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Intermittent systemic hypoxic–hyperoxic training for myocardial protection in patients undergoing coronary artery bypass surgery: first results from a single-centre, randomised controlled trial

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ABSTRACT

Background Although remote ischaemic preconditioning (RIP) provides protection against myocardial ischaemia and reperfusion injury during cardiac surgery, it is not widely used. Systemic intermittent hypoxic–hyperoxic training (IHHT) may be a suitable alternative.

Methods This is a prospective, single-centre, randomised controlled trial. 127 patients with ischaemic heart disease and indication for coronary artery bypass graft (CABG) surgery from the Cardiology Clinic IM Sechenov First Moscow State Medical University were randomly assigned to IHHT, IHHT-control or RIP. Primary endpoint was serum concentration of troponin I and lactate 2 and 24 hours after surgery.

Results Median value for troponin I 24 hours after surgery was 1.068 (0.388–1.397) ng/mL in the IHHT group and was significantly lower compared with IHHT-controls with 1.980 (1.068–3.239) ng/mL (p=0.012) and to the RIP group with 1.762 (1.288–2.186) ng/mL (p=0.029), while there was no significant difference between RIP and the IHHT-control. Serum lactate after surgery was 1.74 (1.23–2.04) mmol/L in the IHHT group and was also significantly lower compared with IHHT-controls with 2.10 (1.80–2.29) mmol/L (p=0.045) and RIP with 2.12 (1.91–2.33) mmol/L (p=0.032). No significant complications or serious adverse events were observed during IHHT. Intraoperative and early postoperative complications did not differ significantly between groups.

Conclusions The results of this first trial using IHHT for myocardial protection against perioperative ischaemic myocardial injury in patients undergoing CABG surgery are promising and further larger trials should be done with adequate power to detect clinical rather than surrogate marker benefits.

Key messages

What is already known about this subject?

- There is no scientific evidence for the effects of systemic intermittent hypoxic–hyperoxic training as an alternative to remote ischaemic preconditioning for myocardial protection from injury by myocardial ischaemia and reperfusion during cardiac surgery.

What does this study add?

- The results of this first study evaluating safety and effectiveness of systemic intermittent hypoxic–hyperoxic training for myocardial protection from perioperative ischaemia and reperfusion injury during elective aortocoronary bypass surgery are promising. Further larger trials should be done with adequate power to evaluate safety and clinical benefits of this intervention

How might this impact on clinical practice?

- Systemic intermittent hypoxic–hyperoxic training may turn out to be a suitable alternative to remote ischaemic preconditioning for myocardial protection from ischaemia and reperfusion injury during elective aortocoronary bypass surgery.

INTRODUCTION

In cardiac and coronary artery bypass graft (CABG) surgery, adverse outcome is related to a great extent to perioperative myocardial injury.[1] Remote ischaemic preconditioning (RIP) by brief episodes of ischaemia and reperfusion in a remote vascular territory or organ has shown to provide perioperative myocardial protection and improved the prognosis of patients undergoing elective CABG surgery.[2 3] Furthermore, randomised controlled trials have shown decreased release of myocardial biomarkers after CABG surgery,[4] congenital cardiac and valve surgery.[5 6] However, despite its beneficial effects, RIP is not widely used. This is mainly

because beneficial effects are marginal and even controversial, and because the practicality of the intervention in the early phase of anaesthesia and immediately before surgery seems not to be very appealing. Therefore, RIP may not be a suitable intervention for widespread use under such conditions.

The purpose of this first randomised controlled trial was to evaluate the safety and efficacy of a systemic intermittent hypoxic–hyperoxic training (IHHT) for protection against myocardial injury from ischaemia and reperfusion during elective CABG surgery and to compare results with those of RIP and with those of an IHHT-control group.

METHODS

Study design and participants

This is a prospective, single-centre, randomised controlled trial. Patients were recruited consecutively during preadmission consultation at the IE Sechenov First Moscow State Medical University Cardiac Surgery Department. All patients had a diagnosis of coronary artery disease and indications for elective myocardial revascularisation by coronary artery bypass according to the 2014 European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines.[7] Exclusion criteria were additional surgeries planned simultaneously with CABG surgery, occlusive atherosclerotic disease of upper and lower limbs, acute coronary syndrome within 4 weeks before entry, coronary artery bypass without cardiopulmonary bypass, preoperative percutaneous coronary intervention and European heart surgery risk classification (EuroSCORE II) more than 4 including preoperative renal insufficiency (serum creatinine higher than 200 mmol/L) and other conditions that could potentially increase perioperative cTnI release. Lack of sufficient time from hospitalisation to surgery for a planned number of training sessions was another exclusion criterion.

The study conforms to the principles of the Declaration of Helsinki.

Randomisation and masking

Five days before the operation, patients were randomly assigned to three groups using a computer-generated randomisation table: two main groups (IHHT and RIP) and a IHHT-control group. No stratification factors were used and no block randomisation was applied.

Procedures

Patients in the IHHT group underwent four daily procedures of interval hypoxic–hyperoxic training before CABG surgery using a normobaric device to obtain hypoxic and hyperoxic gas mixtures (ReOxy Cardio; Aimediq S.A., Luxemburg).[8] Before the start of training, each patient underwent a hypoxic test to assess the individual response to hypoxia and to determine the rate of reduction of blood oxygen saturation (SpO_2) with a finger pulse oxymeter (Masimo SET, measurement accuracy ±2%). During 5 min, the patient received air with reduced oxygen content (12%) through a mask under constant monitoring of heart rate (HR) and SpO_2. As a safety measure, minimal SpO_2 was set at 82% and maximal accepted increase of HR was set to +50% of the initial HR. When these values were reached, the supply of oxygen automatically switched to a hyperoxic gas mixture (35%–40% O_2), inhaling of which was continued until SpO_2 reached 100% (even if SpO_2 was lower before the procedure), which, depending on the rate of saturation reduction, has taken 1 to 3 min (mean 1 min and 50 s). The intention was to create hyperoxic arterial oxygen tension and not simply to reduce the time required to recover from hypoxia. IHHT was considered successful if there were no significant side effects during the procedure such as angina pain, loss of consciousness, severe dizziness or other variants of significant subjective deterioration of the patient's condition. In case of successfully passing the test, patients proceeded to the basic IHHT training. During the training, the hypoxic gas mixture was given to the patient again in intermittent mode based on the individual test parameters and alternating with the supply of a hyperoxic gas mixture. One cycle of the procedure consisted of 'hypoxic' and 'hyperoxygenated' intervals, the duration of which was regulated automatically according to the biofeedback principle based on monitoring of individual values of SpO_2 and HR. Duration of the hypoxic period ranged from 3 to 5 min, and duration of the hyperoxic period was from 1 to 3 min, depending on the SpO_2 recovery rate. Total time of the hypoxic gas mixture inhalation during one procedure was 20–30 min. A final training was conducted on the evening before surgery.

Patients in the RIP group underwent RIP before induction of anaesthesia and skin incision. Three cycles of 10 min of ischaemia were applied to the right lower limb at the level of the upper third of the thigh by inflation of a blood pressure cuff to 200 mm Hg, followed by 10 min reperfusion while the cuff was deflated. The time from the end of the RIP procedure to the end of cardiopulmonary bypass (CPB) averaged 2 hours and 46 min, and only in three patients the period exceeded 3 hours. Maximum time was 3 hours and 20 min.

Patients in the IHHT-control group also underwent four daily procedures before surgery using 40 min training periods with simulation of IHHT by using the same equipment, whereas moistened air was delivered through the mask.

Only the person who conducted the training knew about the patient's allocation to a particular intervention group. Anaesthesiologists and cardiac surgeons had no access to this information.

At the time of enrolment, there were no differences between groups in resting HR, systolic and diastolic blood pressure. In the IHHT group, the inhalation period of the hypoxic gas mixture was accompanied by a temporary increase in HR (on average by 15%), but HR slowed down to the baseline level with SpO_2 normalisation.

The level of high-sensitivity troponin I was monitored in all patients immediately before, 2 and 24 hours after the operation and was measured using an immunoassay test set (Architect stat, 'Abbott') and an iMark photometer with a detection range of 0.01–40.00 ng/mL; reference range was 0–0.026 ng/mL. Also, the level of lactate in the venous blood was measured before and 24 hours after surgery by a blood gas analyser (RAPIDLab 1200 System; Siemens Healthcare, Erlangen, Germany). Creatinine and glomerular filtration rate were determined at baseline and frequently within the first 2 days of surgery, as per normal hospital procedure.

Episodes of cardiac arrhythmias, hypotension with a need for inotropic drug prescription, changes in ECG, pulse values and blood pressure levels were recorded during surgery and the postoperative period.

CABG surgery was performed by standard operative approach via median sternotomy under condition of CPB and antegrade cardioplegia (Consol; Custodiol Solutions) through the aortic root with permanent antegrade cerebral perfusion. The same scheme was used as an anaesthesia, including propofol, fentanyl, arduan (pipecuronium bromide) and diazepam. The duration of CPB did not differ between the three groups (56±14.8 min in the IHHT group, 61±15.9 min in the RIP group and 59±15.1 min in the control group). The aortic clamping time was also not significantly different: 42±7.3 min in the IHHT group, 45±8.4 min in the RIP group and 43±7.8 min in the control group. The adequacy of CPB was assessed by mean arterial pressure (60–80 mm Hg), central venous pressure (8–10 mm Hg), arterial blood gas and acid–base blood composition analysis.

