулярная терапия и профилактика 2014; 13(1):16–21).
11. Borukaeva I.H., Cyganova T.N. The combined applicationuse of hypoxytherapy and oxygen therapy for the spa and resort-based treatment of bronchial asthma. Problems of Balneology, Physiotherapy, and Exercise Therapy 2012;4:10–14. Russian (Борукаева И.Х., Цыганова Т.Н. Комбинированное применение гипокситерапии и оксигенотерапии в санаторно-курортном лечении бронхиальной астмы. Вопросы курортологии, физиотерапии и лечебной физической культуры 2012;4:10–14).
12. Glazachev O.S., Zvenigorodskaja L.A., Jarceva L.A., et al. Interval Hypo-hyperoxic training in the treatment of the metabolic syndrome. Experimental and Clinical Gasteroenterology 2010;7:51–56. Russian (Глазачев О.С., Звенигородская Л.А., Ярцева Л.А., и др. Интервальные гипо-гипероксические тренировки в коррекции индивидуальных компонентов метаболического синдрома. Экспериментальная и клиническая гастроэнтерология 2010;7:51–56).
13. Glazachev O.S., Smolenskij A.V., Dudnik E.N., et al. Periodic hypoxic-hyperoxic training in the rehabilitation of sportsmen with the chronic overtraining syndrome (a pilot study). Exercise Therapy And Sports Medicine 2010;2:19–25. Russian (Глазачев О.С., Смоленский А.В., Дудник Е.Н., и др. Интервальные гипоксически-гипероксические тренировки в реабилитации спортсменов с синдромом хронической перетренированности (пилотное исследование). Лечебная физкультура и спортивная медицина 2010;2:19–25).
14. Urdampilleta A., González-Muniesa P., Portillo M.P., Martínez J.A. Usefulness of combining intermittent hypoxia and physical exercise in the treatment of obesity. J Physiol Biochem 2011; 68 (2): 289–304.
15. Kostin A.I., Glazachev O.S., Platonenko A.V., Spirina G.K. Apparatus for integrated intermittent normobaric hypoxic-hyperoxia training for human, RF patent for invention №2365384 27 august 2009. Russian (Костин А.И., Глазачев О.С., Платоненко А.В., Спирина Г.К. Устройство для проведения комплексной интервальной нормобарической гипоксическо-гипероксической тренировки человека. Патент РФ на изобретение №2365384 от 27 августа 2009 г.).
16. Syrkin A.L., Poltavskaja M.G., Novicova N.A. Manual functional diagnostics of heart disease. M.: Zolotoj standart 2009:202p. Russian (Сыркин А.Л., Полтавская М.Г., Новикова Н.А. Руководство по функциональной диагностике болезней сердца. М.: Золотой стандарт 2009:202с).
17. Poltavskaja M.G., Mkrtumjan Je.A., Svet A.V., et al. Exercise testing with gas analysis. Pod red. A.L. Syrkina. Uchebnoe posobie. M.: Russkij vrach 2009:44 p. Russian (Полтавская М.Г., Мкртумян Э.А., и др. Нагрузочные пробы с газовым анализом. Под ред. А.Л. Сыркина. Учебное пособие. М.: Русский врач 2009: 44 с).
18. Ware J., Snow K., Kasinski M. et al. SF-36 health survey: Manual and Interpretation Guide. Boston 1993:143.
19. Spertus J.A., Winder J.A., Dewhurst T.A., et al. Development and evaluation of the Seattle Angina Questionnaire: a new functional status measure for coronary artery disease. J Am Coll Cardiol 1995,25(2):333–341.
20. Pogosova N.V., Bajchorov I.H., Jufereva Ju.M., Koltunov I.E. Quality of life of patients with cardiovascular disease: contemporary state of the problem. Cardiology 2010;4:66–78. Russian (Погосова Н.В., Байчоров И.Х., Юферева Ю.М., Колтунов И.Е. Качество жизни больных с сердечно-сосудистыми заболеваниями: современное состояние проблемы. Кардиология 2010;4:66–78).
21. Chernjavskij A.M., Efanova O.S., Jefendiev V.U., et al. Quality of life in patients with coronary heart disease with severe myocardial dysfunction of the left ventricle with medical and surgical treatments. Cardiology 2015;4:5–13. (Чернявский А.М., Ефанова О.С., Эфендиев В.У., и др. Качество жизни больных ишемической болезнью сердца с выраженной дисфункцией миокарда левого желудочка при медикаментозном и хирургическом методах лечения. Кардиология 2015;4:5–13). DOI: http://dx.doi.org/10.18565/cardio.2015.4.5-13
22. Burtscher M., Gatterer H., Szubski C. et al. Effects of interval hypoxia on exercise tolerance: special focus on patients with CAD or COPD. SleepBreath 2009;2:29–34.
23. Zagajnaja E.Je., Kopylov F.Ju., Glazachev O.S., et al. Effect of interval hypoxic-hyperoxic training on exercise tolerance in patient with angina pectoris functional class II-III on background of optimal medical therapy. Cardiology & Cardiovascular Surgery 2015; 8(3):33–40. DOI: http://dx.doi.org/10.17116/kardio20158333–38. Russian (Загайная Е.Э., Копылов Ф.Ю., Глазачев О.С., и др. Влияние интервальных гипоксических-гипероксических тренировок на переносимость физических нагрузок у пациентов со стабильной стенокардией напряжения II—III ФК на фоне оптимальной медикаментозной терапии. Кардиология и сердечно-сосудистая хирургия 2015;8(3):33–40).
24. Glazachev O.S., Dudnik E.N. Medical and physiological basis of hypoxic-hyperoxic training application in adaptive physical training. Adaptive physical culture 2012;1(49):2–4. Russian (Глазачев О.С., Дудник Е.Н. Медико-физиологическое обоснование применения гипоксическо-гипероксических тренировок в адаптивной физической культуре. Адаптивная физическая культура 2012,1(49):2–4.).

