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Adaptations following an intermittent hypoxia-hyperoxia training in coronary artery disease patients: a controlled study

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Background: Repeated exposure to intermittent normobaric hypoxia improves exercise tolerance in cardiac patients. Little is known on the effects of intermittent normobaric hypoxia-hyperoxia exposure in coronary artery disease (CAD) patients (New York Heart Association II–III).

Hypothesis: IHHT improves exercise tolerance, cardiometabolic profile, and quality of life in CAD patients.

Methods: The study design was a nonrandomized, controlled, before-and-after trial. Forty-six CAD patients volunteered to take part in the study: a group of 27 patients undertook the intermittent hypoxia (O_2 at 10%)–hyperoxia (O_2 at 30%) training (IHHT), whereas a control group (CTRL) of 19 patients, who already completed an 8-week standard cardiac rehabilitation program, was allocated to sham-IHHT treatment (breathing room air, O_2 at 21%). Exercise performance, blood and metabolic profiles, and quality of life (Seattle Angina Questionnaire [SAQ]) were measured before and after in the IHHT group (IHHG) and sham-IHHT in the CTRL group.

Results: The IHHG showed improved exercise capacity, reduced systolic and diastolic blood pressures, enhanced left ventricle ejection fraction, and reduced glycemia, but only at 1-month follow-up. Angina as a reason to stop exercising was significantly reduced after treatment and at 1-month follow-up. The IHHT SAQ profile was improved in the IHHG and not significantly different to the CTRL group after standard rehabilitation. The IHHG was also compared to the CTRL group at 1-month follow-up, and no differences were found.

Conclusions: In CAD patients, an IHHT program is associated with improved exercise tolerance, healthier risks factors profile, and a better quality of life. Our study also suggests that IHHT is as effective as an 8-week standard rehabilitation program.

KEYWORDS
Intermittent hypoxia-hyperoxia training, exercise tolerance, cardiometabolic profile, coronary artery disease, cardiac rehab

1 | INTRODUCTION

Coronary artery disease (CAD) is the leading cause of death worldwide. Exercise, as well as regular physical activity, improves cardiometabolic risk profiles and cardiopulmonary fitness, a recognized cardiovascular risk major marker.[1,2] Exercise is a cornerstone in cardiac prevention, and it reduc es total and cardiovascular mortality in patients with CAD.[3] Exposure to normobaric intermittent hypoxia training (IHT) has been shown to improve exercise capacity without exercising in the elderly and in cardiac patients.[4–7] IHT also positively affects autonomic nervous system functioning in various patients.[8,9] This technique consists of intermittent exposures to hypoxic–normoxic stimuli (1 cycle of up to 5 hypoxic exposures lasting at least 5–6 minutes, followed by at least 5–6 minutes of normoxic air breathing) repeated almost daily (4–5 days a week) over 2 to 3 weeks.

This study was conducted at the Normal Physiology Laboratory, I. M. Sechenov First Moscow State Medical University, Moscow, Russia.

Professor Glazachev provided consultancy to Ai Mediq to develop their ReOxy equipment's software.

In our study we used normobaric intermittent hypoxic-hyperoxic training (IHHT) as a new alternative treatment. Replacing normoxia with hyperoxia during intermittent exposure to hypoxia has been proven to be effective in preliminary studies focused on exercise performance.[9,10] This new approach is more convenient than IHT, as the recovery time between bouts of exposure to hypoxia is shortened to 3 minutes, allowing for a higher number of hypoxia–hyperoxia cycles during the same session. Also, as IHHT does not involve exercising, it could be a viable conditioning option to patients who are not able to exercise (eg, because of osteoarthritis, a common comorbidity in CAD/cardiometabolic patients). In addition, because of the additional oxidative stress triggered by hypoxia being followed by hyperoxia, this new approach is likely to foster the antioxidant defenses (please see the Discussion section for further details on the potential mechanisms).

Therefore, we aimed to conduct a controlled trial to investigate the effects of an IHHT program on exercise tolerance, cardiometabolic risk factors, and patient-relevant subjective parameters in CAD patients.