Statistical analysis

Statistical analysis of the results was carried out using the SPSS Statistics software V.23.0. Kolmogorov-Smirnov test was performed to assess normal distribution. For variables with normal distribution, the data are represented as the mean and SD and for variables with a non-parametric distribution as median with IQRs (the values of 25th and 75th percentiles are indicated in parentheses). The main characteristics of the groups were compared using Kruskal-Wallis test for independent samples. Due to the non-parametric distributions for troponin and lactate values, the following tests were used: Mann-Whitney U test for pairwise comparison, the Kruskal-Wallis test for comparison of all three groups and Friedman two-way analysis of variance by ranks for repeated measures in order to determine differences in the dynamics of troponin I and lactate. Differences were considered significant at p value <0.05.

RESULTS

Of 356 patients screened for the trial, 127 patients were randomised to either systemic IHHT (40), remote RIP (40) or to the IHHT-control group (40), and were included into the final analysis (figure 1). Seven patients had to be excluded before the start of the intervention because they did not tolerate RIP during pre-intervention tests. EuroSCORE II was 1.27±1.12 in the IHHT group, 1.24±1.07 in the RIP group and 1.17±0.76 in the IHHT-control group.

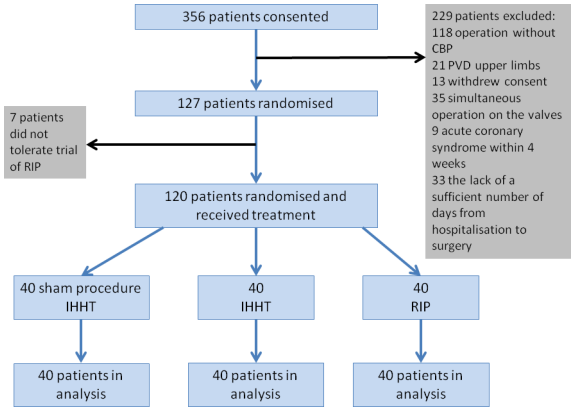

Figure 1 Trial profile. CPB, cardiopulmonary bypass; IHHT, intermittent hypoxic–hyperoxic training; PVD, peripheral vessel disease; RIP, remote ischaemic preconditioning.

Baseline and intraoperative characteristics (table 1) and preoperative drug therapy (table 2) did not differ between groups.

Significant complications and adverse reactions were not observed during hypoxic tests and IHHT. There were no episodes of angina pectoris, syncopal or presyncopal events. During the first procedures, some patients in the IHHT group had complaints of short-term unexpressed dizziness, which did not require interruption of the procedure. None of the patients refused further participation after the first procedure. Minimal values of SpO_2 were 85% on average; the lowest value of SpO_2 was 79%. The duration of the period during which SpO_2 decreased to less than 82% did not exceed 30 s. In the IHHT group, HR increased on average by 15% during the inhalation of the hypoxic gas mixture.

Incidence of adverse events was significantly higher in the RIP group: seven patients included in this group refused further participation in the study after the first procedure. All participants noted discomfort from mechanical pressure during inflation of the cuff at the thigh, which was the reason for most refusals to participate further. All patients had a feeling of numbness and tingling in the squeezed limb and showed pallor of the skin during the procedure. RIP was accompanied by pain of varying intensity almost in each patient (two patients refused to continue participating because of severe pain, but more often pain were modest and did not require interruption of the procedure).

The frequency of intraoperative and early postoperative complications during inpatient stay is shown in table 3.

One death was recorded and was due to intraoperative myocardial infarction with subsequent ventricular fibrillation and transition to asystole. There were two episodes of life-threatening arrhythmias (ventricular fibrillation), one of which resulted in the patient's death, whereas the

Table 1 Baseline characteristics

Characteristic	IHHT group (n=40), abs. (%)	RIP group (n=40), abs. (%)	Control group (n=40), abs. (%)	P values
Gender, male	30 (75%)	33 (82.5%)	31 (77.5%)	NS
Age, years	63±8.4	64±8.1	64±7.6	NS
HHB	38 (95%)	37 (92.5%)	37 (92.5%)	NS
DM type 2	11 (27.5%)	10 (25%)	10 (25%)	NS
Smoking	28 (70%)	31 (77.5%)	25 (62.5%)	NS
Angina pectoris, FC:				
II	12 (30%)	13 (32.5%)	12 (30%)	NS
III	15 (37.5%)	19 (47.5%)	17 (42.5%)	NS
IV	8 (20%)	5 (12.5%)	7 (17.5%)	NS
Silent myocardial ischaemia	5 (12.5%)	3 (7.5%)	4 (10%)	NS
Postinfarction cardiosclerosis	21 (52.5%)	20 (50%)	25 (62.5%)	NS
Coronary artery bypass/PCI in the medical history	7 (17.5%)	8 (20%)	6 (15%)	NS
Paroxysmal AF	5 (12.5%)	5 (12.5%)	6 (15%)	NS
COPD without respiratory failure	8 (20%)	11 (27.5%)	5 (12.5%)	NS
No of bypass grafts (median)	2.58±0.81	2.5±0.91	2.52±0.82	NS
1	3 (7.5%)	6 (15%)	4 (10%)	NS
2	16 (40%)	13 (32.5%)	15 (37.5%)	NS
3	16 (40%)	16 (40%)	17 (42.5%)	NS
4	5 (12.5%)	5 (12.5%)	4 (10%)	NS

ABS, absolute number of patients; AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; FC, functional class; HHB, hypertensive heart disease; IHHT, intermittent hypoxic–hyperoxic training; NS, no significant difference between all three groups; PCI, percutaneous coronary intervention; RIP, remote ischaemic preconditioning.

second one was successfully stopped by defibrillation. All of these events occurred in the control group. However, there were no significant intergroup differences due to the low number of complications.

The incidence of hypotension did not significantly differ between groups. There was a trend towards a decrease in the number of episodes with paroxysmal atrial fibrillation in the IHHT group compared with the other groups. Significant reductions in cognitive function (encephalopathy) requiring consultation by a neurologist were equally rare in both groups.

Table 2 Preoperative drug therapy

Drug class	IHHT group (n=40), abs. (%)	RIP group (n=40), abs. (%)	Control group (n=40), abs. (%)	P values
Antithrombotic drugs				
Aspirin	40 (100%)	37 (92.5%)	38 (95%)	NS
Clopidogrel	4 (10%)	6 (15%)	6 (15%)	NS
Statins	32 (80%)	34 (85%)	29 (72.5%)	NS
Beta-blockers	25 (62.5%)	25 (62.5%)	29 (72.5%)	NS
Calcium channel blockers	18 (45%)	17 (42.5%)	20 (50%)	NS
ACE inhibitors	26 (65%)	30 (75%)	23 (57.5%)	NS
ARB	8 (20%)	7 (17.5%)	4 (10%)	NS
Prolonged nitrates	7 (17.5%)	4 (10%)	8 (20%)	NS
Molsidomine	2 (5%)	1 (2.5%)	0	NS
Trimetazidine	4 (10%)	6 (15%)	3 (7.5%)	NS
Amiodarone	3 (7.5%)	5 (12.5%)	5 (12.5%)	NS

ARB, angiotensin II receptor blocker; IHHT, intermittent hypoxic–hyperoxic training; NS, no significant difference between all three groups; RIP, remote ischaemic preconditioning.

Table 3 Complications in patients in the IHHT, RIP and IHHT-control group

Complications	IHHT group (n=40), abs. (%)	RIP group (n=40), abs. (%)	Control group (n=40), abs. (%)	P values
Perioperative myocardial infarction	0	0	1 (2.5%)	NS
Death	0	0	1 (2.5%)	NS
Ventricular fibrillation	0	0	2 (5%)	NS
Hypotension (need for inotropic therapy)	7 (17.5%)	8 (20%)	9 (22.5%)	NS
Atrial fibrillation	8 (20%)	13 (32.5%)	12 (30%)	NS
Encephalopathy	2 (5%)	2 (5%)	3 (7.5%)	NS
Pericarditis	2 (5%)	4 (10%)	1 (2.5%)	NS
Hydrothorax (centesis)	3 (7.5%)	2 (5%)	3 (7.5%)	NS
ECG disorders				
ST depression	2 (5%)	3 (7.5%)	2 (5%)	NS
AV block 2nd degree	1 (2.5%)	0	2 (5%)	NS
Bundle branch block	1 (2.5%)	6 (15%)	5 (12.5%)	NS
Overall	22	38	39	NS

IHHT, intermittent hypoxic–hyperoxic training; NS, no significant difference between all three groups; RIP, remote ischaemic preconditioning.

There were three episodes of second-degree AV block (Mobitz type I and II) requiring the installation of a temporary pacemaker, but with restoration of atrioventricular node function during follow-up. Seven episodes of short-term ST depression were recorded. Totally, transient ECG changes during the operation were observed less frequently in the IHHT group than in the RIP and the IHHT-control group, but the differences were not significant.

