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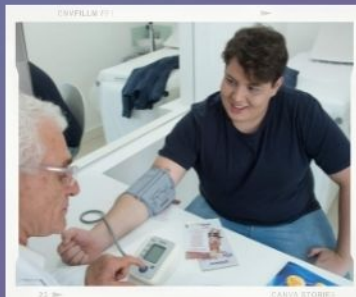
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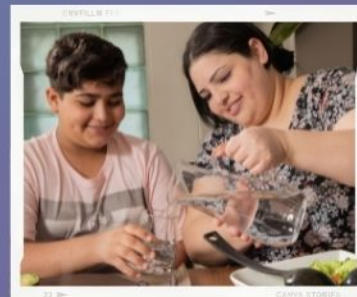
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Influences of Normobaric Hypoxia Training on Physical Fitness and Metabolic Risk Markers in Overweight to Obese Subjects

Susanne Wiesner¹, Sven Haufe¹, Stefan Engeli^{1,2}, Harry Mutschler³, Ute Haas³, Friedrich C. Luft¹ and Jens Jordan^{1,2}

Previous studies suggested that hypoxia and exercise may have a synergistic effect on cardiovascular and metabolic risk factors. We conducted a single blind study in overweight to obese subjects to test the hypothesis that training under hypoxia (HG, $n = 24$, $\text{FiO}_2 = 15\%$) results in similar or even greater improvement in body weight and metabolic risk markers compared with exercise under normoxia (NG, $n = 21$, $\text{FiO}_2 = 21\%$). After an initial metabolic evaluation including incremental exercise testing, subjects trained in normoxic or hypoxic conditions thrice weekly over a 4-week period at a heart rate corresponding to 65% of maximum oxygen uptake ($\text{VO}_{2\text{max}}$). The experimental groups were similar at the start of the investigation and weight stable during the training period. Subjects in the hypoxia group trained at a significantly lower workload ($P < 0.05$). Yet, both groups showed similar improvements in $\text{VO}_{2\text{max}}$ and time to exhaustion. Respiratory quotient and lactate at the anaerobic threshold as well as body composition improved more in the hypoxia group. We conclude that in obese subjects, training in hypoxia elicits a similar or even better response in terms of physical fitness, metabolic risk markers, and body composition at a lower workload. The fact that workload and, therefore, mechanic strain can be reduced in hypoxia could be particularly beneficial in obese patients with orthopedic comorbidities.

Obesity (2009) **18**, 116–120. doi:10.1038/oby.2009.193

INTRODUCTION

High altitude training improves exercise performance in elite athletes (1). Moreover, hypoxia and exercise regulate pathways that are crucial to glucose and lipid metabolism. Both stimuli increase hypoxia-inducible factor-1 production (2,3). The transcription factor hypoxia-inducible factor-1 α targets genes involved in oxygen transport, glycolysis, glucose transport, and satiety (4). Moreover, hypoxia upregulates leptin expression *in vitro* (5,6). The mechanism may contribute to involuntary weight loss at high altitude (7). Finally, training under hypoxia increases peroxisome proliferator-activated receptor- γ co-activator-1 α mRNA expression (8). Peroxisome proliferator-activated receptor- γ co-activator-1 α induces mitochondrial biogenesis and plays a key role in regulation of muscle fatty acid oxidation (9). Therefore, we reasoned that combination of hypoxia and exercise may have a synergistic effect on body composition and metabolism (10,11). Indeed, in a pilot study in lean healthy men, endurance training in normobaric hypoxia over a four-week period elicited

similar or even better response in terms of cardiovascular and metabolic risk factors than endurance exercise in normoxia. However, training workload was significantly lower in the hypoxia group (12). We conducted a single blind study in obese patients to test the hypothesis that training under hypoxia results in similar or even better changes in body composition and metabolic risk markers compared with exercise under normoxia.

METHODS AND PROCEDURES

Subjects

We included 50 sedentary, nondiabetic or insulin-resistant, overweight or obese, otherwise healthy men and women in our study. Of those, four in the hypoxia and one in the normoxia group terminated the study prematurely for personal reasons. Forty-five subjects completed the training period and were included in the analysis (age: 42 ± 7.1 years, BMI: 30.2 ± 3.6 kg/m², and heart rate (rest): 69 ± 7.9 beats/min). In the weeks before and during the study, subjects lived at an altitude between 30 and 80 m above sea level and were weight stable prior to entering the study. Subjects with acute or chronic infections, any diseases that required treatment or

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Received 10 February 2009; accepted 12 May 2009; published online 18 June 2009. doi:10.1038/oby.2009.193

known abuse of drugs or alcohol were excluded. Our institutional review board approved the study, and written informed consent was obtained before study entry.

