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Intermittent Hypoxia-Hyperoxia Exposures Improve Cardiometabolic Profile, Exercise Tolerance and Quality of Life: A Preliminary Study in Cardiac Patients

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ABSTRACT

Study design: randomized controlled before-and-after and in follow-up trial. Forty-six CAD patients volunteered to take part in the study: a group of 27 patients undertook an Intermittent Hypoxia (O₂ at 10%) - Hyperoxia (O₂ at 30%) Training (IHHT), while a control group (CTRL) of 19 patients was allocated to sham IHHT treatment (breathing via face mask by room air, O₂ at 21%). Exercise performance, blood and metabolic profile, quality of life (MOS SF-36, Seattle Angina Questionnaire, SAQ) were measured before and after IHHT/sham IHHT in both groups; the intervention group was also assessed one month after completing the IHHT.

The IHHT intervention group showed improved exercise capacity (+1,8 ml O₂/min/kg, p=0,02), reduced resting systolic and diastolic blood pressures (151/85 before vs 130/73 after p<0,01), enhanced Left Ventricle Ejection Fraction (62,6±5,5% vs 58±6,2%, p<0,01), glycemia was significantly reduced only at 1-month follow-up (6,18±1,7 after vs 7,10±2,34 mmol/l at baseline, p=0,037). Frequency of angina as reason to stop exercising was significantly reduced after treatment and at 1-month follow-up.

In CAD patients an Intermittent Hypoxia-Hyperoxia Training program is associated with improved exercise tolerance, risks factors profile and quality of life (SF-36, SAQ). IHHT has proved to be safe, well tolerable and easily applicable in cardiac patients.

Keywords: *Intermittent hypoxia-hyperoxia training, exercise tolerance, cardiometabolic profile, coronary artery disease, quality of life, cardiac rehabilitation*

INTRODUCTION

In recent years, the structure of cardiac rehab methods is expanding due to the combined use (along with individually adjusted exercise training) of new high-tech instrumental techniques - enhanced external counterpulsation, extracorporeal shock wave therapy, etc. One of the promising approaches is the use of repeated multiple episodes of adaptation to hypoxia - interval hypoxic training (IHT).

Intermittent exposure to normobaric hypoxia (IHT) has been shown to improve exercise capacity without exercising in the elderly and in cardiac patients ^{2,3}. IHT also positively affects the Autonomic Nervous System and pulmonary functioning in various patients ⁴. This technique consists of intermittent exposures to hypoxic and normoxic stimuli through a face mask (one cycle of up to 5 hypoxic exposure lasting at least 5–6 min, and being followed by at least 5–6 min of normoxic air breathing) repeated almost daily (4-5 days a week) over 2–3 weeks ².

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In our study we used normobaric Intermittent Hypoxic-Hyperoxic Training (IHHT) as a new alternative treatment, more effective than adaptation to interval hypoxia-normoxia: replacing normoxia with hyperoxia

during intermittent exposures to hypoxia produces a faster membrane-stabilizing effect in cells of the heart, liver, and brain compared to IHT in experimental research of T.Sazontova et al.⁸. During periods of the induced hyperoxia, the induction of reactive oxygen species (ROS), which is necessary to start the cascade of the redox signaling pathways, takes place, which leads to enhanced synthesis of protective intracellular protein molecules, mainly with antioxidant function (antioxidant defense enzymes, iron-binding proteins, heat shock proteins etc.)⁷. IHHT has been proven to be effective and better tolerable in preliminary studies focused on exercise performance⁵. Very recent studies reported that IHHT improved exercise performance in athletes with overtraining syndrome¹⁰, contributed significantly to improvements in cognitive function and functional exercise capacity in multi-morbid geriatric patients¹.

We aimed to conduct a controlled trial to investigate the effects of an IHHT program on exercise tolerance, cardio-metabolic risk-factors and patient-relevant subjective parameters of life quality assessment in CAD patients.

METHOD

Population

Fifty-four patients with diagnosis of CAD (NYHA functional class II and III) in stable clinical condition for the last six months were invited to participate in the study.

Twenty-seven patients were people waiting to start a usual cardiac rehabilitation program and they were allocated to IHHT group. Twenty-seven patients were allocated to control/sham-IHHT group (CTRL), but eight of them dropped out before initial baseline assessment, so that only 19 patients volunteered as controlled group. Participants' drugs plan was unchanged during the entire study period (drugs used by participants included beta-blockers, calcium channel blockers, ACE-inhibitors, ATR-blockers, anti-aggregants, statins, nitrates and diuretics). All participants were blinded to group allocation. Participants were also advised not to change nutrition and levels of daily physical activity during the study.