Before and 2 hours after surgery, mean values of serum troponin I and serum lactate were not significantly different between groups (table 4). Twenty-four hours after surgery, statistically significant differences of serum troponin I values (median with IQRs) were found between the groups: median value of troponin I was 1.068 (0.388–1.397) in IHHT patients and significantly lower compared with 1.762 (1.288–2.186) ng/mL in RIP patients and 1.980 (1.068–3.239) ng/mL in the control group. Mean lactate values 24 hours after surgery were 1.74 (1.23–2.04) in the IHHT group and again significantly lower compared with 2.12 (1.91–2.33) mmol/L in RIP patients and 2.10 (1.80–2.29) mmol/L in the IHHT-control group (figure 2).

There was no evidence of an influence of IHHT or RIP on the length of stay in the intensive care unit (mean 1 day) and the duration of the overall inpatient stay (mean 6 days).

DISCUSSION

This study shows for the first time in a randomised controlled trial that IHHT may be effective to protect myocardium against perioperative myocardial injury during elective aortocoronary bypass surgery. Furthermore, IHHT was better tolerated than RIP if performed before anaesthesia. Troponin I levels as biomarker for myocardial injury were statistically significantly lower with IHHT compared with RIP and IHHT-controls. No significant complications were observed during IHHT.

Effects of hypoxia

Studies of adaptation mechanisms of the human body to the effects of hypoxia started in the first half of the 20th century and have been mainly performed by scientists of the former USSR (Sirotinin NN 1931, Barbashova ZI 1942, Vasilyeva PV 1967, Meerson FZ 1973). They found

Table 4 P values for differences of troponin I and serum lactate between groups

Comparable groups		Troponin I before surgery	Troponin I 2 hours after surgery	Troponin I 24 hours after surgery	Lactate after surgery
All three groups		0.504	0.739	0.023	0.047
IHHT	RIP	0.304	0.518	0.029	0.032
IHHT	Control group	0.341	0.891	0.012	0.045
RIP	Control group	0.943	0.494	0.675	0.856

IHHT, intermittent hypoxic–hyperoxic training; RIP, remote ischaemic preconditioning.

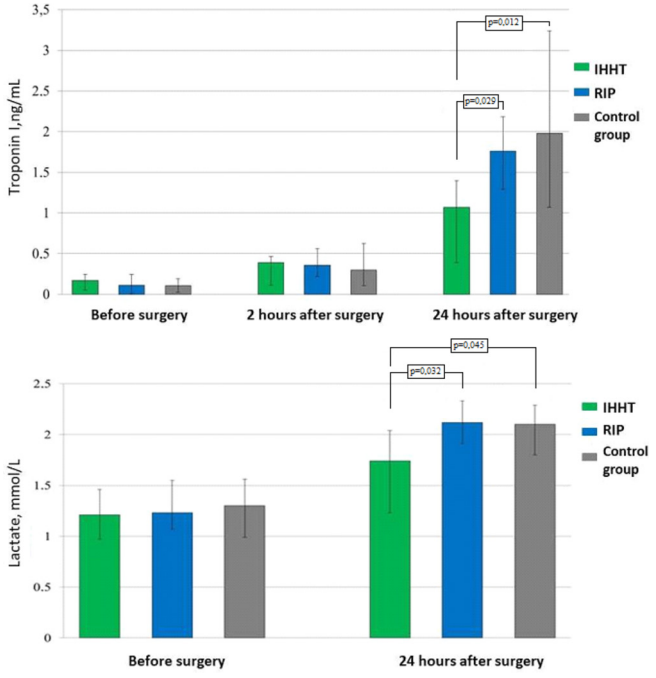

figure 2 Median values for troponin I and lactate before, 2 and 24 hours after surgery in patients with intermittent hypoxic–hyperoxoc training (IHHT), remote ischaemic preconditioning (RIP) and IHHT-controls.

that short-term exposure to mild hypoxia leads to functional and metabolic changes of the organism, which enhances its adaptation to hypoxia and also carries a wide range of protective properties.[9] Although the exact mechanism of adaptation is not fully understood, it is known that one of the key mechanisms triggering adaptive responses to hypoxia is the induction of reactive oxygen species (ROS), which in turn promotes the activation of a number of protective mechanisms: antioxidant defence, anti-inflammatory potential and initiation of redox signalling.[10 11]At the same time, energy efficiency of metabolic processes is improved and transport of oxygen into cell increases.[12 13] There are data on the effectiveness of the use of normobaric hypoxic training to prevent complications in cardiac surgery.[12 14] However, the formation of sustainable adaptive protection using these methods requires a long time (3–5 weeks), which seriously limits the possibility of their use in clinical practice. Further studies have shown that interval hypoxic training can be improved by replacing normoxic pauses (re-oxygenation) by giving the patient a hyperoxic gas mixture, which led to the method of interval hypoxic–hyperoxic training.[10 15] Induction of ROS occurs at the beginning of re-oxygenation when the supplied gas mixture is switched from hypoxic to normoxic. By using consecutive hypoxic and hyperoxic instead of normoxic stimuli during training, ROS-induced signals may be reinforced without further deepening hypoxia. The rationale of such an approach is supported by the results of a study on the effectiveness of IHHT as a method to increase exercise tolerance in patients with stable coronary heart disease.[10 16 17]

Effects of RIP

The history of research of RIP to prevent myocardial injury during vascular surgery extends back several decades. There are two ways in which the protective effect extends from the zone of local limb ischaemia to the whole organism: the formation and release of a number of biologically active substances into the systemic blood, including adenosine, bradykinin, endorphins, nitric oxide, interleukin 1a and micro-RNA 144, and a sensory-neural pathway. In 2006, the first study showing the cardioprotective effect of RIP in human during surgery for valve prosthesis has been published.[5] However, results in regard to the potential of RPI to effectively protect the heart from ischaemic and reperfusion injury are controversial. Two major studies (RIPHeart and ERICCA) as well as several meta-analyses[18–20] did not reveal any significant protective effect by the use of RIP before isolated CABG or in combination with valve replacement. Limitations are mainly associated with the use of different anaesthesia protocols and with different variants of the procedure. There is evidence that the anaesthetic propofol, which is most often used during cardiac surgery (as also in our patients), may abolish or neutralise the benefits of RIP.[4 18 21 22] However, there is no definitive answer so far.[20] There are studies that failed to show significant differences between groups with different anaesthetics.[23] In a recent meta-analysis, no difference in the therapeutic effect of RIP was found when using propofol and volatile anaesthetics.[24] Keeping this in mind, we tried to avoid such a potential interaction and thus a negative impact of anaesthetics on the procedures of preconditioning. Therefore, we decided to conduct RIP prior to initial anaesthesia. Due to the 'early window' of preconditioning, we expected that the protective effect would be preserved for 2–3 hours after RIP, and according to some authors even up to 4 hours after RIP.[25] In our study, the time from the end of the RIP procedure until the end of CPB averaged 2 hours and 46 min, whereas only in three patients the period exceeded 3 hours with a maximum time of 3 hours and 20 min.

Furthermore, different authors used different limb selections or simultaneous application of several cuffs to different limbs to create local ischaemia. The upper limb has been used in the overwhelming majority of the last large studies and the procedure was carried out after the introduction of anaesthetics, which may reduce the effectiveness of the sensory-neural defense mechanism. In view of these results, we decided to use the lower extremity in our study (which has a much larger volume of muscle mass) and to perform the RIP procedure before the initiation of anaesthesia. This allowed to decrease the total anaesthesia time and to increase the potential of a stronger cardioprotective effect. In addition, it allowed blinding of anaesthesiologists and surgeons. This approach is also supported by results of a study of the late effect of RIP ('second' protective window of preconditioning), during which local ischaemia was

created without the preliminary use of anaesthetics resulting in a significant reduction of the level of postoperative troponin.[26]

Safety of ischaemic preconditioning

The issue of safety of hypoxia in patients with ischaemic heart disease is of concern. There is a risk of provoking serious myocardial ischaemia with or without angina symptoms. However, this problem can be avoided to a great extent by performing a hypoxic test prior to the IHHT and by constant monitoring of oxygen saturation during the procedure. In case of a decrease of oxygen saturation of the blood below the predefined safety level, a switch to the supply of a hyperoxic gas mixture is done immediately. This may allow the patient's body to remain within the 'zone of incomplete compensation', which can trigger adaptation processes but does not lead to irreversible myocardial ischaemia.

It has to be noted that lactate levels after surgery were lower in patients who received training with IHHT, while lactate value in patients of the RIP group did not differ from those of the IHHT-control group. Lactate concentration in the blood increases in case of deficiency of oxygen supply to the tissues of the body. A relationship between the duration of cardiac arrest and increase of lactate in patients surviving paroxysmal ventricular fibrillation has been shown.[27] In many studies, a direct correlation between the lactate level and mortality has been demonstrated in patients admitted to the intensive care unit irrespective of the diagnosis.[28] Metabolic processes in cardiomyocytes change under conditions of ischaemia, the role of free fatty acids in the synthesis of ATP increases and, in parallel, the consumption of glucose decreases, and the heart turns from the consumer of lactate into its source.[29] Thus, the energy efficiency of cellular metabolism decreases, intracellular acidosis increases and - as a result - the cardiac function progressively worsens. Normalization of metabolic processes in cardiomyocytes and optimisation of glucose use is an effective mechanism of cardioprotection in conditions of hypoperfusion. However, lactate may originate from different sources and both IHHT and RIP are systemic and not only local protective procedures.

