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Hypoxic Conditioning in Rehabilitation and Secondary Prevention Programs in Cardiac Patients with Multimorbidity: a Review

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ABSTRACT

INTORDUCTION. Patients with multiple chronic diseases are at higher risk of premature death, hospitalization, longer hospital stays, and reduced health-related quality of life compared to patients with a single disease. On the other hand, the presence of comorbid conditions limits the enrolment of traditional exercise-based cardiac rehabilitation programs. It is predicted that as life expectancy increases, the level of multimorbidity will increase, making it even more important to find new additional methods and technologies for the rehabilitation of cardiac patients with comorbidities.

AIM. To analyze the data from the current publications or to define the validity and effectiveness of using different hypoxic conditioning regimens in cardiac patients with concomitant chronic pathology (arterial hypertension, obesity, diabetes mellitus, and chronic bronchopulmonary diseases) as well as in multimorbid elderly patients.

MATERIAL AND METHODS. The search for relevant papers was carried out using the Medline, e-library, and Web of Science Core Collection databases, as well as the following keywords: "hypoxic conditioning", "hypoxic training", "hypoxic therapy", "interval hypoxic therapy", "intermittent hypoxia", "hypoxic conditioning", "interval hypoxia training", and "hypoxic exposure". The analysis included publications regarding the use of the hypoxic conditioning method in cardiac and elderly patients with multimorbid pathology, as well as publications on the use of the method in the rehabilitation of patients with certain nosologies to identify potential mechanisms in correcting bronchopulmonary violations and lipid and carbohydrate metabolism disorders. The last search date was April 05, 2022.

RESULTS. Most of the analyzed studies proved that the hypoxic conditioning technology in passive interval exposure regimes is an effective method for non-pharmacological correction of cardiometabolic risks in cardiac patients with multimorbid pathology and can increase exercise tolerance, optimize hemodynamic parameters (HR, SBP and DBP), reduce the manifestations of bronchial obstruction and respiratory failure, and improve cognitive function and metabolic indicators. Personalized physical activity doses in oxygen-depleted ambient air appear to be promising, but require additional studies to establish optimal application protocols.

CONCLUSION. The data presented may recommend hypoxic conditioning technologies for wider implementation in cardiac rehabilitation programs for patients with multimorbid pathologies.

KEYWORDS: Cardiac rehabilitation, comorbidity, hypoxic conditioning, interval hypoxic training

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Гипоксическое кондиционирование в программах реабилитации и вторичной профилактики кардиологических пациентов с коморбидной и мультиморбидной патологией: обзор

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РЕЗЮМЕ

ВВЕДЕНИЕ. У пациентов с множественными хроническими заболеваниями риск преждевременной смерти, госпитализации, длительного пребывания в стационаре и снижения качества жизни, связанного со здоровьем выше, чем у пациентов с одним заболеванием. С другой стороны, наличие коморбидных заболеваний ограничивает охват традиционными программами кардиологической реабилитации, основанными на физических упражнениях. Прогнозируется, что по мере увеличения продолжительности жизни уровень полиморбидности будет расти, что делает еще более важным поиск новых дополнительных методов и технологий для реабилитации кардиологических пациентов с сопутствующими заболеваниями.
ЦЕЛЬ. Проанализировать данные современных публикаций или определить обоснованность и эффективность использования различных режимов гипоксического кондиционирования у кардиологических пациентов с сопутствующей хронической патологией (артериальная гипертензия, ожирение, сахарный диабет и хронические бронхолегочные заболевания), а также пожилых пациентов с полиморбидными заболеваниями.
МАТЕРИАЛ И МЕТОДЫ. Поиск соответствующих работ проводился с использованием баз данных «Medline», «E-library» и «Core Collection» (Web of Science), а также следующих ключевых слов: "гипоксическое кондиционирование", "гипоксическая тренировка", "гипоксическая терапия", "интервальная гипоксическая терапия", "прерывистая гипоксия", "гипоксическое кондиционирование", "интервальная гипоксическая тренировка" и "гипоксическое воздействие". В анализ были включены публикации, касающиеся применения метода гипоксического кондиционирования у кардиологических и пожилых пациентов с полиморбидной патологией, а также публикации об использовании метода в реабилитации пациентов с определенными нозологиями для выявления потенциальных механизмов в коррекции бронхолегочных нарушений и нарушений липидного и углеводного обмена. Дата последнего поиска – 05 апреля 2022 года.
РЕЗУЛЬТАТЫ. Большинство проанализированных исследований показали, что технология гипоксического кондиционирования в режимах пассивного интервального воздействия является эффективным методом нефармакологической коррекции кардиометаболических рисков у кардиологических больных с полиморбидной патологией и позволяет повысить толерантность к физической нагрузке, оптимизировать гемодинамические параметры (ЧСС, SBP и DBP), уменьшить проявления бронхиальной обструкции и дыхательной недостаточности, улучшить когнитивные функции и метаболические показатели. Персонализированные дозы физической активности в обедненном кислородом окружающем воздухе представляются перспективными, но требуют дополнительных исследований для установления оптимальных протоколов применения.
ЗАКЛЮЧЕНИЕ. Представленные данные могут быть использованы для рекомендаций технологии гипоксического кондиционирования для более широкого внедрения в программы кардиологической реабилитации пациентов с полиморбидной патологией.