2 | METHODS

2.1 | Population

Fifty-four patients with a diagnosis of CAD (New York Heart Association [NYHA] functional class II and III) in stable clinical condition for the last 6 months were invited to participate in the study. Twenty-seven patients were patients waiting to start the usual cardiac rehabilitation program, and they were allocated to the IHHT group (IHHG). Twenty-seven patients who already completed the usual 8-week/twice-a-week cardiac rehabilitation program were allocated to the sham-IHHT group (CTRL) to allow for comparison between IHHT and standard rehabilitation program efficacies. Eight patients in the control group dropped out before our study baseline assessment; 19 patients volunteered to be assessed. Participants' drugs plans was unchanged during the entire study period (drugs used by participants included β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, antiaggregants, 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 (systolic blood pressure [SBP] >180 and/or diastolic blood pressure [DBP] >110 mm Hg).

2.2 | Intervention

Participants in the intervention group undertook a program of IHHT consisting of personalized repeated exposures to hypoxia (10%–12% O_2) and to hyperoxia (30%–35% O_2), 3 sessions a week, 5 to 7 hypoxic periods lasting 4 to 6 minutes, with 3-minute hyperoxic recovery intervals for 15 sessions in total (ReOxy; Ai Mediq, Luxembourg). This program was based on a 10-minute continuous hypoxia test and was tailored on individual responses to hypoxia exposure according to previously published principles and protocols guiding the clinical use of intermittent hypoxia exposure.[11,12] Participants in the CTRL group were enrolled in the study after completing a standard rehabilitation program lasting 8 weeks (16 sessions in total) and were exposed to sham-IHHT (normobaric normoxic air) following a protocol/schedule similar to the IHHT group (15 daily sham sessions over 3 weeks). During each session of both the IHHT and sham-IHHT treatments, all participants were continuously monitored (blinded) using fingertip pulse oximeter (pulse rate and SaO_2) and supervised by physicians and/or nurses.

2.3 | Outcomes

Primary outcome was exercise tolerance measured as stress test response and aerobic capacity (Bruce and modified Bruce incremental workload test protocols and indirect calorimetry). Secondary outcomes were patient-centered quality of life (Seattle Angina Questionnaire [SAQ][13]) and clinically relevant variables to better manage CAD.

2.4 | Study protocol

The study's baseline assessment included:

- Anthropometrics (height, weight, body mass index [stadiometer; Seca, Vogel & Halke, Hamburg, Germany),
- Resting blood pressure and heart rate (Omron Healthcare, Kyoto Japan), cardiopulmonary stress test (Cardiovit AT-104 PC ergospiro; Schiller, Bern, Switzerland). A 6-lead electrocardiogram was recorded continuously. The selected exertion protocols were Bruce and modified Bruce depending on patients clinical conditions. Peak oxygen uptake (VO_2 peak) was defined as the highest 15-second average of oxygen uptake obtained at the end of the test (ie, at the highest mechanical output achieved). The test was stopped according to internationally agreed upon criteria.[3] Blood pressure, and ratings of perceived exertion according to the Borg scale were determined at the end of each workload.
- Echocardiographic study in M-mode (Mylab Alpha; Esaote, Genoa, Italy) was conducted before starting the program and within 1 week after completing the program.
- Blood samples (fasting): red and white blood cell count, hemoglobin concentration, reticulocytes, serum total and high-density lipoprotein 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.
- SAQ[13]

The CTRL group entered our study after completing a standard rehabilitation program, so their baseline values were those measured after the rehabilitation program. Participants in the CTRL group were not assessed before entering the standard 8-week rehabilitation program.

All assessments were repeated 3 days (range, 2–5 days) after completion of the IHHT program (or sham-IHHT in the CTRL group). The IHHG was also assessed at 1-month follow-up to allow for comparison at 1-month follow-up with CTRL group, as the post–sham-IHHT treatment in the CTRL group coincided with the 1-month follow-up after the end of the standard rehabilitation program). None of the participants in both groups were allowed to exercise during the IHHT or sham-IHHT.

2.5 | Data analysis

Statistical analyses were performed using SAS statistical software version 9.3 for windows (SAS Institute Inc., Cary, NC). All data are reported as mean ± standard deviation, and statistical significance was set at $P < 0.05$. Wilcoxon matched-pairs signed rank test was used to compare values before and following the IHHT program in the IHHG using repeated measures 1-way analysis of variance (ANOVA). Additionally, comparisons were performed between the IHHG vs CTRL group within 1 week after the end of their respective treatments and at 1-month follow-up (repeated measures 2-way ANOVA).