Поступила 15.02.16 (Received 15.02.16)

Randomisiert
Placebo kontrolliert

Adaptation to intermittent hypoxia-hyperoxia improves cognitive performance and exercise tolerance in the elderly

Article · July 2017

DOI: 10.1134/S2079057017030038

CITATIONS
2

READS
192

10 authors, including:

Oleg Glazachev
I.M. Sechenov First Moscow State Medical University
87 PUBLICATIONS 134 CITATIONS
SEE PROFILE

Rudolf Likar
274 PUBLICATIONS 4,725 CITATIONS
SEE PROFILE

Martin Burtscher
University of Innsbruck
382 PUBLICATIONS 4,380 CITATIONS
SEE PROFILE

Walter Kofler
I.M. Sechenov First Moscow State Medical University
30 PUBLICATIONS 602 CITATIONS
SEE PROFILE

ISSN 2079-0570, Advances in Gerontology, 2017, Vol. 7, No. 3, pp. 214–220. © Pleiades Publishing, Ltd., 2017.
Original Russian Text © U. Bayer, O.S. Glazachev, R. Likar, M. Burtscher, W. Kofler, G. Pinter, H. Stettner, S. Demschar, B. Trummer, S. Neuwersch, 2017, published in Uspekhi Gerontologii, 2017, Vol. 30, No. 2, pp. 255–261.

Adaptation to Intermittent Hypoxia-Hyperoxia Improves Cognitive Performance and Exercise Tolerance in the Elderly

U. Bayer[a], O. S. Glazachev[b, *], R. Likar[a], M. Burtscher[c], W. Kofler[b], G. Pinter[a], H. Stettner[d], S. Demschar[a], B. Trummer[a], and S. Neuwersch[a]

[a] *Klinikum Klagenfurt, Klagenfurt am Wörthersee, 9020 Austria*
[b] *Sechenov First Moscow State Medical University, Moscow, 119991 Russia*
[c] *University of Innsbruck, Institute of Sport Science, Innsbruck, 6020 Austria*
[d] *Alpen-Adria University Klagenfurt, Klagenfurt, 9020 Austria*
**e-mail: glazachev@mail.ru*

Abstract—To maintain physical performance and cognitive functions in the elderly, multimodal training programs (MTP) are used, which are based on physical training, physiotherapy procedures, psychological training, etc. To increase the efficiency of MTP in the elderly, it is suggested to apply a new variant of adaptation to interval normobaric hypoxia, interval hypoxic-hyperoxic training (IHHT). A placebo-controlled clinical trial included 34 patients aged 64–92 years of the day geriatric hospital of the Klagenfurt Clinic (Carinthia, Austria) who were randomized into two groups: experimental (EG), those who received MTP and IHHT, and control (CG), those who passed the course of MTP during the simulation of IHHT procedures. Before and after the rehabilitation course, cognitive functions and exercise endurance of the patients were evaluated using the dementia detection test DeTect, the clock-drawing test, and a 6-minute walk test (6MWT). During the course of IHHT, cognitive capabilities of EG patients significantly improved in comparison with CG patients: the increase in values in the dementia test was +16.7% (in CG + 0.39%, $p < 0.001$), and that in the clock-drawing test was +10.7% (in CG –8%, $p = 0.031$). The distance covered in the 6-minute test increased in both the groups but significantly more in OG, 24.1% (in CG +10.8%, $p = 0.021$). Direct significant correlations between increment in exercise tolerance and cognitive tests were revealed. Thus, the inclusion of procedures for adaptation to interval hypoxia-hyperoxia in MTP in the elderly leads to a significant increase in their effectiveness, which is manifested in the improvement of cognitive functions and physical endurance. IHHT procedures are well tolerated and do not cause side effects.

Keywords: interval hypoxia-hyperoxy, elderly patients, cognitive functions, physical endurance, multimodal rehabilitation programs

DOI: 10.1134/S2079057017030031

INTRODUCTION

The modern world trends in increasing life expectancy inevitably actualize the problems of cognitive dysfunction and disability of the elderly. Just in Russia, by the beginning of 2021, the proportion of people older than working age in the total population of the country will increase to 26.7%, and their number will reach 39.5 million [1]. A significant part of chronic diseases in the elderly and senile age is associated with cognitive dysfunctions and neurodegenerative diseases, which is a serious economic and social challenge for society and national health systems [15]. It is no accident that the medical and pharmaceutical industry is actively working on developing new strategies aimed at rehabilitating geriatric patients and maintaining their cognitive functions and self-service capabilities [4, 23, 29].

Recently, more and more attention of researchers and doctors has been attracted to the possibility of using physical rehabilitation and aerobic exercises in improving the cognitive status of the elderly [7, 8, 11]. In a number of systematic studies, it has been proven that the combined course application of individually selected physical activities, physiotherapy techniques, psycho-training, and training of the elderly in managing chronic risk factors in the form of multimodal rehabilitation programs (MTP) is an effective approach to the rehabilitation of the elderly with cognitive dysfunctions, especially in case of their early detection [6, 21, 29].