Exclusion criteria were: history of exercise induced syncope, NYHA class IV, decompensated heart failure,

severe angina, grade 3 hypertension at rest (SBP >180 and/or DBP >110 mmHg).

Intervention

Participants in the intervention group undertook a program of Interval Hypoxia-Hyperoxia Training (IHHT) consisting of personalized repeated exposures to hypoxia (breathing through a face mask by gas mixture with 10–12% O₂) and to hyperoxia (30–35% O₂): 3 sessions a week, 5–7 hypoxic periods lasting 4–6 min, with 3-min hyperoxic recovery intervals for 15 sessions in total (ReOxy-Cardio, AiMediq, Luxembourg). This program was based on a 10-min continuous hypoxia test and tailored on individual responses to hypoxia exposure according to previously published principles and protocols guiding the clinical use of intermittent hypoxia exposure (9, 21). Participants in the control group completed a sham program breathing room air (normobaric normoxic mixture following the same schedule of the IHHT group), so completing at least 15 daily sessions over three weeks, each session including up to seven normoxia-normoxia cycles of up to 6 minutes of sham exposure and 3 minutes sham recovery between periods of sham exposure. During each session of both the IHHT and sham IHHT treatments all participants were continuously monitored (blinded) using fingertip pulseoxymeter (pulse rate and SaO₂) and supervised by physicians and/or nurses. Blood pressure measurements were performed before and after each session.

Study protocol

Baseline assessment included:

- Anthropometrics (height, weight, BMI, Seca stadiometer, Vogel & Halke, Germany),
- Resting blood pressure and heart rate (Omron; Omron Healthcare, Japan);
- Cardiopulmonary stress test (Cardiovit AT-104 PC Ergo-Spiro, Switzerland). A six-lead electrocardiogram was recorded continuously. The selected exertion protocols were Bruce and Modified Bruce depending on patients' clinical conditions. Peak oxygen uptake (VO₂ peak) was defined as the highest 15-s average of oxygen uptake obtained at the end of the test (i.e. at the highest mechanical output achieved). Test was stopped according to internationally agreed criteria (8). Blood pressure, and Ratings of Perceived intensity

of Exertion according to the Borg scale were determined at the end of each workload;

- Echocardiographic study in M-mode (ESAOTE Mylab Alpha) was conducted before starting the program and within one week after completing the program;

- Blood samples (fasting): Red and white blood cell count, haemoglobin concentration, reticulocytes, serum total and high density lipoprotein (HDL) cholesterol, triglycerides and glucose concentrations were analyzed by the central biochemical laboratory of our University (I.M. Sechenov Moscow State Medical University) using standardized analytical methods on fasting blood samples;

- Health related quality of Life (HRQoL) was tested by the Medical Outcomes Study 36-item Short Form Health Survey (MOS SF-36), one of the most often-used generic instruments to measure HRQoL in cardiac populations (23) and is reported to be the most appropriate in its validity, reliability, and sensitivity. Russian version of the SF-36 Health Survey was used in the study and reflects the eight scales: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health (5)

- Additionally HRQoL was monitored by disease-specific survey - Seattle Angina Questionnaire SAQ, (22).

All assessments were repeated 3 days (range 2–5 days) after completion of the IHHT program (or sham program in control group) and at 1-month follow-up (only in IHHT group).

Data analysis

Statistical analyses were performed using SAS statistical software version 9.3 for Windows (SAS Institute Inc, Cary, USA). All data are reported as Mean±SD and statistical significance was at $p<0.05$. After testing for normality by Shapiro-Wilk test, Student's paired t-test or Wilcoxon's signed rank test were used to compare values before and following the IHHT program. Also comparisons were performed between IHHT and Control groups at same time points.

The study was approved by the Ethical Committee of I.M. Sechenov Moscow State Medical University and carried out in conformity with the ethical standards laid

down in the Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects (Bulletin of World Health Organization 2001). Written informed consent was obtained from all participants.

RESULTS

Primary outcome was exercise tolerance measured as stress test response and aerobic capacity (Bruce and modified Bruce incremental workload tests protocols and indirect calorimetry). Secondary outcomes were patient-centered (Health related quality of Life (HRQoL) assessed by MOS SF-36 and Seattle Angina Questionnaire, ^{20,21}) and clinically relevant to better manage CAD (blood pressure, lipid profile, glycemia, Left Ventricular Ejection Fraction, LVEF).

Eight patients in the control group withdrew before baseline assessment. All the patients allocated in the IHHT group completed the program and were tested before and after the IHHT and at 1-month follow-up. Characteristics of the participants are shown in Table 1. In the control group only 19 participants (out of 27 initially recruited) made themselves available to be assessed before starting and after the sham program.