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INTRODUCTION

The problem of rehabilitation of cardiac patients with multimorbidity

Cardiac rehabilitation (CR) has proven to be beneficial in reducing mortality, improving quality of life and preventing rehospitalization associated with cardiovascular disease (CVD) [1]. However, the level of participation and adherence to CR programs remains extremely low [2].

CR programs have traditionally been "single-disease" programs focusing on the needs of patients with myocardial infarction (MI), and heart failure (HF) following cardiac and vascular surgery. Meanwhile, cardiac patients are increasingly suffering from two or more associated chronic diseases. According to an analysis by the British Heart Foundation National Audit of Cardiac Rehabilitation (NACR) Quality and Outcomes Report 2019, approximately 50% of the 6,502 patients receiving cardiac rehabilitation treatment had two or more comorbidities [3].

It is predicted that the level of multimorbidity will increase due to demographic changes (increased life expectancy and increased survival rates). It is important to note that patients with multiple chronic diseases are at higher risk of premature death, hospitalization, longer hospital stays and reduced quality of life compared to patients with a single disease [3].

On the other hand, the number of comorbid conditions, such as neurological disorders (stroke, paraplegia and gait disturbances), restrictive lung diseases, obesity, connective tissue diseases, musculoskeletal disorders and depression are often barriers to participation in traditional CR programs and increase the risk of dropping out of CR, since not all programs consider the needs and capabilities of patients with multimorbid pathology [3-6].

It should also be noted that in patients with CVD, many concomitant chronic conditions remain undiagnosed. This applies to diseases such as chronic obstructive pulmonary disease (COPD) and restrictive lung diseases, where symptoms like shortness of breath and reduced exercise tolerance “impersonate” cardiac pathology [5].

Thus, the increasing burden and complexity of multimorbidity makes it even more important to search for additional, novel methods and technologies for the rehabilitation of cardiac patients with both comorbid and concomitant pathologies.

AIM

To analyze the possibilities and effectiveness of hypoxic conditioning (interval hypoxic exposures at rest and physical activity in an oxygen-depleted ambient air) in rehabilitation programs for cardiac patients with comorbid and multimorbid pathologies. Previously, we provided data about the use of different protocols for interval hypoxic therapy in rehabilitation programs for patients with CVD, but without separate focus on comorbidities [7].