Protocol

Beside the endurance exercise given by the study protocol, subjects were asked not to participate in additional physical activity during the investigation period. Furthermore, we advised subjects to continue their current dietary behavior to avoid bias due to lifestyle changes throughout the study. Subjects visited the laboratory after an overnight fast. We measured height, weight, and waist circumference in a standardized fashion. At baseline, blood pressure and heart rate were measured with an automated blood pressure cuff (Dinamap; Critikon, Tampa, FL). Multifrequency bioimpedance analysis (BIA 5 series; Denner, Weikersheim, Germany) was conducted to obtain body composition values for each subject. We obtained blood samples for the determination of fasting insulin, glucose, and blood lipids. Homeostasis model assessment (HOMA) index of insulin resistance was calculated from fasting insulin and glucose data by the following formula: $(\text{insulin } (\mu\text{U/ml}) \times \text{glucose } (\text{mmol/l}))/22.5$ (ref. 13). Furthermore, patients were submitted to incremental exercise testing under normoxic conditions. Then, subjects were randomized to four weeks training under normoxia or training under hypoxia in a single blinded fashion. After completion of the training period, anthropometric and metabolic measurements were repeated within 3 days with at least 48 h after the last training session. After another 1–3 days, subjects underwent post-training exercise testing.

Exercise testing

Subjects were tested at room temperature of 21–22 °C 4 h after they had eaten a light breakfast. Incremental exercise testing was conducted on a motorized treadmill (h/p cosmos mercury 4.0; h/p cosmos sports & medical, Nussdorf-Traunstein, Germany) with 0% slope. The initial running speed was set at 1.8 m/s and increased every 3 min by 0.3 m/s with a pause of 1 min between steps. Patients were encouraged to give a maximal effort. We assessed gas exchange breath by breath using a Vmax Spectra Model 229D analyzer (SensorMedics, Yorba Linda, CA). Heart rate was recorded online from an electrocardiogram (GE Medical Systems, Waukesha, WI) throughout the exercise test. We assumed that subjects had reached maximal oxygen uptake ($\text{VO}_{2\text{max}}$) when two or more of the following criteria were met: (i) Respiratory exchange ratio > 1.10, (ii) VO_2 leveling off despite increase in power output, and (iii) heart rate within 10 beats/min of the predicted maximum heart rate. At baseline and after each exercise step, we obtained blood samples from the hyperemic earlobe to determine blood lactate concentration. Blood samples were analyzed with a lactate photometer (DP 100; Diagnostics, Berlin, Germany). To assess the individual anaerobic threshold, we applied a specialized lactate software program (Winlactat 2.5; Mesics, Münster, Germany).

Table 1 Subject characteristics

	Hypoxia group	Normoxia group
Men/women (n)	10/14	8/13
Age (years)	42.2 ± 1.2	42.1 ± 1.7
Body weight (kg)	93.4 ± 2.6	87.5 ± 3.6*
BMI (kg/m ²)	33.1 ± 0.3	32.5 ± 0.8
Heart rate, rest (bpm)	69.6 ± 1.9	68.4 ± 1.7
Plasma triglycerides (mg/dl)	122.7 ± 10.9	128.9 ± 18.1
Body fat (%)	32.1 ± 1.8	33.1 ± 1.6

Data are mean ± s.e.m.

bpm, beats/min.

* $P < 0.05$.

Normoxia and hypoxia training

Subjects were submitted to a four-week training program. They trained on a treadmill 60 min a day, 3 days a week, for 4 weeks at a heart rate corresponding to 65% of maximum oxygen consumption at the pretraining exercise test. The same relative exercise intensity was chosen to achieve comparable cardiorespiratory conditions for both intervention groups. Training sessions under normoxia (partial pressure of inhaled oxygen (P_iO_2) 150 mm Hg) and under normobaric hypoxia (P_iO_2 103 mm Hg) were conducted in a hypoxia chamber. The latter P_iO_2 corresponds to that at 2740 m altitude. Oxygen content within the chamber could be reduced by insufflating nitrogen that was produced from room air through a molecular sieve. Room oxygen and carbon dioxide within the room was continuously monitored by a sensor electrode throughout test and training sessions. We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research.

Statistical analysis

Data were first tested for distribution normality and variance homogeneity. Differences between values obtained pre- and post-training for a particular group were analyzed using Student's paired *t*-test. To test for both intervention and time (before vs. after), we used an ANOVA for repeated measures followed by Student–Newman–Keuls posttest. Differences were considered to be significant for $P < 0.05$. If not otherwise indicated, values are given as mean ± s.d.

RESULTS

A total of 21 patients in the normoxia and 24 in the hypoxia group completed the entire study protocol. Demographic and physiological baseline characteristics for both treatment groups are given in **Table 1**. Groups were well matched for age, BMI, lipid levels, HOMA index, and blood pressure as well as endurance capacity before the training period.