A relatively new approach to the rehabilitation of the elderly with various diseases is the method of adaptation to short episodes of moderate hypoxia, interval hypoxic training (IHT), which are procedures for interval breathing through a mask with a hypoxic gas mixture interrupted by normal air breathing [2,

Table 1. Initial clinical and demographic characteristics of elderly patients of both the groups

Index		Experimental group, $n = 18$	Control group, $n = 16$
sex, n (%)	male	5 (28)	2 (12.5)
	female	13 (72)	14 (87.5)
Age, years		80.9 ± 7.8	83.4 ± 5.5
Height, cm		163.7 ± 8.3	163.19 ± 8.52
Body weight, kg		72.03 ± 9.32	66.83 ± 12.27
BMI		26.98 ± 3.91	25.02 ± 3.62
Mini-Mental State Examination (MMSE-Score), points		24.94 ± 3.75	24.5 ± 3.93
SBP, mm Hg		137.22 ± 18.9	134.64 ± 15.9
DBP, mm Hg		77.5 ± 6.9	77.86 ± 8.7
Blood saturation with O_2–SpO_2, %		94.21 ± 6.2	93.65 ± 7.5

Data are presented as $M \pm SD$ or the number of patients (ratio in %); no intergroup differences at $p > 0.05$.

20]. Several studies have shown that IHT increases exercise tolerance in patients with cardiovascular and bronchopulmonary diseases and metabolic syndrome [9, 10], improves the cardiometabolic status in the elderly [10], and increases cognitive potential in modeling the Alzheimer's disease and in clinical observations [18, 22, 27]. In their study, L. Shega et al. (2013) for the first time identified positive effects of IHT on the cognitive function of elderly patients aged 60–70 years [26].

To improve the effectiveness of IHT, we proposed a new technology for adaptation to hypoxia: the method of interval hypoxic-hyperoxic training (IHHT), where normoxic pauses between breathing with a hypoxic gas mixture are replaced by breathing with a hyperoxic mixture (30–40% O_2) [13].

During periods of induced hyperoxia, the blood oxygen saturation is rapidly restored and the induction of ROS necessary for triggering the redox-signaling cascade is more pronounced than with normoxic reoxygenation. This leads to a significant synthesis of protective intracellular protein molecules, mainly with an antioxidant function (antioxidant defense enzymes, iron-binding proteins, and heat shock proteins) [5, 15]. Experimental studies have shown more pronounced membrane-stabilizing effects, a significant increase in myocardial and brain resistance and antioxidant protection levels, and tolerance to exercise loads as a result of adaptation to IHHT in comparison with IHT [5]. The IHHT method has been tested in pilot studies in patients with metabolic syndrome and IHD and in skilled athletes with overtraining syndrome [3, 5, 28].

The purposes of this study are to evaluate the efficacy and safety of IHHT in complex MTP in elderly patients and to identify the effects of IHHT in the dynamics of cognitive status and exercise tolerance in patients of the geriatric clinic.

MATERIALS AND METHODS

A randomized, placebo-controlled study involved elderly 63–92-year-old volunteers undergoing MTP in the geriatric day care unit of Klagenfurt Clinic (Carinthia, Austria). After a routine examination (clinical and biochemical blood tests, ECG at rest), volunteers signed informed consent and underwent a comprehensive psychoneurological examination using a brief scale of quantitative assessment of mental status and cognitive dysfunction (MMSE) [12]. Exclusion criteria were inability to move unaided, uncontrolled hypertension (SBP > 180 mm Hg), chronic bronchopulmonary diseases, decompensated heart failure (NYHA, III–IV FC), previous intracerebral hemorrhages, and marked cognitive disorders (MMSE < 12 points).

Randomly selected patients ($n = 41$) were divided into two groups: experimental (EG), 20 individuals who underwent MTP and IHHT, and control (CG), 21 individuals who underwent MTP and the course of IHHT placebo procedures. The groups did not differ in age, main parameters of cardiorespiratory and cognitive status, and intake of medications; their initial characteristics are presented in Table 1. At the time of the examination, all participants were advised not to change their diet, motor activity, or intake of drugs (except for emergency cases, which were recorded in the cards).

All patients underwent individualized MTP for the elderly, consisting of 16–20 visits 2–3 times per week, consisting of: (1) 30 min of physiotherapy procedures aimed at metabolism stimulation, balance training, coordination of movements, and the like; (2) 60 min of occupational therapy with the inclusion of motor-functional and perceptual trainings, psychotraining, and cognitive training using computer technology; (3) 20 min of cardiorespiratory endurance training on the MOTOmed^R Viva-1 bicycle ergometer (Germany)

when seated with individual dosing of the increasing load, not exceeding the heart rate of 120 beats/min.

In parallel with MTP, EG patients underwent IHHT procedures (2–3 times per week, 14–15 trainings in 5–6 weeks) on the days of visiting the geriatric department. The study used a normobaric unit for the production of hypoxic and hyperoxic gas mixtures based on the feedback ReOxy Cardio (Aimediq S.A., Luxembourg) [13]. The patient was sitting in a comfortable armchair and breathing through the orinasal mask with a hypoxic or hyperoxic gas mixture in an interval mode.

Before the beginning of the course of procedures, the individual sensitivity of patients to hypoxia was determined by means of a 10-minute hypoxic test: breathing through the mask with a gas mixture with 12% O_2 content, with an hourly monitoring of heart rate and saturation of hemoglobin with oxygen (SaO_2). The results of the hypoxic test (the degree and the rate of blood oxygen desaturation and the degree of tachycardia) were used for individual selection of the duration of feeding the hypoxic (12% O_2) and hyperoxic (35% O_2) gas mixtures during the IHHT procedure on the principle of biofeedback: when reaching individual minimum values of SaO_2, the feed of the hypoxic mixture was switched to hyperoxic until the initial values of saturation were restored, etc. [13].

The duration of one procedure was 35–45 min. The time of each hypoxic period averaged 4–6 min and the hyperoxic period approximately 1–2 min, depending on the recovery rate of SaO_2 in the patient. After each training, a mark was put in the observation diary, indicating the date of the procedure, patient's assessment of the procedure's tolerability, and all possible changes in the state during the training and in the periods between them. Before and after training, blood pressure and heart rate were measured.