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 the World Health Organization* [2001]). Written informed consent was obtained from all participants.

3 | RESULTS

In the CTRL group, 19 participants (out of 27 recruited) made themselves available to be assessed at the end of the standard rehabilitation program (ie, before starting the sham-IHHT program). All of the patients in the IHHG completed the program (n = 27) and were tested before and after IHHT and at 1-month follow-up. Characteristics of the participants are shown in Table 1. The IHHG included more women, more participants with diabetes and more participants in NYHA functional class III.

TABLE 1 Participants' descriptive statistics

	IHHG, n = 27	CTRL, n = 19
Males n (%)	9 (33%)	9 (47%)
Average age, y (range)	63.9 (52–77)	63.2 (43–83)
Body mass, kg	81.6 ± 13.9	79.1 ± 12.5
Current smoker, 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%)
Paroxismal AF, n (%)	5 (18.5%)	2 (10.5%)
COPD, n (%)	2 (7.4%)	2 (10.5%)

Abbreviations: AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; CTRL, control group; FC, functional class NYHA; IHHG, intermittent hypoxia–hyperoxia training group; MI, myocardial infarction.

3.1 | Cardiovascular adaptations

The IHHG significantly improved cardiorespiratory fitness after IHHT (16.1 ± 4.2 vs 14.3 ± 4.2 mL O_2/min/kg), and values at 1-month follow-up were significantly higher than before the treatment. No differences were found after treatment and at the 1-month follow-up (16.1 ± 4.2 vs 15.4 ± 4.5 mL O_2/min/kg). SBP and DBP were also lower after treatment and at the 1-month follow-up. Table 2 shows all of the changes within the IHHG.

When compared to the CTRL group, the IHHG showed significantly higher blood pressure values (151 ± 19 mm Hg vs SBP 131 ± 18, DBP 85 ± 11 vs 78 ± 10 mm Hg), and lower aerobic capacity measured as VO_{2peak} (14.25 ± 4.2 vs 16.8 ± 3.9 mL O_2/min/kg) before IHHT/sham-IHHT. These findings were expected, as the control group included people who already completed their rehabilitation program. There were no differences between groups after their respective treatments and at the 1-month follow-up, except for cardiorespiratory fitness at 1-month follow-up that was significantly higher in the CTRL group, and for angina as a reason to stop exercising at the 1-month follow-up that was reported by a smaller number of IHHG participants compared to the CTRL group (3/27 vs 6/19).

Table 3 summarizes comparisons between groups at the end of the treatments and after the 1-month follow-up.

3.2 | Blood biochemistry

In the IHHG, hemoglobin and glycemia were unchanged after IHHT, but glycemia was significantly lower at the 1-month follow-up. Total cholesterol and low-density lipoprotein (LDL) were lower after IHHT, and total cholesterol at the 1-month follow-up showed values similar to pretreatment (Table 4).

Reticulocytes were significantly higher in the IHHG compared to the CTRL group at the end of treatment and at 1-month follow-up. Total cholesterol and LDL were lower at the end of treatments. Glycemia was similar in the IHHG and CTRL group at both measurement times. Table 5 shows the comparison between IHHG and CTRL for all the measured metabolic variables.

3.3 | Quality of life

Indicators of quality of life according to the SAQ (physical limitation, angina stability, angina frequency, treatment satisfaction, and disease perception) in the IHHG are reported in Table 6. A statistically significant improvement after IHHT and at 1-month follow-up as well is shown. Table 7 summarizes comparison between the IHHG and CTRL group; no differences between groups at the end of treatments and at 1-month follow-up were found.

3.4 | Safety

No severe adverse effects occurred during the study period in both groups. Dyspnea, palpitations, dizziness, and headache were experienced by 4 individuals in HHG participants during the first 2 to 5 sessions. These symptoms disappeared after increasing the inhaled O_2 concentration without interrupting the hypoxia–hyperoxia session. Angina attacks (without electrocardiogram

TABLE 2 Cardiopulmonary and hemodynamics variables in the IHHG before, after IHHT, and at 1-month follow-up

