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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

^aDepartment of Sport Science, Medical Section, University of Innsbruck, Fürstenweg 185, 6020 Innsbruck, Austria

^bDivision of Cardiology, Internal Medicine, University of Innsbruck, Anichstrasse 35, 6020 Innsbruck, Austria

^cClinical Research Laboratory, Hypoxia Medical Academy, 3, Ivankovskoye shosse, 123367 Moscow, Russia

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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.

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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 haematopoietic 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).

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,

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 (FEV₁), Maximal Voluntary Ventilation (MVV), Peak Oxygen Uptake (VO₂peak), Angiotensin-Converting-Enzyme-Inhibitors (ACE-inhibitors); myocardial infarction (MI).

and blood gas analyses), electrocardiography, echocardiography, blood pressure measurements and basic pulmonary function testing.

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					
<i>Days 1–5</i>					
Duration of breathing periods (min)	3	3	3	3	3
Fraction of oxygen (%)	14	21	14	21	14
<i>Days 8–12</i>					
Duration of breathing periods (min)	4	3	4	3	4
Fraction of oxygen (%)	12	21	12	21	12
<i>Days 15–19</i>					
Duration of breathing periods (min)	5	3	5	3	5
Fraction of oxygen (%)	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 down-sloping 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.

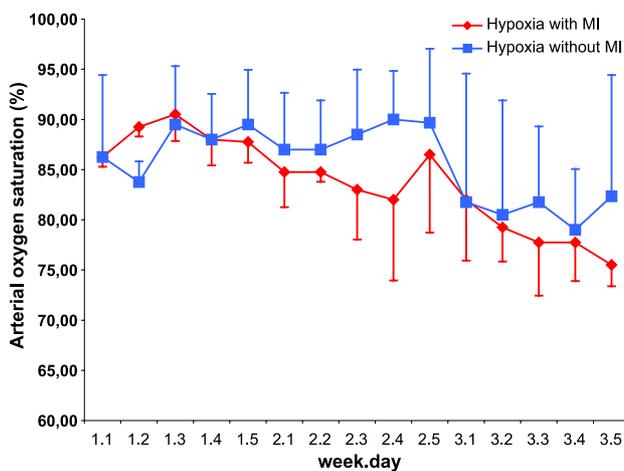


Fig. 1. Arterial oxygen saturation during the last hypoxic period of each day in subjects with ($n=4$) and without ($n=4$) prior myocardial infarction (MI) of the hypoxia group. Data represent means (SD).

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 ($n=8$)		<i>p</i> -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 ($n=8$)		<i>p</i> -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.

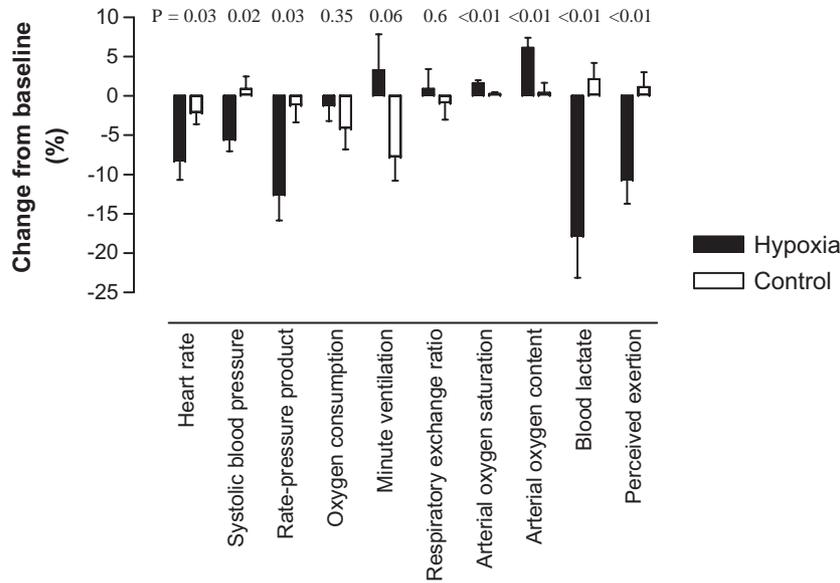


Fig. 2. Changes (in percentages) from baseline of cardiorespiratory responses at sub-maximal workload (1 W/kg) after the 3-week breathing program of the hypoxia ($n=8$) and the control group ($n=8$). Data represent means (SEM). p -values for differences in changes between groups.

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.

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

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.