Training workload was lower in the hypoxia group (–17.5%, $P < 0.01$; **Figure 1b**) whereas heart rate was not significantly different between groups (**Figure 1a**). After the training period,

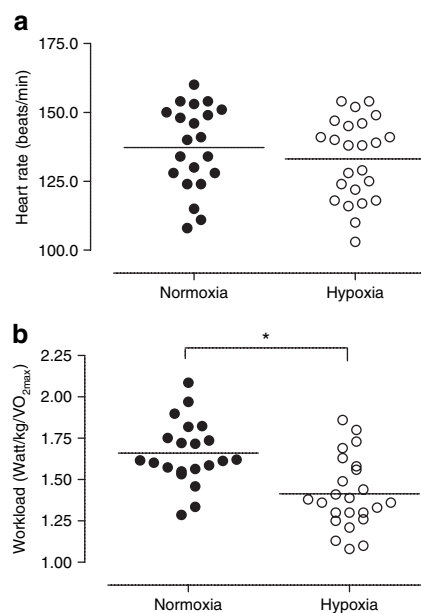


Figure 1 Individual data and mean of (a) training heart rate and (b) training workload during the 4-week training period in subjects randomized to training in normoxia or hypoxia. * $P < 0.05$.

Table 2 Exercise testing and metabolic/cardiovascular risk factors before and after training

	Hypoxia group		Normoxia group	
	Before	After	Before	After
Maximal				
VO _{2max} , ml/kg/min	36 ± 1.5	38 ± 1.4	32 ± 1.2	33 ± 1.3
Lactate _{max} , mmol/l	7.5 ± 0.6	6.7 ± 0.4	8.7 ± 0.7	7.6 ± 0.5
TtE, min:ss	18:47 ± 01:29	22:02 ± 01:21	16:05 ± 01:08	18:47 ± 01:15
Anaerobic threshold				
RQ	0.99 ± 0.02	0.93 ± 0.01*	0.97 ± 0.02	0.95 ± 0.02
Lactate, mmol/l	4.1 ± 0.4	3.5 ± 0.3*	4.4 ± 0.3	4.3 ± 0.3
Risk factors				
Systolic BP, mm Hg	128 ± 3.0	126 ± 2.6	129 ± 2.9	126 ± 2.5
Diastolic BP, mm Hg	83 ± 2.1	80 ± 1.7	80 ± 2.2	79 ± 1.7
LDL, mg/dl	115 ± 5.1	112 ± 6.1	121 ± 7.8	116 ± 9.8
Fat-free mass, %	69 ± 1.9	71 ± 2*	68 ± 1.4	68 ± 1.6
Waist circumference, cm	99 ± 2.9	95 ± 2.5*	92 ± 2.9	90 ± 2.7
Fasting insulin, mU/ml	8.4 ± 1.3	5.3 ± 0.7*	9.7 ± 1.5	6.5 ± 0.7*
HOMA index	1.9 ± 0.3	1.1 ± 0.2*	2.1 ± 0.3	1.4 ± 0.2*

Data are mean ± s.e.m.

BP, blood pressure; HOMA, homeostasis model assessment; LDL, low-density lipoprotein; RQ, respiratory quotient; TtE, time to exhaustion; VO₂, oxygen uptake.

**P* < 0.05 compared with before training.

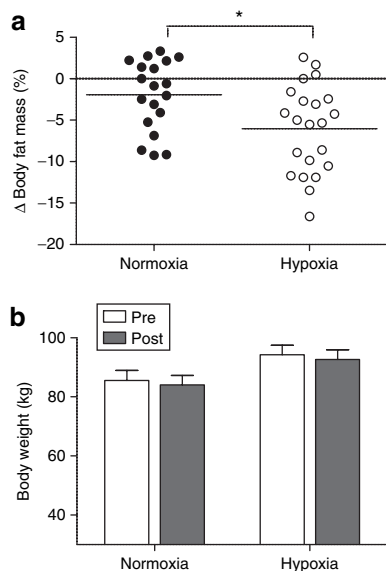


Figure 2 Data of changes from pre- to post-training in (a) body fat mass and (b) body weight in subjects randomized to training in normoxia or in hypoxia. **P* < 0.05.

time to exhaustion and VO_{2max} levels increased (HG: 5.5 ± 2.1; NG: 3.1 ± 2.2%) and Lactate_{max} decreased (HG: -10.6 ± 3.3%; NG: -12.6 ± 2.8%) similarly in the normoxia and in the hypoxia group. Respiratory quotient and lactate at the individual anaerobic threshold decreased only in the hypoxia group (Table 2, *P* < 0.05).