	Before	After Treatments	1-Month Follow-up
Angina as a reason to stop test, n (%)	12 (44.4%)	6 (22.2%)[1]	3 (11.1%)[2,3]
Exercise time, s, modified Bruce, n = 13	354 ± 194	383 ± 141	395 ± 130[2]
Exercise time, s, Bruce, n = 14)	280 ± 126	295 ± 79	332 ± 113[2]
VO_{2peak}, mL O_2/min/kg	14.3 ± 4.2	16.1 ± 4.2[1]	15.4 ± 4.5[2]
SBP, mm Hg	151 ± 19	130 ± 13[1]	129 ± 11[2]
DBP, mm Hg	85 ± 11	73 ± 7[1]	75 ± 9[2]
Heart rate at rest, bpm	71.5 ± 11.4	67.7 ± 8.3[1]	66.6 ± 10.0[2]
Heart rate maximum, bpm	122 ± 19	120 ± 14[1]	116 ± 14[2]
Left ventricle ejection fraction, %	58.0 ± 6.2	62.6 ± 5.5[1]	61.6 ± 6.3[2]

Abbreviations: DBP, diastolic blood pressure; IHHG, IHHT group; IHHT, intermittent hypoxia–hyperoxia training; SBP, systolic blood pressure; VO_{2peak}, peak oxygen consumption.

P values <0.05 for differences between:

[1] Before and after IHHT.

[2] Before and at 1-month follow-up.

[3] After IHHT and at 1-month follow-up.

TABLE 3 Cardiopulmonary and hemodynamics variables comparison between the IHHG and CTRL group after treatments and at 1-month follow-up

	Group	After	1-month follow-up
Angina as a reason to stop test, n (%)	IHHG	6 (22.2%)	3 (11.1%)[1]
	CTRL	4 (21.1%)	6 (31.6%)
Exercise time, s, modified Bruce	IHHG (n = 13)	383 ± 141[2]	395 ± 130
	CTRL (n = 5)	280 ± 92	323 ± 64
Exercise time, s, Bruce	IHHT (n = 14)	295 ± 79	332 ± 113
	CTRL (n = 14)	335 ± 121	355 ± 96
VO_{2peak}, mL O_2/min/kg	IHHT	16.1 ± 4.2	15.4 ± 4.5[1]
	CTRL	16.8 ± 3.9[3]	17.8 ± 4.9
SBP, mm Hg	IHHT	130 ± 13	129 ± 11
	CTRL	131 ± 18	131 ± 17
DBP, mm Hg	IHHT	73 ± 7	75 ± 9
	CTRL	78 ± 10	79 ± 10
Heart rate at rest, bpm	IHHT	67.7 ± 8.3	66.6 ± 10.0
	CTRL	68.9 ± 9.6	66.8 ± 10.2
Heart rate maximum, bpm	IHHT	120 ± 14	116 ± 14
	CTRL	124 ± 13	119 ± 17
Left ventricle ejection fraction %	IHHT	62.6 ± 5.5	61.6 ± 6.3
	CTRL	62.2 ± 7.2	61.3 ± 6.0

Abbreviations: CTRL, control; HHG, IHHT group; IHHT, intermittent hypoxia–hyperoxia training.

[1] *P* values <0.05 for differences between IHHG and CTRL at 1-month follow-up.

[2] *P* values <0.05 for differences between IHHG and CTRL after their treatments.

[3] *P* values <0.05 for differences within CTRL after standard rehabilitation and after sham IHHT.

abnormalities) occurred in only 6 out of 408 IHHT sessions (only during hypoxia exposure in 3 patients). No other problems were reported by the participants.

4 | DISCUSSION

Our results show that after 15 daily sessions of IHHT, cardiopulmonary fitness was significantly improved as the values of VO_{2peak} were significantly higher than those measured at baseline. These value are not likely to be clinically meaningful, as their magnitude is around 0.5 metabolic equivalents, but they show that improving cardiopulmonary fitness without exercising is feasible in patients with very low baseline values and comorbidities. 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. Our results are aligned with previous studies on intermittent hypoxia–normoxia exposure in different forms: intermittent hypoxia training (breathing

TABLE 4 Hematological and metabolic variables in the IHHG before, after IHHT, and at 1-month follow-up