MATERIAL AND METHODS

The search for related works was carried out using the Medline, e-library, and Web of Science Core Collection databases, as well as the following keywords: “hypoxic conditioning”, “hypoxic training”, “hypoxic therapy”, “interval hypoxic therapy”, “intermittent hypoxia”, “hypoxic conditioning”, “interval hypoxia training”, and “hypoxic exposure”. Considering the results of recent clinical studies and individual experimental studies, we analyzed the data on the use of different modes of hypoxic conditioning in cardiac patients with the most commonly diagnosed conditions: arterial hypertension (AH), obesity, diabetes mellitus (DM) and chronic bronchopulmonary diseases, as well as in elderly patients, which contained data from controlled clinical trials, experimental studies explaining pathogenetic mechanisms, and systematic reviews through meta-analysis and publications review performed over the past 5 years. In the absence of studies of a specific nosology in the last 5 years, we included earlier studies. The analysis included publications regarding the use of the method in the previously mentioned areas in cardiac patients, as well as publications on the use of the method in individual nosologies to identify potential mechanisms in correcting bronchopulmonary violation, as well as lipid and carbohydrate metabolism disorder.

Abstracts of conferences and studies with incomplete data were excluded from the analysis. In accordance with the narrative style of this review, a search was also conducted for additional publications concerning the physiological mechanisms of hypoxic effects.

The results of the studies selected for analysis are summarized in Table 1 (see Appendix).

Hypoxic conditioning as a therapeutic factor

The therapeutic effect of air with reduced oxygen content can be understood from the works of Hippocrates, descriptions of Marco Polo’s mountain travels and other sources. Observations of the Andean population (~4260 m, FiO ~11%) indicate that coronary heart disease (CHD) and, in particular, myocardial infarctions are quite rare among residents living at high altitudes. In consecutive autopsy series, not a single case of MI or even CAD was found [8]. In Switzerland, age-standardized mortality rates (per 100,000 person-years) for coronary artery disease were significantly higher in men (289) and women (104) living below 300 m above sea level compared to men (242) and women (74) living at altitudes above 1500 m [9]. Burtscher pointed out that, from a biological point of view, it is the hypoxia-inducible factor (HIF)-mediated mechanisms that can contribute to the reduction of cardiovascular mortality in residents of medium-high mountainous areas [8]. Activation of the HIF protein family under the action of various stressors, particularly periodic hypoxia, is used to explain a wide range of hematological and other effects from the molecular to organ and systemic levels. In this case, the degree of tissue hypoxia related to the frequency of stress-stimulating effects and recovery/reoxygenation periods is not that much, which justifies the techniques of interval hypoxic exposure [10, 11].

The most commonly used protocols in clinical practice are interval hypoxic therapy at rest (IHT – hypoxia-normoxia regimen, IHHT – hypoxia-hyperoxia regimen) and physical training with individual doses in oxygen-deprived ambient air.

Hypoxic conditioning in arterial hypertension patients

A recently published systematic review analyzed available data on the effectiveness of incorporating IHT/IHT courses in the rehabilitation of patients with CVD [12]. Of the 320 patients included in the study, the vast majority were elderly patients with comorbid pathologies: CAD/CHF and AH. The analysis revealed a significant decrease in heart rate (MD = -5.35 bpm, $p = 0.006$), systolic blood pressure (SBP) (MD = -13.72, $p < 0.001$) mm Hg and diastolic blood pressure (DBP) (MD = -7.88 mm Hg, $p = 0.003$) in patients after a course of IHHT/IHT compared to the control group. Moreover, the course of hypoxic therapy has been shown to determine the trend towards lower total cholesterol and low-density lipoprotein (LDL) levels [12].

In 2019, Ignatenko et al. [13] comparatively analyzed the effect of two modes of hypoxic conditioning (IHT with timed dosing and IHHT with calculated procedural parameters based on individual sensitivity to hypoxia) on the clinical manifestations of ischemia and hypertensive syndrome in 219 patients with stable angina pectoris together with arterial hypertension. For the first time, this work evaluates the overall long-term (within one year) effectiveness of 4 courses of hypoxic training. The authors showed that the use of IHT/IHHT can potentiate the antihypertensive effect of the underlying drug therapy: the frequency of achieving the optimal blood pressure level was observed in 40% of patients receiving drug therapy, 50% of patients receiving a combination of drug therapy and IHT, and 63.4% of patients receiving a combination of drug therapy and IHHT. In the IHHT group, normalization of diurnal BP variability was achieved in 50.7% of patients. The antianginal effect of IHT/IHT techniques was manifested by a significant reduction in angina attacks and a lower incidence of painless myocardial ischemia [13].

