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Article in *High altitude medicine & biology* · September 2018

DOI: 10.1089/ham.2018.0014

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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 mL O₂ minutes^{−1} kg^{−1}) compared with the CTRL group ($n = 14$, 20.6 ± 4.9 mL O₂ minutes^{−1} kg^{−1}). CRF in IHHT increased significantly from baseline (6.05 ± 1.6 mL O₂ 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

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(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% O₂) 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% O₂)—hyperoxia (30%–33% O₂) 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 HR_{max}, 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 SaO₂ 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 $\pm$ STANDARD DEVIATION) AND COMORBIDITIES

	IHHT (n = 15)	CTRL (n = 14)
Age (years)	66.7 $\pm$ 5.7	65.0 $\pm$ 6.2
BMI (kg/m ²)	27.7 $\pm$ 2.3	28.9 $\pm$ 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 mL O₂ minutes⁻¹ kg⁻¹). In the IHHT group, the aerobic capacity was significantly higher (mean difference 6.05 mL O₂ 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 mL O₂/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 $\times$ 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 <i>p</i> = 0.94	F(1,54) = 0.34 <i>p</i> = 0.94	0.12
SBP	F(1,54) = 3.42 <i>p</i> = 0.07	F(1,54) = 0.34 <i>p</i> = 0.56	0.74
DBP	F(1,54) = 4.96 <i>p</i> = 0.03	F(1,54) = 0.42 <i>p</i> = 0.52	0.70
VO_{2peak}	F(1,54) = 2.21 <i>p</i> = 0.14	F(1,54) = 14.65 <i>p</i> = 0.0003	1.10
RBC	F(1,54) = 0.007 <i>p</i> = 0.93	F(1,54) = 0.018 <i>p</i> = 0.89	0.01
Hemoglobin	F(1,54) = 0.052 <i>p</i> = 0.82	F(1,54) = 0.078 <i>p</i> = 0.78	0.01
Reticulocytes	F(1,54) = 0.74 <i>p</i> = 0.39	F(1,54) = 0.027 <i>p</i> = 0.87	0.23
WBC	F(1,54) = 0.77 <i>p</i> = 0.38	F(1,54) = 0.47 <i>p</i> = 0.50	0.47
Platelets	F(1,54) = 2.56 <i>p</i> = 0.12	F(1,54) = 0.69 <i>p</i> = 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 (Burtcher 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 (Burtcher 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 $\pm$ STANDARD DEVIATION)

	IHHT (n = 15)		CTRL (n = 14)	
	Baseline	After	Baseline	After
HR rest (beat/min)	70.9 $\pm$ 13.2	69.6 $\pm$ 8.3	67.6 $\pm$ 8.0	65.9 $\pm$ 9.2
SBP (mmHg)	140.5 $\pm$ 14.1	131.3 $\pm$ 9.5	136.4 $\pm$ 14.8	135.1 $\pm$ 18.1
DBP (mmHg)	82.1 $\pm$ 11.1	74.7 $\pm$ 8.9	77.9 $\pm$ 9.7	82.0 $\pm$ 9.3
VO _{2peak} (mlO ₂ minutes ⁻¹ kg ⁻¹)	13.9 $\pm$ 2.5	19.9 $\pm$ 6.1*	17.9 $\pm$ 2.8	20.6 $\pm$ 4.9
RBC ($\times 10^{12}$ /L)	4.38 $\pm$ 0.33 [^]	4.38 $\pm$ 0.30 [^]	4.77 $\pm$ 0.42	4.79 $\pm$ 0.28
Hemoglobin (g/dL)	13.6 $\pm$ 0.8 [^]	13.6 $\pm$ 1.1	14.5 $\pm$ 1.1	14.3 $\pm$ 1.1
Reticulocytes (%)	0.9 $\pm$ 0.6	1.1 $\pm$ 0.5 [^]	0.6 $\pm$ 0.4	0.6 $\pm$ 0.3
WBC ($\times 10^9$ /L)	6.12 $\pm$ 1.05	5.49 $\pm$ 1.58	6.55 $\pm$ 1.71	6.63 $\pm$ 1.76
Platelets ($\times 10^9$ /L)	215.5 $\pm$ 30.0	251.6 $\pm$ 74.8	227.2 $\pm$ 51.8	215.8 $\pm$ 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 (O₂ 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 (O₂ at 30%) immediately after being exposed to hypoxia (O₂ 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 is 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.

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