Although the number of complications did not differ significantly between the three groups, the level of troponin was significantly lower in the IHHT group 24 hours after surgery compared with the other groups, whereas the value of troponin did not differ between the RIP and the IHHT-control group.

The absence of significant side effects and of patient refusals to perform IHHT should be noted. Performance of RIP without prior anaesthesia was accompanied by severe discomfort and was poorly tolerated. This led to the refusal of seven patients to participate in the study.

Study limitations

Although large, this was a single-centre trial and it was only powered adequately to analyse prospectively a surrogate cardiac biomarker which is cTnI. Future larger studies should be performed with adequate power to detect clinical rather than surrogate benefits. Our approach using both RIP and controls with usual care as comparators may be questioned, and doing a future trial with two rather than with three groups would be preferable to maximise power. The number of patients is relatively small and does not allow firm conclusions in regard to rare but important safety events. Causal relations between cardioprotection and outcome remain speculative. Results are not applicable to critically ill and unstable patients. Results may have been influenced by differences in the time and numbers of application (four IHHT vs one RIP) and delayed versus early time windows. There is the possibility that ischaemia–reperfusion time was beyond the protective time window, at least in some cases. In regard to practical aspects, there may be barriers for the use of IHHT due to the fact that special equipment and close monitoring are necessary for the intervention. Our results are restricted to patients with CABG surgery and have to be extrapolated to other types of cardiac surgery with caution. Furthermore, the use of IHHT training before cardiac surgery is restricted to patients with elective surgery.

CONCLUSIONS

For the first time, safety and effectiveness of intermittent hypoxic–hyperoxic training as a method of preconditioning and cardioprotection during CABG surgery with CPB are demonstrated in this randomised controlled clinical trial. Troponin dynamics indicate that patients in the IHHT group had less damage of myocardium in the postoperative period and they also showed a lower degree of serum lactate accumulation compared with RIP patients and IHHT-controls. The benefits of IHHT compared with RIP may be explained by a stronger systemic effect of hypoxia–hyperoxia on the patient's body compared with local ischaemia of an individual limb. Further studies are required to determine whether it is possible to protect both the heart and other organs from ischaemia/reperfusion injury by IHHT and larger trials should be done with adequate power to detect clinical rather than surrogate marker benefits.

Contributors DST: study design, research protocol, data collection, data analysis and interpretation, writing and final approval of the manuscript. PYK: study design, research protocol, final approval of manuscript. ALS: study design, research protocol, final approval of manuscript. OSG: study design, data analysis and interpretation, final approval of manuscript. RNK: study design, research protocol, final approval of manuscript. AIK: data collection, data analysis and interpretation, final approval of manuscript. LPS: data collection, data analysis, final approval of manuscript. EVI: data collection, data analysis, final approval of manuscript. YZ: study design, study protocol, final approval of manuscript. HS: data analysis and interpretation, writing and final approval of manuscript. DST, PYK, OSG, YZ and HS are all responsible for the overall content as guarantors.

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WILEY CLINICAL CARDIOLOGY

CLINICAL INVESTIGATIONS

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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openheart

Intermittent systemic hypoxic–hyperoxic training for myocardial protection in patients undergoing coronary artery bypass surgery: first results from a single-centre, randomised controlled trial

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ABSTRACT

Background Although remote ischaemic preconditioning (RIP) provides protection against myocardial ischaemia and reperfusion injury during cardiac surgery, it is not widely used. Systemic intermittent hypoxic–hyperoxic training (IHHT) may be a suitable alternative.

Methods This is a prospective, single-centre, randomised controlled trial. 127 patients with ischaemic heart disease and indication for coronary artery bypass graft (CABG) surgery from the Cardiology Clinic IM Sechenov First Moscow State Medical University were randomly assigned to IHHT, IHHT-control or RIP. Primary endpoint was serum concentration of troponin I and lactate 2 and 24 hours after surgery.

Results Median value for troponin I 24 hours after surgery was 1.068 (0.388–1.397) ng/mL in the IHHT group and was significantly lower compared with IHHT-controls with 1.980 (1.068–3.239) ng/mL (p=0.012) and to the RIP group with 1.762 (1.288–2.186) ng/mL (p=0.029), while there was no significant difference between RIP and the IHHT-control. Serum lactate after surgery was 1.74 (1.23–2.04) mmol/L in the IHHT group and was also significantly lower compared with IHHT-controls with 2.10 (1.80–2.29) mmol/L (p=0.045) and RIP with 2.12 (1.91–2.33) mmol/L (p=0.032). No significant complications or serious adverse events were observed during IHHT. Intraoperative and early postoperative complications did not differ significantly between groups.

Conclusions The results of this first trial using IHHT for myocardial protection against perioperative ischaemic myocardial injury in patients undergoing CABG surgery are promising and further larger trials should be done with adequate power to detect clinical rather than surrogate marker benefits.

Key messages

What is already known about this subject?

- There is no scientific evidence for the effects of systemic intermittent hypoxic–hyperoxic training as an alternative to remote ischaemic preconditioning for myocardial protection from injury by myocardial ischaemia and reperfusion during cardiac surgery.

What does this study add?

- The results of this first study evaluating safety and effectiveness of systemic intermittent hypoxic–hyperoxic training for myocardial protection from perioperative ischaemia and reperfusion injury during elective aortocoronary bypass surgery are promising. Further larger trials should be done with adequate power to evaluate safety and clinical benefits of this intervention

How might this impact on clinical practice?

- Systemic intermittent hypoxic–hyperoxic training may turn out to be a suitable alternative to remote ischaemic preconditioning for myocardial protection from ischaemia and reperfusion injury during elective aortocoronary bypass surgery.

INTRODUCTION

In cardiac and coronary artery bypass graft (CABG) surgery, adverse outcome is related to a great extent to perioperative myocardial injury.[1] Remote ischaemic preconditioning (RIP) by brief episodes of ischaemia and reperfusion in a remote vascular territory or organ has shown to provide perioperative myocardial protection and improved the prognosis of patients undergoing elective CABG surgery.[2 3] Furthermore, randomised controlled trials have shown decreased release of myocardial biomarkers after CABG surgery,[4] congenital cardiac and valve surgery.[5 6] However, despite its beneficial effects, RIP is not widely used. This is mainly

because beneficial effects are marginal and even controversial, and because the practicality of the intervention in the early phase of anaesthesia and immediately before surgery seems not to be very appealing. Therefore, RIP may not be a suitable intervention for widespread use under such conditions.

The purpose of this first randomised controlled trial was to evaluate the safety and efficacy of a systemic intermittent hypoxic–hyperoxic training (IHHT) for protection against myocardial injury from ischaemia and reperfusion during elective CABG surgery and to compare results with those of RIP and with those of an IHHT-control group.

METHODS

Study design and participants

This is a prospective, single-centre, randomised controlled trial. Patients were recruited consecutively during preadmission consultation at the IE Sechenov First Moscow State Medical University Cardiac Surgery Department. All patients had a diagnosis of coronary artery disease and indications for elective myocardial revascularisation by coronary artery bypass according to the 2014 European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines.[7] Exclusion criteria were additional surgeries planned simultaneously with CABG surgery, occlusive atherosclerotic disease of upper and lower limbs, acute coronary syndrome within 4 weeks before entry, coronary artery bypass without cardiopulmonary bypass, preoperative percutaneous coronary intervention and European heart surgery risk classification (EuroSCORE II) more than 4 including preoperative renal insufficiency (serum creatinine higher than 200 mmol/L) and other conditions that could potentially increase perioperative cTnI release. Lack of sufficient time from hospitalisation to surgery for a planned number of training sessions was another exclusion criterion.

The study conforms to the principles of the Declaration of Helsinki.

Randomisation and masking

Five days before the operation, patients were randomly assigned to three groups using a computer-generated randomisation table: two main groups (IHHT and RIP) and a IHHT-control group. No stratification factors were used and no block randomisation was applied.