In 2020, Muangritdech et al. [14] provided data from a randomized clinical trial (RCT) aimed at evaluating the effectiveness of two IHT regimens (at rest and in combination with exercise) in patients with grade I AH, who were regularly taking antihypertensive medications. The patients, who received antihypertensive drugs without any physical intervention, were in the control group. A significant decrease in SBP was found in both groups that received a course of IHT at rest (-12.0±8.0 mm Hg, P = 0.004 and -9.9±8.8 mm Hg, P = 0.028, mean±95%) and in combination with exercise (-13.0±7.8 mmHg, P = 0.002 and -10.0±8.4 mmHg, p = 0.016) on the 2nd and 28th day after the end of the intervention, respectively. Furthermore, these changes were accompanied by an increase in values of the nitric oxide metabolites NOx and HIF-1α, compared to the control group, as well as a significant increase in the distance covered during a 6-minute walk test [13].

The presented results confirm one of the proposed mechanisms to lower blood pressure by increasing the bioavailability of NO, which leads to vasodilation and a decrease in total peripheral resistance. Previously, similar results were obtained by Lyamina et al. [15]. The authors found that 20 daily sessions of IHT (FiO_2 – 0.10) increased NO synthesis and reduced BP to a level healthy for patients with stage I AH, while the decrease in BP persisted for at least 3 months.

Hypoxic conditioning and obesity

The World Health Organization (WHO) has recognized obesity as a new non-communicable "epidemic of the 21st century". According to the Russian epidemiological study ESSE-RF, the prevalence of obesity in various regions of Russia varies between 22.5% and 44.5%, when measured by BMI and between 43% and 67% in terms of waist circumference [16]. Obesity is an important risk factor for the development of cardiovascular diseases (CVD), being responsible for more than 23% of CAD cases and one of the leading risk factors for the development of fatal cardiovascular events. Obesity is closely associated with other risk factors (AH, dyslipidemia, physical inactivity, etc.) that affect the survival of cardiac patients, contributing to early disability and a decrease in both overall life expectancy and quality of life due to the development of concomitant diseases. Therefore, it is essential to correct metabolic disorders and BMI during CR.

Back in 2010, clinical studies were conducted to evaluate the effectiveness of IHHT in patients with metabolic syndrome (MS) who received basic therapy to resolve comorbidities without the use of drugs for correcting eating behaviour and body weight. A course of 15 IHHT procedures in passive mode alone or in combination with moderate systemic hyperthermia (one of the groups of patients received hypoxic conditioning procedures in combination with alpha-capsule) has been demonstrated to lead to a significant reduction in body weight, mainly due to a reduction in fat mass, accompanied by a decrease in the level of total cholesterol, LDL, optimization of BP, increased hypoxic resistance, physical endurance and improved psychological status [17].

In a review by New Zealand colleagues, Lizamore and Hamlin [18], based on their analysis of 22 studies involving subjects leading a sedentary lifestyle, showed that a 4-week course of IHT at rest improved submaximal exercise tolerance and reduced sympathetic predominance in the dynamics of heart rate variability parameters.

Results of one study conducted in 2020 at the University of Grenoble showed that in obese patients with low levels of physical activity (less than 2 hours per week), passive hypoxic exposures in interval or continuous regimens without individual dosing caused a decrease in SBP and DBP. However, in this mode, IHT in patients does not contribute to significant changes in anthropometric indices or lipid profiles [19].