Cardiovascular adaptations

At baseline, control group showed significantly ($p<0.05$) lower Blood Pressure values (SBP 131 ± 18 vs 151 ± 19 mmHg, DBP 78 ± 10 vs 85 ± 11 mmHg), higher aerobic capacity (16.8 ± 3.9 vs 14.25 ± 4.2 mlO₂/min/kg measured as VO_{2peak} using modified Bruce and Bruce protocols depending on patients' clinical conditions). These findings were somewhat unexpected and were explained by less pronounced CAD and Heart Failure symptoms and better medication in the control group, allocated later to sham treatment.

Table 2 summarizes cardiovascular responses after IHHT (stress test according to Bruce and modified Bruce protocols, VO_{2peak} measurement using indirect calorimetry and gas analysis, Resting Systolic and Diastolic Blood Pressure, Resting and maximal effort Heart Rates, Left Ventricle Ejection Fraction): The IHHT group showed after treatments and at follow-up lower frequency of 'angina as reason to stop exercising', significant increase in aerobic capacity, lowering in resting systolic and diastolic blood pressure, resting heart rate and improved myocardial performance. No significant changes have been observed in CTRL.

Blood biochemistry

Table 3 shows relevant blood biochemistry and hematological parameters (Hemoglobin and Reticulocytes, Total Cholesterol and Low-Density Lipoproteins, Glycemia). Lipid profile improved as well as the Atherogenic Index, mainly because of a significantly lowered Total Cholesterol. In IHHT group hemoglobin and glycemia were unchanged after IHHT, but glycemia was significantly lower at 1-month follow-up. No significant hematological changes have been revealed in CTRL.

DISCUSSION

Our results show that, after 15 daily session of IHHT, cardiopulmonary fitness was significantly improved as the values of VO_{2peak} were higher than those measured at baseline. These values are not likely to be clinically meaningful as their magnitude is around 0.5 METS but they show that improving cardiopulmonary fitness without exercising is feasible in patients with very low baseline values and co-morbidities. Linked to this it is worth putting emphasis on the significant reduction of the number of patients reporting angina as a reason to stop exercising while undertaking a stress test. Our results are aligned with previous studies on Intermittent Hypoxia-Normoxia exposure in different forms: Intermittent Hypoxia Training (breathing hypoxic mixtures via a facial mask while resting, usually comfortably sitting) and Training in Hypoxia (continuous exposure to hypobaric or normobaric hypoxia while exercising). Both these “strategies” have been shown to be effective in improving exercise tolerance and performance in athletes by triggering hematological and non-hematological adaptations ⁶.

Table 1. Descriptive statistics at baseline of the IHHT and Control groups.

	IHHT group (n=27)	Control group (n=19)
Males n (%)	9 (33%)	9 (47%)
Average age, years (range)	63,9 (52-77)	63,2 (43-83)
Body mass (kg)	81,6 ± 13, 9	79,1 ± 12,5
Heart Rate (bpm)	71,5 ± 11,4	68,9 ± 9,6
Systolic Blood Pressure (SBP, mmHg)	151 ± 19	131 ± 18
Diastolic Blood Pressure (DBP, mmHg)	85 ± 11	78 ± 10 (p=0,05)
Current smokers, n (%)	5 (18,5%)	4 (18,5%)
Hypertension, n (%)	22 (81,5%)	17 (89,5%)
Diabetes, n (%)	8 (29,6%)	3 (15,8%) (p=0,04)
Exertional Angina, II FC	20 (74,1%)	17 (89,5%)
Exertional Angina, III FC	7 (25,9%)	2 (10,5%) (p=0,04)
Previous MI, n (%)	8 (29,6%)	8 (42,1%)
Paroxysmal AF, n (%)	5 (18,5%)	2 (10,5%)
COPD, n (%)	2 (7,4%)	2 (10,5%)
VO_2 peak (ml/min/kg)	14,3 ± 4,2	16,5 ± 4,2 (p=0,05)
LV Ejection fraction (%)	58,0 ± 6,2	62,2 ± 7,2

Table 2. Cardiovascular responses and haemodynamic parameters of the IHHT and the control groups before and after the program and at 1-month follow-up (in IHHT group only)

	Group	Before (HT1)	After (HT2)	1 Month follow up (HT3)
Angina as a reason to stop test, n (%)	IHHT	12 (44,44%)	6 (22,22%)*	3 (11,11%)**
	Control	4 (21,05%)	6 (31,57%)	---
Exercise time, s (M-BRUCÉ)	IHHT (n=13)	354 ± 194	383 ± 141	395 ± 130** p=0,01
	Control (n=5)	280 ± 92	323 ± 64 # p=0,02	---