Procedures

Patients in the IHHT group underwent four daily procedures of interval hypoxic–hyperoxic training before CABG surgery using a normobaric device to obtain hypoxic and hyperoxic gas mixtures (ReOxy Cardio; Aimediq S.A., Luxemburg).[8] Before the start of training, each patient underwent a hypoxic test to assess the individual response to hypoxia and to determine the rate of reduction of blood oxygen saturation (SpO_2) with a finger pulse oxymeter (Masimo SET, measurement accuracy ±2%). During 5 min, the patient received air with reduced oxygen content (12%) through a mask under constant monitoring of heart rate (HR) and SpO_2. As a safety measure, minimal SpO_2 was set at 82% and maximal accepted increase of HR was set to +50% of the initial HR. When these values were reached, the supply of oxygen automatically switched to a hyperoxic gas mixture (35%–40% O_2), inhaling of which was continued until SpO_2 reached 100% (even if SpO_2 was lower before the procedure), which, depending on the rate of saturation reduction, has taken 1 to 3 min (mean 1 min and 50 s). The intention was to create hyperoxic arterial oxygen tension and not simply to reduce the time required to recover from hypoxia. IHHT was considered successful if there were no significant side effects during the procedure such as angina pain, loss of consciousness, severe dizziness or other variants of significant subjective deterioration of the patient's condition. In case of successfully passing the test, patients proceeded to the basic IHHT training. During the training, the hypoxic gas mixture was given to the patient again in intermittent mode based on the individual test parameters and alternating with the supply of a hyperoxic gas mixture. One cycle of the procedure consisted of 'hypoxic' and 'hyperoxygenated' intervals, the duration of which was regulated automatically according to the biofeedback principle based on monitoring of individual values of SpO_2 and HR. Duration of the hypoxic period ranged from 3 to 5 min, and duration of the hyperoxic period was from 1 to 3 min, depending on the SpO_2 recovery rate. Total time of the hypoxic gas mixture inhalation during one procedure was 20–30 min. A final training was conducted on the evening before surgery.

Patients in the RIP group underwent RIP before induction of anaesthesia and skin incision. Three cycles of 10 min of ischaemia were applied to the right lower limb at the level of the upper third of the thigh by inflation of a blood pressure cuff to 200 mm Hg, followed by 10 min reperfusion while the cuff was deflated. The time from the end of the RIP procedure to the end of cardiopulmonary bypass (CPB) averaged 2 hours and 46 min, and only in three patients the period exceeded 3 hours. Maximum time was 3 hours and 20 min.

Patients in the IHHT-control group also underwent four daily procedures before surgery using 40 min training periods with simulation of IHHT by using the same equipment, whereas moistened air was delivered through the mask.

Only the person who conducted the training knew about the patient's allocation to a particular intervention group. Anaesthesiologists and cardiac surgeons had no access to this information.

At the time of enrolment, there were no differences between groups in resting HR, systolic and diastolic blood pressure. In the IHHT group, the inhalation period of the hypoxic gas mixture was accompanied by a temporary increase in HR (on average by 15%), but HR slowed down to the baseline level with SpO_2 normalisation.

The level of high-sensitivity troponin I was monitored in all patients immediately before, 2 and 24 hours after the operation and was measured using an immunoassay test set (Architect stat, 'Abbott') and an iMark photometer with a detection range of 0.01–40.00 ng/mL; reference range was 0–0.026 ng/mL. Also, the level of lactate in the venous blood was measured before and 24 hours after surgery by a blood gas analyser (RAPIDLab 1200 System; Siemens Healthcare, Erlangen, Germany). Creatinine and glomerular filtration rate were determined at baseline and frequently within the first 2 days of surgery, as per normal hospital procedure.

Episodes of cardiac arrhythmias, hypotension with a need for inotropic drug prescription, changes in ECG, pulse values and blood pressure levels were recorded during surgery and the postoperative period.

CABG surgery was performed by standard operative approach via median sternotomy under condition of CPB and antegrade cardioplegia (Consol; Custodiol Solutions) through the aortic root with permanent antegrade cerebral perfusion. The same scheme was used as an anaesthesia, including propofol, fentanyl, arduan (pipecuronium bromide) and diazepam. The duration of CPB did not differ between the three groups (56±14.8 min in the IHHT group, 61±15.9 min in the RIP group and 59±15.1 min in the control group). The aortic clamping time was also not significantly different: 42±7.3 min in the IHHT group, 45±8.4 min in the RIP group and 43±7.8 min in the control group. The adequacy of CPB was assessed by mean arterial pressure (60–80 mm Hg), central venous pressure (8–10 mm Hg), arterial blood gas and acid–base blood composition analysis.

Statistical analysis

Statistical analysis of the results was carried out using the SPSS Statistics software V.23.0. Kolmogorov-Smirnov test was performed to assess normal distribution. For variables with normal distribution, the data are represented as the mean and SD and for variables with a non-parametric distribution as median with IQRs (the values of 25th and 75th percentiles are indicated in parentheses). The main characteristics of the groups were compared using Kruskal-Wallis test for independent samples. Due to the non-parametric distributions for troponin and lactate values, the following tests were used: Mann-Whitney U test for pairwise comparison, the Kruskal-Wallis test for comparison of all three groups and Friedman two-way analysis of variance by ranks for repeated measures in order to determine differences in the dynamics of troponin I and lactate. Differences were considered significant at p value <0.05.

RESULTS

Of 356 patients screened for the trial, 127 patients were randomised to either systemic IHHT (40), remote RIP (40) or to the IHHT-control group (40), and were included into the final analysis (figure 1). Seven patients had to be excluded before the start of the intervention because they did not tolerate RIP during pre-intervention tests. EuroSCORE II was 1.27±1.12 in the IHHT group, 1.24±1.07 in the RIP group and 1.17±0.76 in the IHHT-control group.

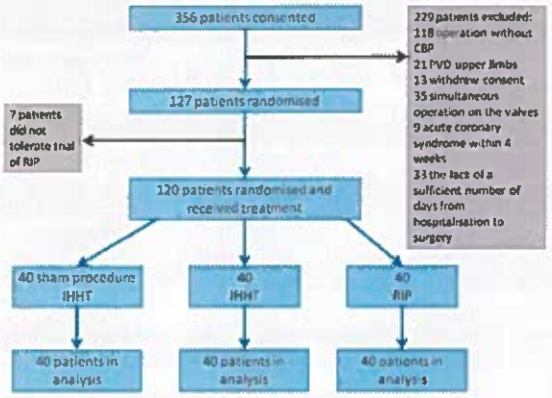

Figure 1 Trial profile. CPB, cardiopulmonary bypass; IHHT, intermittent hypoxic–hyperoxic training; PVD, peripheral vessel disease; RIP, remote ischaemic preconditioning.

Baseline and intraoperative characteristics (table 1) and preoperative drug therapy (table 2) did not differ between groups.

Significant complications and adverse reactions were not observed during hypoxic tests and IHHT. There were no episodes of angina pectoris, syncopal or presyncopal events. During the first procedures, some patients in the IHHT group had complaints of short-term unexpressed dizziness, which did not require interruption of the procedure. None of the patients refused further participation after the first procedure. Minimal values of SpO_2 were 85% on average; the lowest value of SpO_2 was 79%. The duration of the period during which SpO_2 decreased to less than 82% did not exceed 30 s. In the IHHT group, HR increased on average by 15% during the inhalation of the hypoxic gas mixture.

Incidence of adverse events was significantly higher in the RIP group: seven patients included in this group refused further participation in the study after the first procedure. All participants noted discomfort from mechanical pressure during inflation of the cuff at the thigh, which was the reason for most refusals to participate further. All patients had a feeling of numbness and tingling in the squeezed limb and showed pallor of the skin during the procedure. RIP was accompanied by pain of varying intensity almost in each patient (two patients refused to continue participating because of severe pain, but more often pain were modest and did not require interruption of the procedure).

The frequency of intraoperative and early postoperative complications during inpatient stay is shown in table 3.

One death was recorded and was due to intraoperative myocardial infarction with subsequent ventricular fibrillation and transition to asystole. There were two episodes of life-threatening arrhythmias (ventricular fibrillation), one of which resulted in the patient's death, whereas the

Table 1 Baseline characteristics

Characteristic	IHHT group (n=40), abs. (%)	RIP group (n=40), abs. (%)	Control group (n=40), abs. (%)	P values
Gender, male	30 (75%)	33 (82.5%)	31 (77.5%)	NS
Age, years	63±8.4	64±8.1	64±7.6	NS
HHB	38 (95%)	37 (92.5%)	37 (92.5%)	NS
DM type 2	11 (27.5%)	10 (25%)	10 (25%)	NS
Smoking	28 (70%)	31 (77.5%)	25 (62.5%)	NS
Angina pectoris, FC:				
II	12 (30%)	13 (32.5%)	12 (30%)	NS
III	15 (37.5%)	19 (47.5%)	17 (42.5%)	NS
IV	8 (20%)	5 (12.5%)	7 (17.5%)	NS
Silent myocardial ischaemia	5 (12.5%)	3 (7.5%)	4 (10%)	NS
Postinfarction cardiosclerosis	21 (52.5%)	20 (50%)	25 (62.5%)	NS
Coronary artery bypass/PCI in the medical history	7 (17.5%)	8 (20%)	6 (15%)	NS
Paroxysmal AF	5 (12.5%)	5 (12.5%)	6 (15%)	NS
COPD without respiratory failure	8 (20%)	11 (27.5%)	5 (12.5%)	NS
No of bypass grafts (median)	2.58±0.81	2.5±0.91	2.52±0.82	NS
1	3 (7.5%)	6 (15%)	4 (10%)	NS
2	16 (40%)	13 (32.5%)	15 (37.5%)	NS
3	16 (40%)	16 (40%)	17 (42.5%)	NS
4	5 (12.5%)	5 (12.5%)	4 (10%)	NS

ABS, absolute number of patients; AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; FC, functional class; HHB, hypertensive heart disease; IHHT, intermittent hypoxic–hyperoxic training; NS, no significant difference between all three groups; PCI, percutaneous coronary intervention; RIP, remote ischaemic preconditioning.

second one was successfully stopped by defibrillation. All of these events occurred in the control group. However, there were no significant intergroup differences due to the low number of complications.