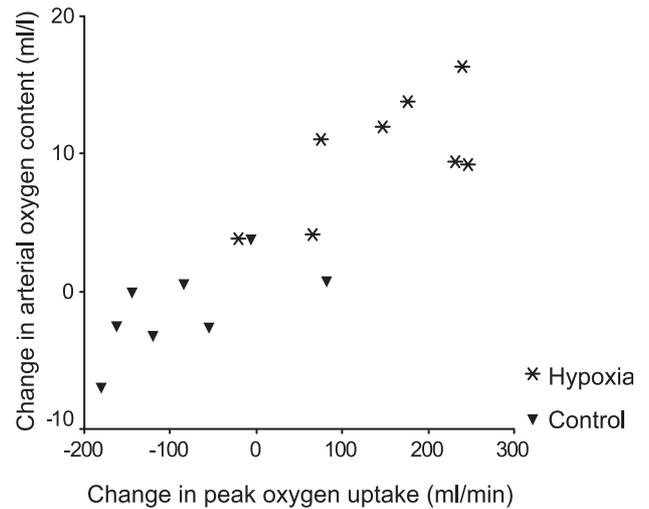


Fig. 3. Relationship between the changes in peak oxygen consumption and the arterial oxygen content in the hypoxia and control group after the 3-week breathing program. $R^2=0.8$, $p<0.001$.

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.

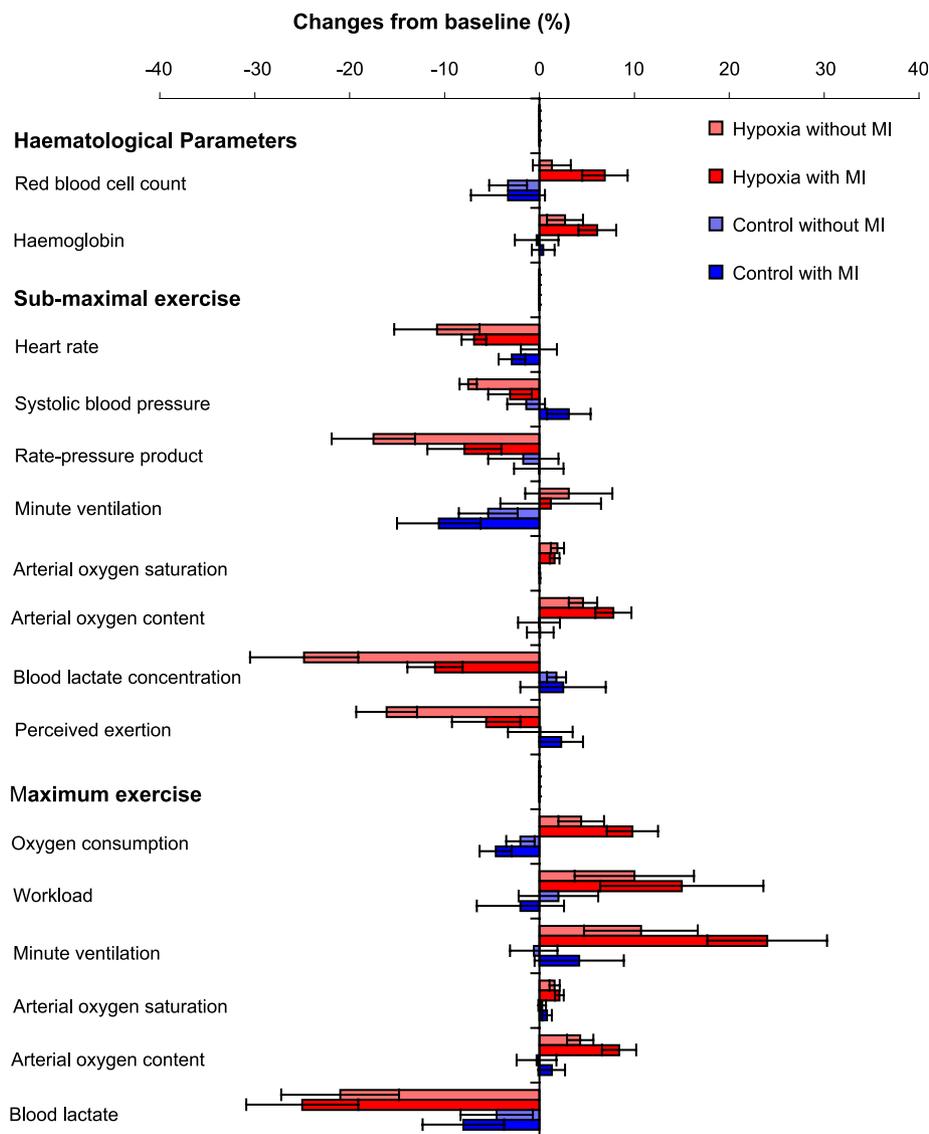


Fig. 4. Changes (in percentages) from baseline for sub-groups with (*n*=4) and without (*n*=4) prior myocardial infarction (MI) of the hypoxia and the control group. All variables with *p*-values <0.1 for differences in changes between the hypoxia and the control group are shown. Data represent means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

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