Both training groups showed similar slight reductions in body weight (HG: -1.8 ± 0.6%; NG: -1.7 ± 0.9%) (Figure 2b) and in BMI (HG: -1.5 ± 0.7%; NG: -1.3 ± 0.6%) with a

differential effect on body composition. The reduction in body fat content with training was greater in the hypoxia group with a concomitant increase in fat-free mass (Figure 2a, *P* < 0.05). Diastolic blood pressure tended to decrease in the hypoxia group (*P* = 0.057) and remained unchanged with normoxia training. Systolic blood pressure did not change in either group. Fasting insulin decreased in both training groups with a significant improvement in the HOMA index (Table 2, *P* < 0.05). We did not observe significant changes in triglycerides, total cholesterol, high-density lipoprotein-cholesterol, or low-density lipoprotein-cholesterol after the training period.

DISCUSSION

Earlier studies suggested that training under moderate hypoxia (“living low–training high”) can improve endurance performance in athletes (11,14). Substrate utilization and maximal oxygen consumption are tightly coupled to muscular mitochondrial oxidative capacity (15). Moreover, improved aerobic performance is associated with quantitative and qualitative mitochondrial adaptations (16,17). Therefore, training under hypoxic conditions might reverse oxidative (18) and mitochondrial dysfunction (19) in obese patients, particularly in those with type 2 diabetes mellitus. However, studies applying training under hypoxia in the clinical setting are rare. In our study, subjects trained at an identical heart rate in hypoxia and in normoxia, suggesting a comparable cardiovascular training stimulus. Training workload was lower with hypoxia training. Yet, hypoxia endurance training elicited similar beneficial adaptations for metabolic markers and even greater effects for adiposity measures than training in normoxia. In both training groups, classical cardiovascular risk factors, such as blood

pressure or low-density lipoprotein-cholesterol did not change significantly.

Previous studies showed a relative increase in glucose oxidation rate during physical activity after hypoxia training (10,14,20). The phenomenon was attributed to *trans*-activation of hypoxia-inducible factor-1. We did not determine insulin sensitivity directly. However, we assessed HOMA index, a measurement that is highly correlated with insulin sensitivity or resistance. In lean healthy men, HOMA index improved with training and even more so when training was combined with hypoxia (12). In the present study, training in hypoxia and in normoxia elicited a similar response in obese patients, suggesting that hypoxia did not have a major exercise independent effect on fasting insulin and glucose metabolism in obese subjects.

Body weight was only slightly reduced in our study with similar responses in the normoxia and in the hypoxia groups with beneficial changes in body composition in the latter group. Another study showed greater body weight reductions in obese subjects when endurance training was combined with hypoxia (21). The authors proposed that additional weight loss might have been secondary to hypoxia-induced leptin production (5). The response has been previously described in animals (22) and may contribute to involuntary weight loss at high altitude (23,24). We did not observe differences in serum leptin responses between normal weight subjects undergoing normoxic and hypoxic training interventions (12). However, adipose tissue oxygenation is altered in obesity such that observations on leptin metabolism in normal weight subjects cannot be simply extrapolated to obese individuals (25). Altered catecholamine, atrial natriuretic peptide, and thyroid hormone levels could also affect substrate metabolism and body composition with hypoxia exposure (26–29).

The beneficial effect of endurance training on triglyceride levels has been attributed to increased postexercise lipid oxidation (30). Hypoxia also tends to raise lipid oxidation through the transcription co-activator peroxisome proliferator-activated receptor- γ co-activator-1 α (8). By co-activating the peroxisome proliferator activated receptor, a family of lipid-activated nuclear hormone receptors, PGC1 α plays a key role in mediating adaptive regulation of muscle fatty acid oxidation (9). In lean healthy men, combination of exercise and hypoxia had a greater effect on triglyceride concentrations than each stimulus alone (12). We did not confirm this observation in obese subjects. We speculate that the greater reduction in body fat in the hypoxia group may have been due to improved lipid oxidation.

We conclude that in obese subjects, endurance training under hypoxia achieves similar improvements in physical fitness and metabolic risk markers compared with training under normoxia at a lower workload. Furthermore, addition of hypoxia to an endurance exercise program may have a beneficial effect on body composition. The reduction in workload might reduce the risk for orthopedic injury, which could be particularly beneficial to patients in whom exercise capacity is limited by orthopedic conditions.

ACKNOWLEDGMENTS

We thank Elke Nickel-Szczeczek and Gritt Stoffels for expert technical help with patient recruitment and study procedures. We also thank Volker Spiegel and Detlef Schwarz from Low Oxygen Systems for technical advice.

DISCLOSURE

H.M. and U.H. work as employees at the hypoxia training institute “Höhenbalance AG” in Cologne, Germany. The other authors declared no conflict of interest.

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