CG patients, after performing HT, underwent a course of placebo training simulating IHHT, receiving atmospheric air through the mask of the same apparatus. Participants were not informed of differences and belonging to different groups; the procedures were controlled only by two nurses.

Before and after MTP and IHHT, all patients underwent complex testing, including evaluation of cognitive functions using the dementia detection test (DemTect), which is a sensitive tool for screening for minimal cognitive impairment and the initial stages of dementia [16]); a free clock-drawing test (CDT), a reliable screening tool that shows significant correlations with global cognitive impairment, executive functions, semantic skills, and visual-spatial orientation [24]; assessment of exercise tolerance by a 6-minute walking test (6MWT) in accordance with accepted guidelines.

Of the 41 patients selected for the study, only 35 completed the program (two patients abandoned IHHT because of claustrophobia from the face mask, two participants stopped visiting procedures because of discomfort from being in the mask, and another two stopped participating without explanation), one patient who completed the examination was excluded from the analysis due to the termination of drug treatment in the dynamics of MTP.

Statistical processing of data was carried out using the software package R (Version 2.7.0 resp. 3.2.3, 2015; the R Foundation for Statistical Computing, http://cran.r-project.org). The data in the paper are presented as the mean and standard deviation of $M \pm SD$. The normalization of the distribution was estimated by the Kolmogorov–Smirnov test, correlations between the indicators and their significance by the nonparametric rank correlation coefficient of Spearman, and the reliability of the differences by the Wilcoxon–Mann–Whitney test.

RESULTS AND DISCUSSION

All participants (EG, 18 individuals; CG, 16 individuals) who underwent the course of IHHT/placebo procedures noted good tolerability of procedures (except for mild dizziness and sleep disturbances after the first few sessions, no other side effects and complications were noted), Table 2.

Initially, the elderly patients from EG and CG did not differ in their cognitive status indicators (see Table 2). After MTP with the course of IHHT, there was a significant increase in indices in dementia detection and clock-drawing tests in EG patients, while no significant changes in the indices of these tests were observed in CG patients. After the rehabilitation course, the cognitive performance indicators were significantly higher in EG patients (Table 3).

The values of the functional exercise endurance evaluated in the 6-min walk test as the maximum distance traveled did not differ significantly from patients in both the groups. After the course of IHHT or placebo procedures in combination with MTP, both the groups showed a significant increase in the distance traveled, but it was significantly higher in EG patients than in CG patients (Table 3). And, after the course of rehabilitation, the 6MWT values were significantly higher in EG patients compared to CG ones.

It is important to note the significant relationship between the values of the increase in distance traveled in the 6-min walk test and the increase in points in the dementia detection test, as well as between the incremental values of the distance traveled in 6MWT and the growth of the values in the clock-drawing test (see figure 1).

There were no statistically significant changes in the values of cardiogemodynamic and metabolic parameters in both EG and CG patients.

For the first time, this study revealed positive clinically significant effects of including the course of

Table 2. Dynamics of indicators of cognitive functions and cardiorespiratory load endurance in the course of multimodal rehabilitation program (MTP) in patients of both the groups, $M \pm SD$

Index	Experimental group, $n = 18$		Control group, $n = 16$		Significance of intergroup differences after MTP, p
	initially	after MTP	initially	after MTP	
Heart rate, bpm	66.4 ± 8.5	66.1 ± 8.5	73.5 ± 8.0	67.7 ± 5.5	0.27
SBP, mm Hg	136.4 ± 17.9	132.5 ± 14.7	134.6 ± 15.8	129.5 ± 16.4	0.41
DBP, mm Hg	80.8 ± 18.3	73.3 ± 5.9	77.8 ± 8.7	72.8 ± 6.7	0.28
SpO_2, %	94.2 ± 6.2	98.3 ± 1.2	93.6 ± 7.5	97.6 ± 1.7	0.48
DemTect, points	11.2 ± 3.5	14.2 ± 3.7	11.4 ± 4.1	11.3 ± 3.6	<0.001
CDT, points	7.8 ± 2.9	8.4 ± 3.0	7.5 ± 2.3	6.8 ± 2.6	0.031
6MWT, m	234.3 ± 94.7	290.7 ± 83.1	250.6 ± 94.3	277.7 ± 96.3	0.021

Here and in Table 3: DemTect, dementia detection test; CDT, clock-drawing test; 6MWT, 6-minute walk test.

Table 3. Indices of the difference in cognitive functions and cardiorespiratory exercise endurance before and after the course of the multimodal rehabilitation program (MTP) in patients of both the groups

Index	Difference before and after MTP		Significance of group differences, p
	experimental group, $n = 18$	control group, $n = 16$	
DemTect, points (%)	+3 (+16.7%)	+0.07 (+0.39%)	<0.001
CDT, points (%)	+1.07 (+10.7%)	−0.8 (−8%)	0.031
6MWT, m (%)	+56.26 (+24.1%)	+27.13 (+10.8%)	0.021

adaptation procedures to interval hypoxia-hyperoxia into MTP of elderly people (mean age > 80 years) in the cognitive status and exercise tolerance.

Important is the fact that geriatric patients tolerated IHHT well and there were no negative side reactions and significant discomfort from the face mask and breathing with hypoxic mixture. This is confirmed by the data of M. Burtcher et al. [10] and L. Shega et al. [26] who used interval hypoxia-normoxia procedures in healthy elderly and in patients from 60 to 70 years of age with CHD and COPD. At the beginning of the IHHT course, elderly patients were skeptical about carrying out procedures with fixing the mask on the face, but, after the first procedures, they began to perceive the episodes of hypoxia and subsequent hyperoxia positively, reporting the state of some euphoria. The only negative point, according to the patients, is the considerable duration of the procedures (up to 35–40 min), which is difficult to tolerate for patients with moderately expressed cognitive dysfunctions. Obviously, in the future, it is possible to recommend showing videos or listening to music during the procedures, which will make spending time in the mask less tedious.