Bestavashvili et al. [20] evaluated the efficacy of IHHT in passive mode, but with individual dosing, based on the results of a hypoxic test in 65 CVD patients with MS. After completing a course of 15 IHHT procedures, a significant decrease in SBP and DBP (p <0.001), a decrease in TC, LDL (p = 0.03), as well as anthropometric indices, NT-proBNP, liver fibrosis and steatosis indices, ALT and AST enzymes were observed (p = 0.001). The degree of reduction in SBP, DBP and resting heart rate correlated significantly with the degree of reduction in arterial stiffness indices.

Recent studies have shown that low-intensity exercise in a hypoxic environment increases metabolic load and oxidative stress, similar to high-intensity exercise, with lower walking speed being more accessible and less traumatic to muscles and joints in obese patients with underlying orthopedic conditions. [21-23]. Ramos-Campo et al. [24], in a systematic review of a meta-analysis, showed that in obese and overweight patients, physical activity under hypoxic conditions led to lower body weight, fat mass, WC/OB index, LDL, SBP and DBP, as well as a more pronounced reduction in the level of triglycerides and an noticeable increase in muscle mass during physical training in hypoxia compared with a normoxic environment.

A group of Korean researchers developed an original protocol for a course of Pilates classes in a hypoxic environment (FiO_2 = 14.5%), the implementation of which for 12 weeks (3 times a week) in obese patients led to a significant reduction in the values of SBP and DBP, TC, TG, elimination of signs of endothelial dysfunction, increased aggregation, improvement of erythrocyte deformability and rheological properties of the blood, compared with the control group of patients exercising in the same mode, but in normoxia [25].

In 2021, De Groote and Deldicque [26], in a descriptive review, presented data from 17 RCTs that assessed the effectiveness of exercise in hypoxia. Although some RCTs did not show weight loss in patients, an improvement in body composition was demonstrated by a reduction in body fat and an increase in lean body mass. The results for the dynamics of physical performance were ambiguous: both a significant increase in maximal oxygen consumption (VO_2max) and maximal aerobic capacity after

NADEZHDA P. LYAMINA ET AL. | REVIEW ARTICLE an 8-week course of hypoxic training with less pronounced effects, especially in elderly multimorbid patients. The authors conclude that the benefits of hypoxic training depend on the type of exercise, exercise regimen, and factors contributing to weight loss after hypoxic training, including increased energy expenditure, decreased appetite coupled with reduced food intake and increased levels of ghrelin and leptin.

Hypoxic conditioning and diabetes mellitus

Experimental studies have shown that HIF-1α plays a significant role in the pathogenesis of β-cell dysfunction and DM, as well as in the development of both macrovascular and microvascular complications of DM. In turn, hyperglycemia destabilizes HIF-1α, thereby disrupting the physiological response to hypoxia [27].

Given the complexity of molecular cascade regulation involving HIF-1α, currently, there is no consensus among researchers on the validity of the HIF-1α level induction strategy for the treatment of diabetes itself and its complications. There are few clinical studies on this topic.

Serebrovskaya et al. [28] demonstrated that a 3-week course of IHT increased insulin sensitivity and reduced fasting glucose levels in patients with pre-diabetes, which correlated with the increase in HIF-1 α mRNA in blood leukocytes.

Two clinical studies reviewed in a systematic review by Neuhoff [29] showed a reduction in blood glucose levels by 0.74–2.1 mmol after a one hour of exposure to moderate hypoxia. However, two other clinical studies into the effects of exposure to 10 sessions of hypoxic conditioning failed to demonstrate a sustainable decrease in fasting blood glucose levels.

In an analytical review, a group of authors from South Korea confirmed that the short- and long-term effects of exercise in a hypoxic environment were associated with improved glucose uptake and insulin sensitivity in patients with T2DM to a greater extent than with exercises done under normoxic conditions [30]. Meanwhile, there is limited evidence suggesting the efficacy and safety of the long-term effects of such exposure in patients with metabolic disorders.