Cont... Table 2. Cardiovascular responses and haemodynamic parameters of the IHHT and the control groups before and after the program and at 1-month follow-up (in IHHT group only)

Exercise time, s (BRUCE)	IHHT (n=14)	280 ± 126	295 ± 79	332 ± 113** p=0,01
	Control (n=14)	335 ± 121	355 ± 96	---
VO _{2peak} (mlO ₂ /min/kg)	IHHT	14,3 ± 4,2	16,1 ± 4,2* p=0,02	15,4 ± 4,5** p=0,03
	Control	16,8 ± 3,9 #	17,8 ± 4,9	---
SBP, mmHg	IHHT	151 ± 19	130 ± 13* p=0,0001	129 ± 11** p=0,005
	Controls	131 ± 18 #	131 ± 17	---
DBP, mmHg	IHHT	85 ± 11	73 ± 7* p=0,0002	75 ± 9** p=0,002
	Controls	78 ± 10 #	79 ± 10	---
Heart Rate at rest (bpm)	IHHT	71,5 ± 11,4	67,7 ± 8,3* p=0,03	66,6 ± 10,0** p=0,02
	Controls	68,9 ± 9,6	66,8 ± 10,2	---
Heart Rate Max (bpm)	IHHT	122 ± 19	120 ± 14* p=0,03	116 ± 14** p=0,01
	Control	124 ± 13	119 ± 17	---
Left Ventricle Ejection Fraction %	IHHT	58,0 ± 6,2	62,6 ± 5,5* p=0,0008	61,6 ± 6,3*** p=0,007
	Controls	62,2 ± 7,2 #	61,3 ± 6,0	---

p-values for differences between:

* HT1 and HT2, ** HT1 and HT3 *** HT2 and HT3; # - IHHT and Control group at same time point.

Table 3. Hematological and metabolic variables of the IHHT and the control groups before and after the program and at 1-month follow-up (in IHHT group only)

	Group	Before (HT1)	After (HT2)	1 Months Follow-up (HT3)
Hemoglobin, g/L Reticulocytes, % Total Cholesterol, (TCh), Mmol/L	IHHT	134 ± 12	136 ± 13	136 ± 12
	Controls	145 ± 10	145 ± 10	---
	IHHT	9,0 ± 5,5	11,3 ± 6,2* p=0,02	9,2 ± 4,8
	Controls	6,4 ± 3,6	5,11 ± 3,13	---
	IHHT	5,6 ± 1,4	5,1 ± 1,2* p=0,041	5,5 ± 1,4
	Controls	5,5 ± 0,9	5,6 ± 1,0#	---

Cont... Table 3. Hematological and metabolic variables of the IHHT and the control groups before and after the program and at 1-month follow-up (in IHHT group only)

Low-density lipoproteins (LDL), Mmol/L	IHHT	3,5 ± 1,2	3,2 ± 0,9* p=0,006	2,6 ± 1,3*** p=0,007
	Controls	3,6 ± 0,8	3,5 ± 0,8	---
Atherogenic Index (TCh - HDL) / HDL	IHHT	4,7 ± 1,8	3,4 ± 1,3* p=0,0018	3,5 ± 1,5** p=0,002
	Controls	3,6 ± 1,1	3,4 ± 1,0	---
Glucose, mmol/L	IHHT	7,10 ± 2,3	6,45 ± 1,7	6,18 ± 1,7** p=0,037
	Controls	5,83 ± 0,65	5,97 ± 0,68	---

p-values for differences between:

* HT1 and HT2, ** HT1 and HT3 *** HT2 and HT3;
- IHHT and Control group at same time point.

CONCLUSION

A novel modality of intermitted hypoxic repeated preconditioning - interval hypoxic-hyperoxic training (IHHT) has been tested and found to be safe, deliverable to cardiac patients and associated with improved exercise tolerance, a more protective cardio-metabolic profile and superior quality of life self-assessment.

Positive multiple effects of IHHT in correction of cardio-metabolic risk factors and quality of life subjective assessments in patients with stable angina raise the prospect of potential using IHHT as an additional method of treatment and rehab of CAD patients with metabolic syndrome, as well as with orthopedic comorbidity and low adherence to exercise training.

These very encouraging results should be confirmed by randomized, well controlled trials. Further research is also needed to explain the mechanisms behind adaptations to IHHT and to better tailor individual exposures to Hypoxia – Hyperoxia cycles.

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