The second important point is to improve the cognitive status of geriatric patients when IHHT is included in MTP. As shown in other works, short courses of MTP do not lead to significant dynamics of the cognitive status; longer cycles of 3–4 months of physical rehabilitation of elderly people are recommended for these purposes [6, 8]. We also found that, in CG patients (in contrast to EG), despite the improvement of exercise tolerance, there were no positive shifts in cognitive functions. Consequently, improvement in cognitive functioning can be directly related to the effects of IHHT. The lack of improvement in cognitive functioning after physical training (in CG) in our study can be explained by the low endurance of patients older than 80 years, which made it impossible for them to perform training of sufficient intensity comparable to that in the group of patients aged 60–70 years. This is confirmed by the data of the meta-analysis by S. Colcombe et al. [11] about the best effects of physical training in elderly patients aged 65–71 years.

Thus, IHHT in combination with MTP is a new technology for improving both cognitive functions and physical endurance in geriatric patients. The study [3]

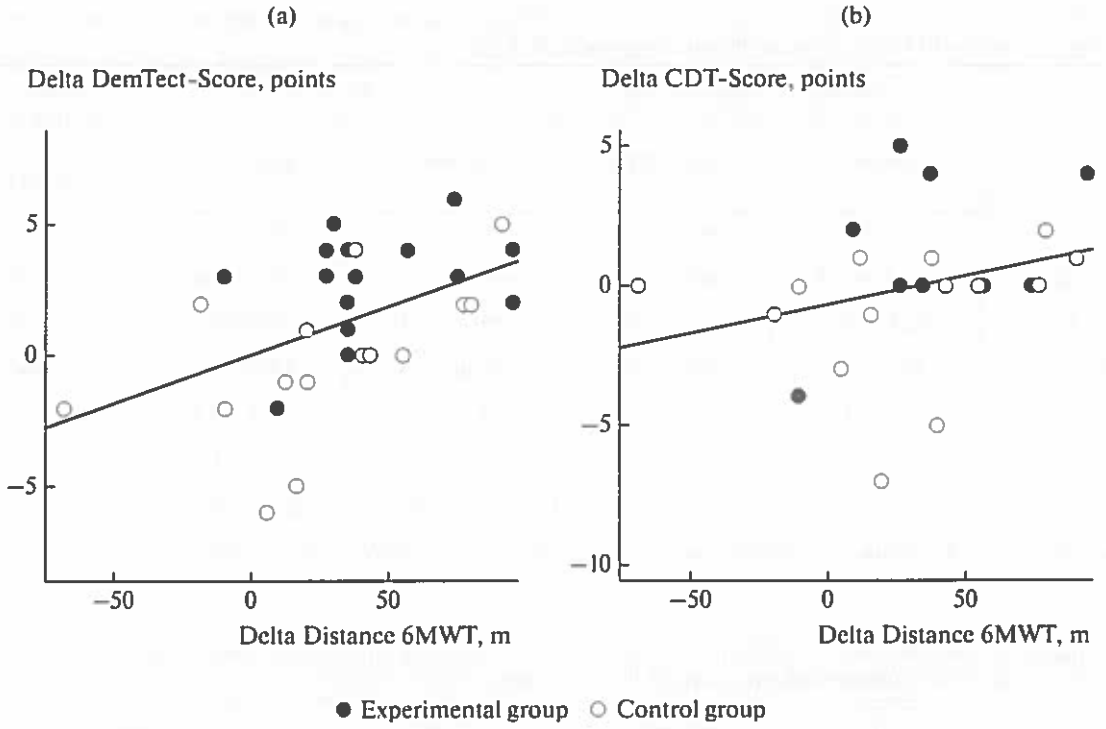


Fig. 1. Relationship between the changes before and after MTP in: (a) distance covered in 6MWT (x-axis) and the increase in scores in the dementia detection test DemTect (y-axis), $r = +0.57$; $p < 0.001$; (b) distance traveled in 6MWT (x-axis) and the increase in the values of the clock-drawing test (y-axis), $r = +0.42$; $p < 0.011$.

even provides data on the increase in physical endurance as a result of adaptation to interval hypoxia without any physical training.

A. Navarrete-Opazo and G. S. Mitchell [19] noted that the positive effects of hypoxic training depend on the dose of hypoxia (duration and intensity of hypoxic stimuli). This fact was taken into account in our study by individual selection of the parameters of the IHHT procedures based on the estimation of the hypoxic sensitivity of each patient in the initial hypoxic test [13, 28].

Among the mechanisms of potentiating cognitive functions under the influence of IHHT, one can assume the expression of neurotrophic growth factor (*BDNF*) in the structures of the hippocampus, an important regulator of neuronal survival, neuroplasticity, and mechanisms of memory and attention [14, 30]. Similar data on stimulation of *BDNF* production are also noted under the influence of physical endurance loads and other stressors [25], which again confirms the validity of the combination of IHHT and MTP. Despite the evidence of the effect of adaptation to interval hypoxia on the structural and functional characteristics of the brain, specific mechanisms are not fully disclosed. A number of reviews suggest that the key protective neuronal mechanisms of adaptation to interval hypoxia may be associated with the limitation of the effects of oxidative stress in the structures of the hippocampus, normalization of *NO* synthesis disturbed by *b*-amyloid, stimulation of antioxidant systems, heat shock proteins, and increased capillary network density in the brain [17, 30]. Further research is needed on the mechanisms of the positive influence of IHHT on the neurophysiological and cognitive functions of the elderly person, as well as comparative analysis of the effectiveness of different regimes (IHT, IHHT) of interval adaptation to hypoxia.