Hypoxic conditioning and respiratory diseases

In 2018, Ignatenko et al. [31] presented the results of a study that included 90 patients with multimorbid pathology: stable angina II-III functional class and COPD stages 1-2, aged between 40 and 60 years. The inclusion of IHT in the standard therapy led to a reduction in the frequency of intermittent and persistent cough (by 11.1% and 22.2%, respectively) and of dyspnea after moderate and strenuous exercises (by 15.5% and 4.5%, respectively). Regarding the cardiovascular system, an increase in exercise tolerance was noted, as evidenced by the increase in distance in the 6-minute walk test (+66.8 m vs. +36.3 m in patients with FC II and +34.5 m vs. +22.5 m in patients with FC III) and reclassification of the functional class of angina in the direction of its decrease (FC I +15.6 – control and +22.2% – exposure and FC II -15.6 and -15.5%, FC III – 0 and -6.6%, respectively).

The work of Borukaeva [32] revealed changes in parameters of external respiratory function. After a course of IHT in patients with mild to moderate asthma, there was a significant improvement in bronchial patency, an increase in respiratory volume and alveolar ventilation, and a decrease in minute respiratory volume. The share of alveolar ventilation in the minute respiratory volume increased due to improved pulmonary ventilation and reduced functional dead space, leading to an increase in the efficiency of gas exchange between alveolar air and venous blood.

Hypoxic Conditioning in Elderly Patients with Polymorbidity

The results of a placebo-controlled study (conducted by U. Bayer et al. in 2017) involving elderly patients with multimorbid pathology (dementia and concomitant cardiac pathology, such as IHD, CHF, AH, and atrial fibrillation) showed the following: an increase in exercise tolerance, i.e., a significant increase in the distance covered during the 6-minute walking test (6MWT) in patients, who received 15 IHHT treatments at rest, as part of a multimodal exercise-based rehabilitation program compared to the control group [33]. A significant improvement in cognitive functions was also observed in this group of patients according to the results of dementia definition test (DemTect) and clock drawing (Clock-drawing Test). The increase in values in the dementia test was +16.7% (in the control group +0.39%, $p < 0.001$) and in the clock drawing test was +10.7% (in the control group +8%, $p=0.031$). It should be noted that the hypoxic load was administered individually, based on the results of a 10-minute hypoxic test, where the degree and rate of blood oxygen desaturation and heart rate were assessed.

Wang et al. [34] studied the safety and therapeutic efficacy of this method in elderly cardiac patients with multimorbidity. Patients with moderate cognitive impairment were diagnosed with CVD (CHD, AH), chronic bronchitis, degenerative arthritis, and other age-related diseases. A course of 3 sessions of IHT per week for 8 weeks resulted in a significant improvement in MMSE test results from 25.7+0.4 to 27.7+0.6 ($P=0.038$) and a 5–7 mmHg reduction in SBP. Art. ($P < 0.05$).

A systematic review with a meta-analysis published in 2020 (M. Jung et al.) showed that exercise under hypoxic conditions had a significant effect on improving cognitive functions in older adults (SMD = 0.3, 95% confidence interval: 0.14±0.45, $I^2 = 54\%$, $p<0.001$) [35]. Various characteristics (age, type of cognitive task, exercise intensity, type of training and hypoxia level) significantly influenced the effectiveness of complex training and the degree of compensation for cognitive dysfunction.

CONCLUSION

Hypoxic conditioning of cardiac patients with multimorbid pathologies can be considered as a universal, pathogenically substantiated method of non-drug intervention during cardiac rehabilitation and secondary prevention, which increases exercise tolerance, optimizes hemodynamic parameters (HR, SBP, and DBP), corrects metabolic disorders, reduces manifestations of bronchial obstruction, respiratory failure and improves cognitive function.

The data presented in the review demonstrate that passive hypoxic conditioning in IHT/IHHT regimens is an effective alternative approach to non-drug correction of cardiometabolic risks in cardiac patients with obesity and metabolic disorders.