The incidence of hypotension did not significantly differ between groups. There was a trend towards a decrease in the number of episodes with paroxysmal atrial fibrillation in the IHHT group compared with the other groups. Significant reductions in cognitive function (encephalopathy) requiring consultation by a neurologist were equally rare in both groups.

Table 2 Preoperative drug therapy

Drug class	IHHT group (n=40), abs. (%)	RIP group (n=40), abs. (%)	Control group (n=40), abs. (%)	P values
Antithrombotic drugs				
Aspirin	40 (100%)	37 (92.5%)	38 (95%)	NS
Clopidogrel	4 (10%)	6 (15%)	6 (15%)	NS
Statins	32 (80%)	34 (85%)	29 (72.5%)	NS
Beta-blockers	25 (62.5%)	25 (62.5%)	29 (72.5%)	NS
Calcium channel blockers	18 (45%)	17 (42.5%)	20 (50%)	NS
ACE inhibitors	26 (65%)	30 (75%)	23 (57.5%)	NS
ARB	8 (20%)	7 (17.5%)	4 (10%)	NS
Prolonged nitrates	7 (17.5%)	4 (10%)	8 (20%)	NS
Molsidomine	2 (5%)	1 (2.5%)	0	NS
Trimetazidine	4 (10%)	6 (15%)	3 (7.5%)	NS
Amiodarone	3 (7.5%)	5 (12.5%)	5 (12.5%)	NS

ARB, angiotensin II receptor blocker; IHHT, intermittent hypoxic–hyperoxic training; NS, no significant difference between all three groups; RIP, remote ischaemic preconditioning.

Table 3 Complications in patients in the IHHT, RIP and IHHT-control group

Complications	IHHT group (n=40), abs. (%)	RIP group (n=40), abs. (%)	Control group (n=40), abs. (%)	P values
Perioperative myocardial infarction	0	0	1 (2.5%)	NS
Death	0	0	1 (2.5%)	NS
Ventricular fibrillation	0	0	2 (5%)	NS
Hypotension (need for inotropic therapy)	7 (17.5%)	8 (20%)	9 (22.5%)	NS
Atrial fibrillation	8 (20%)	13 (32.5%)	12 (30%)	NS
Encephalopathy	2 (5%)	2 (5%)	3 (7.5%)	NS
Pericarditis	2 (5%)	4 (10%)	1 (2.5%)	NS
Hydrothorax (centesis)	3 (7.5%)	2 (5%)	3 (7.5%)	NS
ECG disorders				
ST depression	2 (5%)	3 (7.5%)	2 (5%)	NS
AV block 2nd degree	1 (2.5%)	0	2 (5%)	NS
Bundle branch block	1 (2.5%)	6 (15%)	5 (12.5%)	NS
Overall	22	38	39	NS

IHHT, intermittent hypoxic–hyperoxic training; NS, no significant difference between all three groups; RIP, remote ischaemic preconditioning.

There were three episodes of second-degree AV block (Mobitz type I and II) requiring the installation of a temporary pacemaker, but with restoration of atrioventricular node function during follow-up. Seven episodes of short-term ST depression were recorded. Totally, transient ECG changes during the operation were observed less frequently in the IHHT group than in the RIP and the IHHT-control group, but the differences were not significant.

Before and 2 hours after surgery, mean values of serum troponin I and serum lactate were not significantly different between groups (table 4). Twenty-four hours after surgery, statistically significant differences of serum troponin I values (median with IQRs) were found between the groups: median value of troponin I was 1.068 (0.388–1.397) in IHHT patients and significantly lower compared with 1.762 (1.288–2.186) ng/mL in RIP patients and 1.980 (1.068–3.239) ng/mL in the control group. Mean lactate values 24 hours after surgery were 1.74 (1.23–2.04) in the IHHT group and again significantly lower compared with 2.12 (1.91–2.33) mmol/L in RIP patients and 2.10 (1.80–2.29) mmol/L in the IHHT-control group (figure 2).

There was no evidence of an influence of IHHT or RIP on the length of stay in the intensive care unit (mean 1 day) and the duration of the overall inpatient stay (mean 6 days).

DISCUSSION

This study shows for the first time in a randomised controlled trial that IHHT may be effective to protect myocardium against perioperative myocardial injury during elective aortocoronary bypass surgery. Furthermore, IHHT was better tolerated than RIP if performed before anaesthesia. Troponin I levels as biomarker for myocardial injury were statistically significantly lower with IHHT compared with RIP and IHHT-controls. No significant complications were observed during IHHT.

Effects of hypoxia

Studies of adaptation mechanisms of the human body to the effects of hypoxia started in the first half of the 20th century and have been mainly performed by scientists of the former USSR (Sirotinin NN 1931, Barbashova ZI 1942, Vasilyeva PV 1967, Meerson FZ 1973). They found

Table 4 P values for differences of troponin I and serum lactate between groups

Comparable groups		Troponin I before surgery	Troponin I 2 hours after surgery	Troponin I 24 hours after surgery	Lactate after surgery
All three groups		0.504	0.739	0.023	0.047
IHHT	RIP	0.304	0.518	0.029	0.032
IHHT	Control group	0.341	0.891	0.012	0.045
RIP	Control group	0.943	0.494	0.675	0.856

IHHT, intermittent hypoxic–hyperoxic training; RIP, remote ischaemic preconditioning.

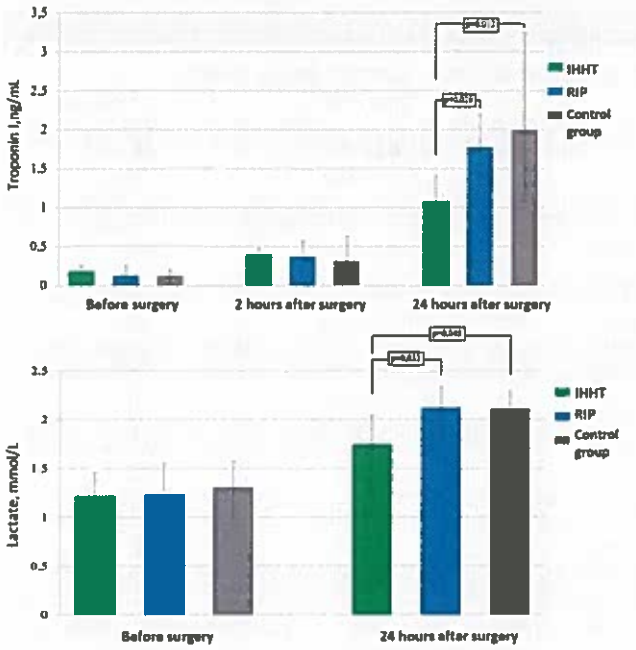

figure 2 Median values for troponin I and lactate before, 2 and 24 hours after surgery in patients with intermittent hypoxic–hyperoxoc training (IHHT), remote ischaemic preconditioning (RIP) and IHHT-controls.

that short-term exposure to mild hypoxia leads to functional and metabolic changes of the organism, which enhances its adaptation to hypoxia and also carries a wide range of protective properties.[9] Although the exact mechanism of adaptation is not fully understood, it is known that one of the key mechanisms triggering adaptive responses to hypoxia is the induction of reactive oxygen species (ROS), which in turn promotes the activation of a number of protective mechanisms: antioxidant defence, anti-inflammatory potential and initiation of redox signalling.[10 11] At the same time, energy efficiency of metabolic processes is improved and transport of oxygen into cell increases.[12 13] There are data on the effectiveness of the use of normobaric hypoxic training to prevent complications in cardiac surgery.[12 14] However, the formation of sustainable adaptive protection using these methods requires a long time (3–5 weeks), which seriously limits the possibility of their use in clinical practice. Further studies have shown that interval hypoxic training can be improved by replacing normoxic pauses (re-oxygenation) by giving the patient a hyperoxic gas mixture, which led to the method of interval hypoxic–hyperoxic training.[10 15] Induction of ROS occurs at the beginning of re-oxygenation when the supplied gas mixture is switched from hypoxic to normoxic. By using consecutive hypoxic and hyperoxic instead of normoxic stimuli during training, ROS-induced signals may be reinforced without further deepening hypoxia. The rationale of such an approach is supported by the results of a study on the effectiveness of IHHT as a method to increase exercise tolerance in patients with stable coronary heart disease.[10 16 17]

Effects of RIP

The history of research of RIP to prevent myocardial injury during vascular surgery extends back several decades. There are two ways in which the protective effect extends from the zone of local limb ischaemia to the whole organism: the formation and release of a number of biologically active substances into the systemic blood, including adenosine, bradykinin, endorphins, nitric oxide, interleukin 1a and micro-RNA 144, and a sensory-neural pathway. In 2006, the first study showing the cardioprotective effect of RIP in human during surgery for valve prosthesis has been published.[5] However, results in regard to the potential of RPI to effectively protect the heart from ischaemic and reperfusion injury are controversial. Two major studies (RIPHeart and ERICCA) as well as several meta-analyses[18–20] did not reveal any significant protective effect by the use of RIP before isolated CABG or in combination with valve replacement. Limitations are mainly associated with the use of different anaesthesia protocols and with different variants of the procedure. There is evidence that the anaesthetic propofol, which is most often used during cardiac surgery (as also in our patients), may abolish or neutralise the benefits of RIP.[4 18 21 22] However, there is no definitive answer so far.[20] There are studies that failed to show significant differences between groups with different anaesthetics.[23] In a recent meta-analysis, no difference in the therapeutic effect of RIP was found when using propofol and volatile anaesthetics.[24] Keeping this in mind, we tried to avoid such a potential interaction and thus a negative impact of anaesthetics on the procedures of preconditioning. Therefore, we decided to conduct RIP prior to initial anaesthesia. Due to the 'early window' of preconditioning, we expected that the protective effect would be preserved for 2–3 hours after RIP, and according to some authors even up to 4 hours after RIP.[25] In our study, the time from the end of the RIP procedure until the end of CPB averaged 2 hours and 46 min, whereas only in three patients the period exceeded 3 hours with a maximum time of 3 hours and 20 min.