CONCLUSIONS

Procedures for adaptation to interval normobaric hypoxia-hyperoxia are easily applicable in the practice of geriatric rehabilitation, do not cause side effects, and are well tolerated by elderly patients under the age of 90 with moderately expressed cognitive disorders. Inclusion of procedures for interval hypoxic-hyperoxic training in multimodal rehabilitation programs in elderly patients leads to a significant improvement in cognitive status and increased tolerance to exercises.

ACKNOWLEDGMENTS

We are grateful to all volunteers participating in the study as well as to the company AiMediq SA (Luxembourg) for providing the ReOxy devices free of charge for conducting IHHT in patients. The company and its representatives did not participate in the design of

the research, collection, analysis and interpretation of data, and preparation of the publication.

REFERENCES

1. Bashkireva, A.S., Vylegzhanin, S.V., and Kachan, E.Yu., Present urgent problems of social gerontology in Russia, *Usp. Gerontol.*, 2016, vol. 29, no. 2, pp. 379–386.
2. Gerasimenko, E.N., Meshchaninov, V.N., Zvezdina, E.M., Katireva, U.E., Tkachenko, E.L., and Gavrilov, I.V., Comparative analysis of geroprophylactic efficiency and membranotropic action of various gas therapies, *Adv. Gerontol.*, 2015, vol. 5, no. 1, pp. 12–17.
3. Zagainaya, E.E., Kopylov, F.Yu., Glazachev, O.S., et al., Influence of interval hypoxic-hyperoxic trainings on the tolerance of physical exercises in patients with stable stenocardia of II–III functional class on the background of optimal drug therapy, *Kardiol. Serdechno-Sosudistaya Khir.*, 2015, no. 3, pp. 32–38.
4. Zakharov, V.V. and Yakhno, N.N., Syndrome of moderate cognitive impairment in elderly age: diagnostics and therapy, *Russ. Med. Zh.*, 2004, vol. 12, no. 10, pp. 573–576.
5. Sazontova, T.G., Bolotova, A.V., Glazachev, O.S., et al., Adaptation to hypoxia and hyperoxia increases physical endurance: the role of active species of oxygen and redox signaling (experimental and practical study), *Ross. Fiziol. Zh. im. I.M. Sechenova*, 2012, vol. 98, no. 6, pp. 793–807.
6. Baker, L.D., Frank, L.L., Foster-Schubert, K., et al., Effects of aerobic exercise on mild cognitive impairment: a controlled trial, *Arch. Neurol.*, 2010, vol. 67, no. 1, pp. 71–79. 2009.307 doi 10/1001/archneurol
7. Barnes, D.E., Santos-Modesitt, W., Poelke, G., et al., The mental activity and exercise (MAX) trial. A randomized controlled trial to enhance cognitive function in older adults, *J.A.M.A. Int. Med.*, 2013, vol. 173, no. 9, pp. 797–804. doi 10.1001/jamainternmed.2013.189
8. Brinke, L.F., Bolandzadeh, N., and Nagamatsu, L.S., Aerobic exercise increases hippocampal volume in older women with probable mild cognitive impairment: a 6-month randomised controlled trial, *Br. J. Sports Med.*, 2015, vol. 49, no. 4, pp. 248–54. doi 10.1136/bjsports-2013-093184
9. Burtscher, M., Haider, T., Domej, W., et al., Intermittent hypoxia increases exercise tolerance in patients at risk or with mild COPD, *Respir. Physiol. Neurobiol.*, 2009, vol. 165, pp. 97–103. doi 10.1016/j.resp.2008.10.012
10. Burtscher, M., Pachinger, O., Ehrenbourg, I., et al., Intermittent hypoxia increases exercise tolerance in elderly men with and without coronary artery disease, *Int. J. Cardiol.*, 2004, vol. 96, pp. 247–254.
11. Colcombe, S. and Kramer, A.F., Fitness effects on the cognitive function of older adults: a meta-analytic study, *Psychol. Sci.*, 2003, vol. 14, no. 2, pp. 125–130.
12. Folstein, M.F., Folstein, S.E., and McHugh, P.R., Mini mental state. A practical method for grading the cognitive state of patients for the clinician, *J. Psychiatr. Res.*, 1975, vol. 12, no. 3, pp. 189–198. doi 10.1016/0022-3956(75)90026-6
13. Glazachev, O., Optimization of clinical application of interval hypoxic training, *Biomed. Eng.*, 2013, vol. 47, no. 3, pp. 134–137.
14. Huang, E.J. and Reichardt, L.F., Neurotrophins: roles in neuronal development and function, *Ann. Rev. Neurosci.*, 2001, vol. 24, pp. 677–736. doi 10.1146/annurev.neuro.24.1.677
15. Hurd, M.D., Martorell, P., Delavande, A., et al., Monetary costs of dementia in the United States, *N. Engl. J. Med.*, 2013, vol. 368, no. 4, pp. 1326–1334.
16. Kalbe, E., Kessler, J., Calabrese, P., et al., DemTect: a new, sensitive cognitive screening test to support the diagnosis of mild cognitive impairment and early dementia, *Int. J. Geriatr. Psychiatry*, 2004, vol. 19, no. 2, pp. 136–143. doi 10.1002/gps.1042
17. Langlois, F., Minh, K., Vu, T.T., et al., Benefits of physical exercise training on cognition and quality of life in frail older adults, *J. Gerontol. Psychol. Sci. Soc.*, 2013, vol. 68, no. 3, pp. 400–404. doi 10.1093/geronb/gbs069
18. Manukhina, E., Downey, F., Shi, X., and Mallet, R., Intermittent hypoxia training protects cerebrovascular function in Alzheimer's disease, *Exp. Biol. Med.*, 2016, vol. 241, pp. 1351–1363. doi 10.1177/1535370216649060
19. Navarrete-Opazo, A. and Mitchell, G.S., Therapeutic potential of intermittent hypoxia: a matter of dose, *Am. J. Physiol.-Regul., Integr. Comp. Physiol.*, 2014, vol. 307, pp. 1181–1197.
20. Neubauer, J.A., Physiological and pathophysiological responses to intermittent hypoxia, *J. Appl. Physiol.*, 2001, vol. 90, no. 4, pp. 1593–1599.
21. Ngandu, T., Lehtisalo, J., Solomon, A., et al., A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomized controlled trial, *Lancet*, 2015, vol. 385, no. 9984, pp. 2255–2263. doi 10.1016/S0140-6736(15)60461-5
22. Prokopov, A., A case of recovery from dementia following rejuvenative treatment, *Rejuvenation Res.*, 2010, vol. 13, nos. 2–3, pp. 217–219.
23. Rabinovicia, G.D., Carrillob, M.C., Formanc, M., DeSantid, S., Millere, D.S., Kozauerf, N., Peterseng, R.C., Randolphh, C., Knopmang, D.S., Smithj, E.E., Isaack, M., Mattssonl, N., Bainn, L.J., Hendrixb, J.A., and Simso, J.R., Multiple comorbid neuropathologies in the setting of Alzheimer's disease neuropathology and implications for drug development, *Alzheimer's Dementia: Transl. Res. Clin. Interventions*, 2017, vol. 3, no. 1, pp. 83–91. doi 10.1016/j.trci.2016.09.002
24. Sunderland, T., Hill, J.L., Mellow, A.M., et al., Clock drawing in Alzheimer's disease: a novel measure of dementia severity, *J. Am. Geriatr. Soc.*, 1989, vol. 37, pp. 725–729.