	Before	After Treatments	1-Month Follow-up
Hemoglobin, g/L	134 ± 12	136 ± 13	136 ± 12
Reticulocytes, %	9.0 ± 5.5	11.3 ± 6.2[1]	9.2 ± 4.8[2]
TCh, mmol/L	5.6 ± 1.4	5.1 ± 1.2[1]	5.5 ± 1.4[2]
LDL (LDL), mmol/l	3.5 ± 1.2	3.2 ± 0.9[1]	2.6 ± 1.3[2,3]
Atherogenic index, (TCh − HDL)/HDL	4.7 ± 1.8	3.4 ± 1.3[1]	3.5 ± 1.5[3]
Glucose, mmol/L	7.10 ± 2.3	6.45 ± 1.7	6.18 ± 1.7[3]

Abbreviations: HDL, high-density lipoprotein; IHHG, IHHT group; IHHT, intermittent hypoxia–hyperoxia training; LDL, low-density lipoprotein; TCh, total cholesterol.

P values <0.05 for differences between:

[1] Before and after IHHT.

[2] After and at 1-month follow-up.

[3] Before and at 1-month follow-up.

TABLE 5 Hematological and metabolic variables comparison between the IHHG and CTRL group after treatments and at 1-month follow-up

	Group	After Treatments	1-Month Follow-up
Hemoglobin, g/L	IHHG	136 ± 13	136 ± 12
	CTRL	145 ± 10	145 ± 10
Reticulocytes, %	IHHG	11.3 ± 6.2[1]	9.2 ± 4.8[2]
	CTRL	6.4 ± 3.6	5.11 ± 3.13
TCh, mmol/L	IHHG	5.1 ± 1.2[1]	5.5 ± 1.4
	CTRL	5.5 ± 0.9	5.6 ± 1.0
LDL, mmol/L	IHHG	3.2 ± 0.9[1]	2.6 ± 1.3[2]
	CTRL	3.6 ± 0.8	3.5 ± 0.8
Atherogenic index (TCh − HDL)/HDL	IHHG	3.4 ± 1.3[1]	3.5 ± 1.5[2]
	CTRL	3.6 ± 1.1	3.4 ± 1.0
Glucose, mmol/L	IHHG	6.45 ± 1.7	6.18 ± 1.7
	CTRL	5.83 ± 0.65	5.97 ± 0.68

Abbreviations: CTRL, control; HDL, high-density lipoprotein; IHHG, IHHT group; LDL, low-density lipoprotein; TCh, total cholesterol.

[1] *P* values <0.05 for differences between IHHG and CTRL after their treatments.

[2] *P* values <0.05 for differences between IHHG and CTRL at 1-month follow-up.

[3] *P* values <0.05 for differences within CTRL after standard rehabilitation and after sham-IHHT.

TABLE 6 Quality of life in the IHHG before, after IHHT, and at 1-month follow-up

Seattle Angina Questionnaire	Before	After	1-Month Follow-up
Physical limitation	43.3 ± 17.7	51.6 ± 13.1[1]	53.7 ± 17.8[2]
Angina stability	56.5 ± 27.4	78.3 ± 23.3[1]	79.6 ± 22.7[2]
Angina frequency	59.6 ± 27.6	81.1 ± 17.9[1]	80.9 ± 18.2[2]
Treatment satisfaction	60.7 ± 16.2	77.4 ± 16.8[1]	80.5 ± 17.7[2]
Disease perception	47.2 ± 18.9	60.8 ± 17.8[1]	63.4 ± 17.4[2]

Abbreviations: IHHG, IHHT group; IHHT, intermittent hypoxia–hyperoxia training.

P values <0.05 for differences between:

[1] Before and after IHHT.

[2] Before and at 1-month follow-up.

[3] After and at 1-month follow-up.

hypoxic mixtures via a facial mask while resting/sitting) and training in hypoxia (continuous exposure to hypobaric or normobaric hypoxia while exercising). Both of these strategies have been shown to be effective in improving exercise tolerance and performance in athletes by triggering hematological and nonhematological adaptations,[14] and we found an increased number of reticulocytes after IHHT. Some authors have suggested that intermittent hypoxia can be useful to improve exercise performance in healthy people and CAD patients[5–7] and other authors have suggested a potential therapeutic role of intermittent hypoxia mainly based on improved hemodynamics and a more efficient respiration.[15] In fact, our results show that IHHT is associated with reduced SBP and DBP and improved left ventricular

TABLE 7 Quality-of-life comparison between IHHG and CTRL after treatments and at 1-month follow-up