Furthermore, different authors used different limb selections or simultaneous application of several cuffs to different limbs to create local ischaemia. The upper limb has been used in the overwhelming majority of the last large studies and the procedure was carried out after the introduction of anaesthetics, which may reduce the effectiveness of the sensory-neural defense mechanism. In view of these results, we decided to use the lower extremity in our study (which has a much larger volume of muscle mass) and to perform the RIP procedure before the initiation of anaesthesia. This allowed to decrease the total anaesthesia time and to increase the potential of a stronger cardioprotective effect. In addition, it allowed blinding of anaesthesiologists and surgeons. This approach is also supported by results of a study of the late effect of RIP ('second' protective window of preconditioning), during which local ischaemia was

created without the preliminary use of anaesthetics resulting in a significant reduction of the level of postoperative troponin.[26]

Safety of ischaemic preconditioning

The issue of safety of hypoxia in patients with ischaemic heart disease is of concern. There is a risk of provoking serious myocardial ischaemia with or without angina symptoms. However, this problem can be avoided to a great extent by performing a hypoxic test prior to the IHHT and by constant monitoring of oxygen saturation during the procedure. In case of a decrease of oxygen saturation of the blood below the predefined safety level, a switch to the supply of a hyperoxic gas mixture is done immediately. This may allow the patient's body to remain within the 'zone of incomplete compensation', which can trigger adaptation processes but does not lead to irreversible myocardial ischaemia.

It has to be noted that lactate levels after surgery were lower in patients who received training with IHHT, while lactate value in patients of the RIP group did not differ from those of the IHHT-control group. Lactate concentration in the blood increases in case of deficiency of oxygen supply to the tissues of the body. A relationship between the duration of cardiac arrest and increase of lactate in patients surviving paroxysmal ventricular fibrillation has been shown.[27] In many studies, a direct correlation between the lactate level and mortality has been demonstrated in patients admitted to the intensive care unit irrespective of the diagnosis.[28] Metabolic processes in cardiomyocytes change under conditions of ischaemia, the role of free fatty acids in the synthesis of ATP increases and, in parallel, the consumption of glucose decreases, and the heart turns from the consumer of lactate into its source.[29] Thus, the energy efficiency of cellular metabolism decreases, intracellular acidosis increases and - as a result - the cardiac function progressively worsens. Normalization of metabolic processes in cardiomyocytes and optimisation of glucose use is an effective mechanism of cardioprotection in conditions of hypoperfusion. However, lactate may originate from different sources and both IHHT and RIP are systemic and not only local protective procedures.

Although the number of complications did not differ significantly between the three groups, the level of troponin was significantly lower in the IHHT group 24 hours after surgery compared with the other groups, whereas the value of troponin did not differ between the RIP and the IHHT-control group.

The absence of significant side effects and of patient refusals to perform IHHT should be noted. Performance of RIP without prior anaesthesia was accompanied by severe discomfort and was poorly tolerated. This led to the refusal of seven patients to participate in the study.

Study limitations

Although large, this was a single-centre trial and it was only powered adequately to analyse prospectively a surrogate cardiac biomarker which is cTnI. Future larger studies should be performed with adequate power to detect clinical rather than surrogate benefits. Our approach using both RIP and controls with usual care as comparators may be questioned, and doing a future trial with two rather than with three groups would be preferable to maximise power. The number of patients is relatively small and does not allow firm conclusions in regard to rare but important safety events. Causal relations between cardioprotection and outcome remain speculative. Results are not applicable to critically ill and unstable patients. Results may have been influenced by differences in the time and numbers of application (four IHHT vs one RIP) and delayed versus early time windows. There is the possibility that ischaemia–reperfusion time was beyond the protective time window, at least in some cases. In regard to practical aspects, there may be barriers for the use of IHHT due to the fact that special equipment and close monitoring are necessary for the intervention. Our results are restricted to patients with CABG surgery and have to be extrapolated to other types of cardiac surgery with caution. Furthermore, the use of IHHT training before cardiac surgery is restricted to patients with elective surgery.

CONCLUSIONS

For the first time, safety and effectiveness of intermittent hypoxic–hyperoxic training as a method of preconditioning and cardioprotection during CABG surgery with CPB are demonstrated in this randomised controlled clinical trial. Troponin dynamics indicate that patients in the IHHT group had less damage of myocardium in the postoperative period and they also showed a lower degree of serum lactate accumulation compared with RIP patients and IHHT-controls. The benefits of IHHT compared with RIP may be explained by a stronger systemic effect of hypoxia–hyperoxia on the patient's body compared with local ischaemia of an individual limb. Further studies are required to determine whether it is possible to protect both the heart and other organs from ischaemia/reperfusion injury by IHHT and larger trials should be done with adequate power to detect clinical rather than surrogate marker benefits.

Contributors DST: study design, research protocol, data collection, data analysis and interpretation, writing and final approval of the manuscript. PYK: study design, research protocol, final approval of manuscript. ALS: study design, research protocol, final approval of manuscript. OSG: study design, data analysis and interpretation, final approval of manuscript. RNK: study design, research protocol, final approval of manuscript. AIK: data collection, data analysis and interpretation, final approval of manuscript. LPS: data collection, data analysis, final approval of manuscript. EVI: data collection, data analysis, final approval of manuscript. YZ: study design, study protocol, final approval of manuscript. HS: data analysis and interpretation, writing and final approval of manuscript. DST, PYK, OSG, YZ and HS are all responsible for the overall content as guarantors.

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Competing interests None declared.

Patient consent Obtained.

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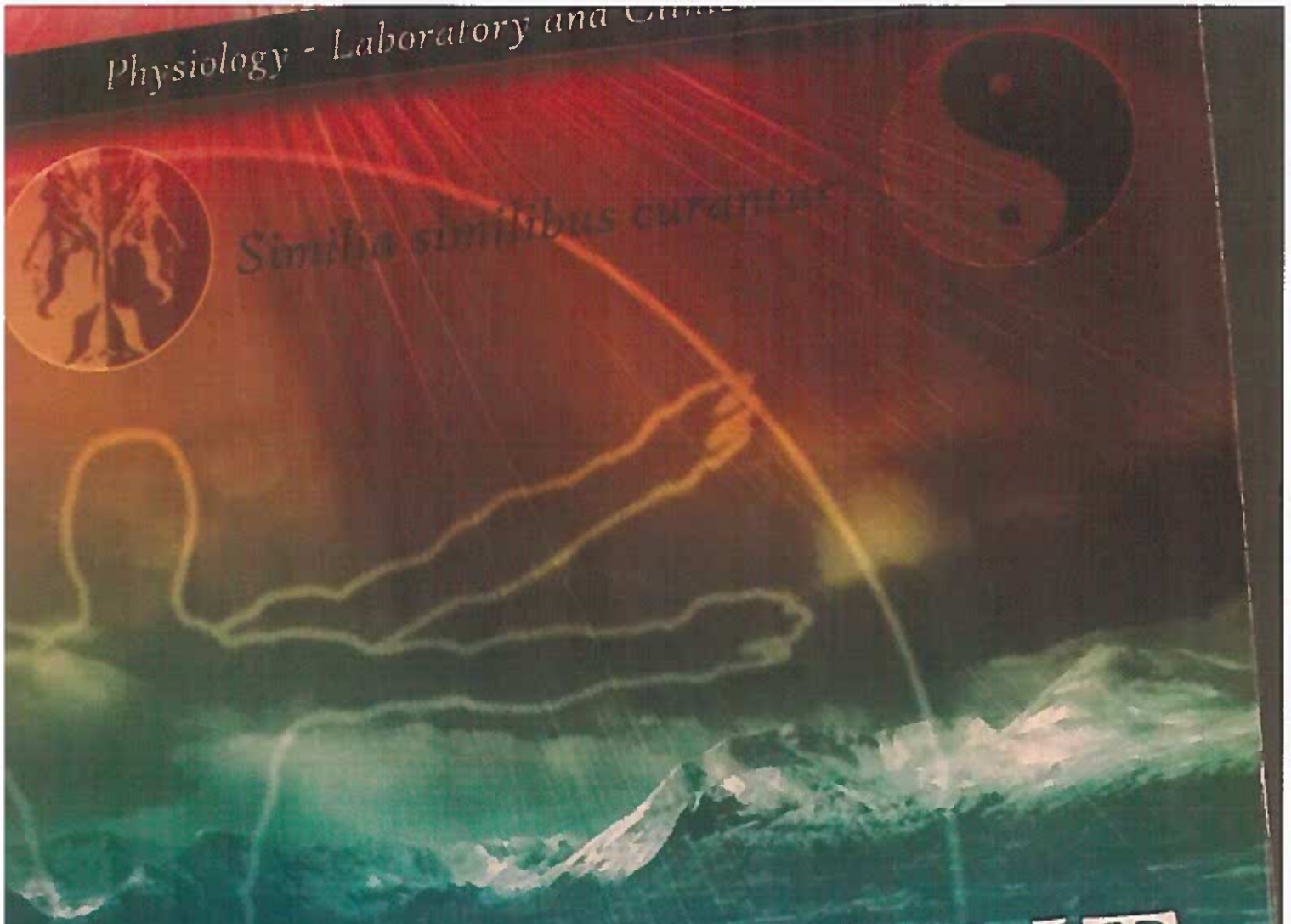