25. Satriotomo, I., Vinit, S., and Flom, A.L., Repetitive acute intermittent hypoxia increases BDNF and TrkB expression in respiratory motor neurons: dose effects, *FASEB J.*, 2010. http://www.fasebj.org/cgi/content/meeting_abstract/24/1_MeetingAbstracts/799.16.

26. Schega, L., Peter, B., Törpel, A., et al., Effects of intermittent hypoxia on cognitive performance and quality of life in elderly adults: a pilot study, *Gerontology*, 2013, vol. 59, pp. 316–323. doi 10.1159/000350927

27. Serebrovskaya, T.V., Manukhina, E.B., Smith, M.L., et al., Intermittent hypoxia: cause of or therapy for systemic hypertension? *Exp. Biol. Med.*, 2008, vol. 233, pp. 627–650.

28. Susta, D., Dudnik, E., and Glazachev, O.S., A program based on repeated hypoxia–hyperoxia exposure and light exercise enhances performance in athletes with overtraining syndrome: a pilot study, *Clin. Physiol. Funct. Imaging*, 2017, vol. 37, no. 3, pp. 276–281. doi 10.1111/cpf.12296

29. Suzuki, T., Shimada, H., Makizako, H., et al., Effects of a multicomponent exercise on cognitive function in older adults with amnestic mild cognitive impairment: a randomized trial, *BMC Neurol.*, 2012, vol. 12, pp. 128. doi 10.1186/1471-2377-12-128

30. Zhu, X.H., Yan, H.C., Zhang, J., et al., Intermittent hypoxia promotes hippocampal neurogenesis and produces antidepressant-like effects in adult rats, *J. Neurosci.*, 2010, vol. 30, no. 8, pp. 12653–12663. doi 10.1523/JNEUROSCI.6414-09.2010

Translated by K. Lazarev

SPELL: 1. bronchopulmonary

- Format: Abstract

Send to

- The following term was not found in PubMed: Jul;60.
- Quoted phrase not found.

Ther Umsch. 2003 Jul;60(7):419-24.

[Effect of hypoxia on muscular performance capacity: "living low--training high"].

[Article in German]

Vogt M[1], Billeter R, Hoppeler H.

Author information

1

Anatomisches Institut, Universität Bern, Bern. vogt@ana.unibe.ch

Abstract

Altitude training is very popular among endurance athletes. But athletes respond very different on acute altitude exposure and altitude training. There are individual differences in the decrement of maximal oxygen consumption making general advices on the effect of altitude training very difficult. During the last few years different altitude training regimes have been developed. Beside "living high--training low," the concept of "living low--training high" becomes more and more popular. By this regime, athletes train under simulated or natural hypoxic conditions, while recovery time is spent at sea-level. Several studies show that with "living low--training high" maximal oxygen consumption as well as aerobic and anaerobic endurance performance can be improved. Molecular analysis reveal that a transcription factor called Hypoxia-Inducible Factor 1 (HIF-1) acts as a master gene in the regulation of hypoxia-dependent gene expression. In human skeletal muscle "living low-training high" induces the expression of glycolytic enzymes, the angiogenic factor VEGF, myoglobin as well as the increase of capillarity and mitochondrial content (die Zunahme der Kapillarität und des mitochondrialen Gehalts) in parallel to the induction of the HIF-1 system. In trained human skeletal muscle, these adaptations cause a shift of substrate selection to an increased oxidation of carbohydrates as well as to an improvement of the conditions for transport and utilization of oxygen. Depending on the kind of sports, "living low--training high" can be used to train these muscular adaptations and to increase exercise performance.