Seattle Angina Questionnaire	Groups	After Treatments	1-Month Follow-up
Physical limitation	IHHG	51.6 ± 13.1	53.7 ± 17.8
	CTRL	51.6 ± 17.8	49.4 ± 18.6
Angina stability	IHHG	78.3 ± 23.3	79.6 ± 22.7
	CTRL	69.7 ± 27.1	72.4 ± 20.2
Angina frequency	IHHG	81.1 ± 17.9	80.9 ± 18.2
	CTRL	69.5 ± 32.7	75.3 ± 26.9
Treatment satisfaction	IHHG	77.4 ± 16.8	80.5 ± 17.7
	CTRL	77.7 ± 19.6	78.6 ± 19.7
Disease perception	IHHG	60.8 ± 17.8	63.4 ± 17.4
	CTRL	50.8 ± 24.2	56.1 ± 24.5

Abbreviations: CTRL, control; IHHG, intermittent hypoxia–hyperoxia training group.

[1] *P* values <0.05 for differences between IHHG and CTRL after their treatments.

[2] *P* values <0.05 for differences between IHHG and CTRL at 1-month follow-up.

[3] *P* values <0.05 for differences within CTRL after standard rehabilitation and after sham- IHHT.

ejection fraction. Some of the cited studies also provide experimental evidence of the mechanisms potentially involved in such adaptations, such as better autonomic nervous system balance, with reduction of the sympathetic drive, an improved endothelial function, and improved antioxidant responses.[10,15–17]

In our study we also found an improved lipid profile (total cholesterol, LDL, and atherogenic index), and this finding is in agreement with previously published studies, reviewed by Wee and Climstein in 2015,[18] providing "some evidence for using hypoxic training to improve total cholesterol and LDL." Further studies in this area are needed to clarify the mechanisms explaining such positive adaptations and how to better use hypoxia–hyperoxia exposure as therapeutic tool in dyslipidemias.

An interesting result worth further investigation in the future is that glycemia was unchanged after the program (7.10 ± 2.34 vs 6.45 ± 1.74 mmol/L, $P > 0.05$) but significantly improved at 1-month follow-up (6.18 ± 1.7 mmol/L, $P = 0.037$). The value of glycemia measured after IHHT at 1-month follow-up is significantly lower that the baseline value, but it failed to hit the target value suggested by European Association for the Study of Diabetes guidelines (6 mmol/L), despite showing a promising trend.

Finally, and probably the most relevant findings from a patient-centered point of view, a very important result of our study is provided by the SAQ administered to the IHHG; all of the quality-of-life–related aspects improved after IHHT, confirming previous results from IHT studies and providing support for this novel approach in terms of applicability and patients' compliance and satisfaction (Tables 6 and 7).

Some positive metabolic adaptations are similar to findings from a study investigating the effect of exercising at high altitude (hiking at 1700 m above sea level) in metabolic syndrome patients.[19] Adaptations of the cardiovascular system after IHHT are also similar to those seen after exercise as reviewed by Bruning et al,[20] with the autonomic nervous system and the endothelium likely to play major roles in the autoregulation and energetics processes preserving coronary blood flow.[21,22]

4.1 | Limitations

It is important to note the limitations to the present study. (1) The IHHG and CTRL group were not balanced in gender, comorbidities, and functional class; thus, data on performance and exercise tolerance may have been affected (against the IHHG). (2) We reported a comparison between groups (the IHHG vs CTRL group), but we could not measure the same variables in the CTRL group before their standard rehabilitation program, so we are not able to compare the effect size of IHHT to the current gold standard intervention. (3) The mechanisms triggered by IHHT were not investigated in the study, therefore limiting our ability to explain its efficacy.

5 | CONCLUSION

A novel modality of interval hypoxic–hyperoxic repeated exposure (IHHT) has been tested and found to be safe, convenient, and efficacious among cardiac patients. Our study showed that IHHT can improve exercise tolerance without exercising, and it is associated with a more protective cardiometabolic profile and superior quality of life. A methodologically stronger study (eg, groups being balanced at baseline, same duration of intervention, a superiority randomized controlled trial design to compare IHHT to standard rehabilitation) is needed to clarify the clinical relevance of this new approach. Further research is also needed to explain the mechanisms behind IHHT efficacy and to better tailor individual hypoxia–hyperoxia programs.

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