Intermittent Hypoxia

From Molecular Mechanisms to Clinical Applications

Lei Xi
Tatiana V. Serebrovskaya
Editors

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Professor John B. West (member, Institute of
ences of the U.S.; editor-in-chief, *High Altitude*
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Chapter 2

EFFECTS OF INTERMITTENT VERSUS CHRONIC HYPOXIA ON MYOCARDIAL ISCHEMIC TOLERANCE

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ABSTRACT

Hypoxia, or low supply of oxygen with respect to need, represents a critical risk factor that augments severity and impairs outcome of myocardial ischemia. However, systemic hypoxia is sometimes a cardioprotective rather than risk factor. Three different models of hypoxia can be distinguished, each with its own specific effects on myocardial tolerance to ischemia: chronic hypoxia, chronic hypoxia with aeration and intermittent hypoxia. Severe chronic hypoxia invariably leads to depressed myocardial tolerance to ischemia, but moderate chronic hypoxia may be considered as cardioprotective. Chronic hypoxia with aeration is almost always protective. The degree of protection afforded by intermittent hypoxia depends on many factors including time, severity and duration of the hypoxic challenge. Although the precise molecular background underlying such differential responses still needs to be worked out, some signaling pathways are being discussed, whose recruitment by one or more of the three models of hypoxia appears prominent in conferring protection against ischemia-reperfusion injury.

INTRODUCTION

The modern world faces high and increasing rates of cardiovascular diseases, which kill more citizens than cancer and until 2005 were the number one cause of death and disability in most Western countries. Cardiovascular diseases are often associated with myocardial ischemia, or insufficient supply of blood with respect to need. Several factors cooperate in determining the degree of the injury led by myocardial ischemia. They include the mode of

Today, it appears that exposure to hypoxia, especially CH, *decreases* the mitochondri content of muscle fibers and shifts the oxidative muscle metabolism towards higher relianc on carbohydrates as a fuel, with accumulation of lipofuscin, a mitochondrial degradatio product [Hoppeler et al., 2003]. Important regional variations have been observed in th various heart compartments, and the effect of 3-week CH on mitochondria morphometry an function is delayed in the right ventricle compared to left ventricle [Nouette-Gaulain et al 2005]. In PC12 cells harvested at varying FO_2 in the 0.01-0.1 range, hypoxia progressivel decreases mitochondrial DNA-encoded gene expression of complex I [Piruat et al., 2005].

CH increases transcription of mitochondrial CytOx subunits II and I, whereas th nuclear-encoded subunit CytOx-IV remains unchanged [Ripamonti et al., 2006]. By contras CHA does not induce appreciable changes with respect to normoxia [Ripamonti et al., 2006] In protective IH, the mitochondrial biogenesis regulatory program is activated [McLeod et al 2005]. Furthermore, opening the mitochondrial membrane transition pores is inhibited i isolated myocytes from the IH-treated animals, which lowers Ca^{2+} overload and prolongs th time taken to induce rigor contracture and cytochrome c release [Zhu et al., 2006].

HP improves tolerance to I/R by maintaining mitochondrial membrane potential [Yuan e al., 2005], indicative of increased capacity to produce ATP after I/R [Matsumoto-Ida et al. 2006; McLeod et al., 2004; Opie et al., 2002]. HP reduces apoptosis after exposure to severe anoxia, with concomitant increase in the antiapoptotic protein Bcl-2 [Lynn et al., 2007]. This explains the increased tolerance to myocardial I/R due to both increased bioenergetics and enhanced activity of mitochondrial K_{ATP} channels [Baker et al., 1997b; Eells et al., 2000; Kong et al., 2001].

Oxidative Stress

The extent of oxidative stress is crucial to understand the function of mi sensors. The basic hypothesis predicts that mi

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The Use of Simulated Altitude Techniques for Beneficial Cardiovascular Health Outcomes in Nonathletic, Sedentary, and Clinical Populations: A Literature Review.

Lizamore CA[1], Hamlin MJ[1].

Author information

Abstract

Lizamore, Catherine A., and Michael J. Hamlin. The use of simulated altitude techniques for beneficial cardiovascular health outcomes in nonathletic, sedentary, and clinical populations: A literature review. High Alt Med Biol 18:305-321, 2017.

BACKGROUND:

The reportedly beneficial improvements in an athlete's physical performance following altitude training may have merit for individuals struggling to meet physical activity guidelines.

AIM:

To review the effectiveness of simulated altitude training methodologies at improving cardiovascular health in sedentary and clinical cohorts.

METHODS:

Articles were selected from Science Direct, PubMed, and Google Scholar databases using a combination of the following search terms anywhere in the article: "intermittent hypoxia," "intermittent hypoxic," "normobaric hypoxia," or "altitude," and a participant descriptor including the following: "sedentary," "untrained," or "inactive."

RESULTS:

1015 articles were returned, of which 26 studies were accepted (4 clinical cohorts, 22 studies used sedentary participants). Simulated altitude methodologies included prolonged hypoxic exposure (PHE: continuous hypoxic interval), intermittent hypoxic exposure (IHE: 5-10 minutes hypoxic:normoxic intervals), and intermittent hypoxic training (IHT: exercising in hypoxia).

CONCLUSIONS:

In a clinical cohort, PHE for 3-4 hours at 2700-4200 m for 2-3 weeks may improve blood lipid profile, myocardial perfusion, and exercise capacity, while 3 weeks of IHE treatment may improve baroreflex sensitivity and heart rate variability. In the sedentary population, IHE was most likely to improve submaximal exercise tolerance, time to exhaustion, and heart rate variability. Hematological adaptations were unclear. Typically, a 4-week intervention of 1-hour-long PHE intervals 5 days a week, at a fraction of inspired oxygen (F_IO_2) of 0.15, was beneficial for pulmonary ventilation, submaximal exercise, and maximum oxygen consumption ([Formula: see text]O_{2max}), but an F_IO_2 of 0.12 reduced hyperemic response and antioxidative capacity. While IHT may be beneficial for increased lipid metabolism in the short term, it is unlikely to confer any additional advantage over normoxic exercise over the long term. IHT may improve vascular health and autonomic balance.

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The Effects of Intermittent Whole-Body Hypoxic Preconditioning on Patients with Carotid Artery Stenosis.

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Author information

Abstract

OBJECTIVE:

To study the effects of intermittent whole-body hypoxic preconditioning on patients with carotid artery stenosis.

METHODS:

Fifty patients with carotid artery stenosis were selected and randomly divided into a hypoxic intervention group (HIG) and a control group (CG). Both groups were treated with a hypoxic respiration device for 7 days (HIG: 18% oxygen, CG: 21% oxygen). Venous blood samples were taken preoperatively and postoperatively. The subjects' vital signs were recorded during and after the intervention. After the completion of the trial, the concentrations of hemoglobin, hypoxia inducible factor-1α, erythropoietin, vascular endothelial growth factor, neuron-specific enolase, S100β protein, brain-derived neurotrophic factor, serum aspartate transaminase, serum alanine aminotransferase, serum creatinine, and blood urea nitrogen were measured in the previously selected blood samples.

RESULTS:

During the intervention, the vital signs of the HIG were significantly different from those of the CG ($P < 0.05$). In the HIG, postoperative concentrations of hemoglobin, erythropoietin, hypoxia inducible factor-1α, and vascular endothelial growth factor were significantly more than the preoperative values ($P < 0.05$). In the CG, postoperative concentrations of neuron-specific enolase and S100β protein were more than the preoperative values ($P < 0.05$). The concentrations of brain-derived neurotrophic factor, serum aspartate transaminase, serum alanine aminotransferase, serum creatinine, and blood urea nitrogen showed no significant differences between their preoperative and postoperative values in either the HIG or the CG ($P > 0.05$).

CONCLUSIONS:

Intermittent hypoxic preconditioning can change the vital signs and hematologic indexes of patients with carotid artery stenosis without causing new postoperative complications or organ damage.