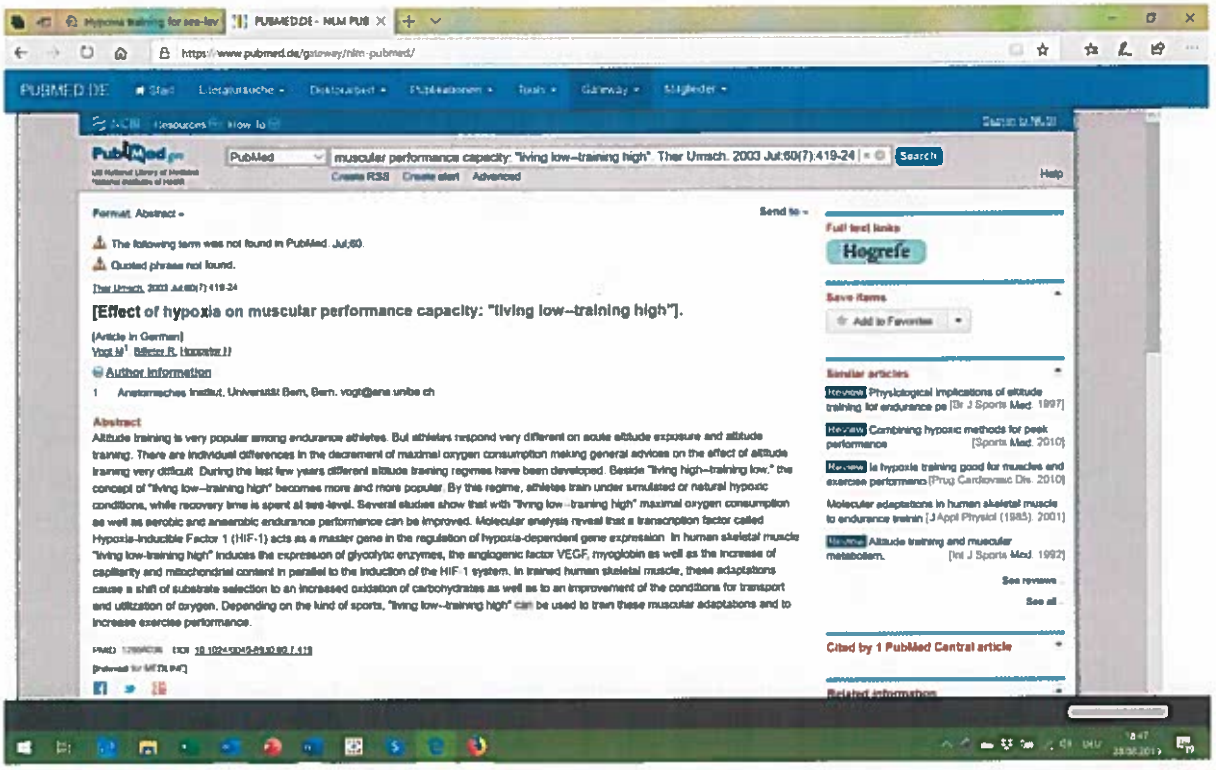
PMID:

12956036

DOI:

10.1024/0040-5930.60.7.419

[Indexed for MEDLINE]


PUBMED - NLM PUB
https://www.pubmed.de/gateway/nlm-pubmed/
PUBMED.DE
PubMed
muscular performance capacity: "living low--training high" Ther Umsch. 2003 Jul;60(7):419-24
Search
Create RSS
Create alert
Advanced
Help
Format: Abstract
Send to
The following term was not found in PubMed: Jul;60.
Quoted phrase not found.
Ther Umsch. 2003 Jul;60(7):419-24
[Effect of hypoxia on muscular performance capacity: "living low--training high"].
(Article in German)
Vogt M[1] Billeter R, Hoppeler H
Author information
1 Anatomisches Institut, Universität Bern, Bern. vogt@ana.unibe.ch
Abstract
Altitude training is very popular among endurance athletes. But athletes respond very different on acute altitude exposure and altitude training. There are individual differences in the decrement of maximal oxygen consumption making general advices on the effect of altitude training very difficult. During the last few years different altitude training regimes have been developed. Beside "living high--training low," the concept of "living low--training high" becomes more and more popular. By this regime, athletes train under simulated or natural hypoxic conditions, while recovery time is spent at sea-level. Several studies show that with "living low--training high" maximal oxygen consumption as well as aerobic and anaerobic endurance performance can be improved. Molecular analysis reveal that a transcription factor called Hypoxia-Inducible Factor 1 (HIF-1) acts as a master gene in the regulation of hypoxia-dependent gene expression. In human skeletal muscle "living low-training high" induces the expression of glycolytic enzymes, the angiogenic factor VEGF, myoglobin as well as the increase of capillarity and mitochondrial content in parallel to the induction of the HIF-1 system. In trained human skeletal muscle, these adaptations cause a shift of substrate selection to an increased oxidation of carbohydrates as well as to an improvement of the conditions for transport and utilization of oxygen. Depending on the kind of sports, "living low--training high" can be used to train these muscular adaptations and to increase exercise performance.
Full text links
Hogrefe
Save items
Add to Favorites
Similar articles
Physiological implications of altitude training for endurance pe [Br J Sports Med. 1997]
Combining hypoxic methods for peak performance [Sports Med. 2010]
Is hypoxia training good for muscles and exercise performance [Prog Cardiovasc Dis. 2010]
Molecular adaptations in human skeletal muscle to endurance trainin [J Appl Physiol (1985). 2001]
Altitude training and muscular metabolism. [Int J Sports Med. 1992]
See reviews
See all
Cited by 1 PubMed Central article
Related information