The use of a course of individually dosed physical activity performed by patients in a hypoxic gas environment (hypoxic rooms or breathing with a hypoxic gas mixture through a mask) has certain prospects. Due to the synergistic effects of hypoxia and exercise hypoxia, the physical exertion stress of high-intensity training is reduced, allowing for faster comprehensive rehabilitation results and improved patient adherence to rehabilitation and preventive programs. This is necessary for cardiac patients of all age categories with comorbid and concomitant pathology. However, additional large-scale controlled studies are needed to establish optimal protocols for the use of hypoxic exposure, to substantiate the criteria for choosing the intensity of hypoxic stimulation and the duration of training courses, depending on the comorbid "burden" of the underlying cardiac disease.

ADDITIONAL INFORMATION

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Authors' contribution:
All authors confirm their authorship according to the ICMJE criteria (all authors contributed significantly to the conception, study design and preparation of the article, read and approved the final version before publication).
Special Contributions:
Lyamina N.P. – development of the structure of the manuscript, writing and scientific revision of the text of the manuscript, verification of critical content, approval of the manuscript for publication;
Spirina G.K. – review of publications on the topic of the article, writing and revision of the text of the manuscript;
Glazachev O.S. – developing a strategy of searching for relevant sources and the manuscript structure, analysis and interpretation of the data, writing and scientific revision of the text of the manuscript and verification of critical content.

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APPENDIX

Table 1. *Application of hypoxic conditioning in clinical populations with various non-infectious diseases*

First author, year of publication	Nosology under study	Study type	Patients-trials number	Hypoxic conditioning mode	Results
Glazachev OS, 2021 [12]	IHD, CHF, AH	SR with meta-analysis	431	IHT/IHHT at rest	↓ HR ↓SBP, DBP
Ignatenko GA, 2019 [13]	IHD, AH	RCT	219	IHT/IHHT at rest	↓SBP, DBP normalization of diurnal variability of the BP ↓ angina attacks
Muangritdech N, 2020 [14]	AH I	RCT	47	IHT at rest IHT + PE	↓SBP, DBP in both group ↑ 6 MWT distance ↑ Nox
Lyamina NP, 2011 [15]	AH I	RCT	57	IHT at rest	↑ NO synthesis ↓ BP to the level of healthy individuals ↓ BP values persisted for at least 3 months
Glazachev OS, 2010 [17]	Metabolic syndrome	RCT	35	IHHT at rest	↓BP ↓cholesterol level ↓endothelial dysfunction ↑microcirculation ↑tolerance to physical load
Lizamore CA, 2017 [18]	IHD, CHF, COPD	SR	4 RCT	IHT at rest IHT + PE CHE	↑ submaximal tolerance to physical load, execution time to failure ↑ heart rate variability
Chacaroun S, 2020 [19]	Obesity	RCT	35	IHT at rest CHE	↓SBP, DBP in both group improved heart rate variability improved hypoxic ventilatory response
Bestavashvili A, 2022 [20]	Metabolic syndrome	RCT	65	IHHT at rest	↓SBP, DBP in both group ↓ total cholesterol, LDL, ALT, AST, NTproBNP ↓ hepatic fibrosis and steatosis indices
Ramos-Campo DJ, 2019 [24]	Obesity	SR with meta-analysis	13 RCT -336 patients	PE under hypoxic condition	↓body weight, fat mass, LDL, SBP and DBP, but no difference from the control group (exercise under normoxic conditions) ↑ muscle mass ↓ triglycerides

Jung K, 2020 [25]	Obesity	RCT	32	PE under hypoxic condition	↓SBP and DBP ↓ total cholesterol, triglycerides elimination of signs of endothelial dysfunction and improvement of rheological properties of blood
De Groote E, 2021 [26]	Obesity Diabetes mellitus	SR	17 RCT	PE under hypoxic condition	conflicting data on weight loss, fat mass and exercise tolerance the effectiveness of hypoxic training depends on the type of exercise and the mode of hypoxic load
Serebrovska TV, 2019 [28]	Prediabetes	CT	18	IHT at rest	↑ insulin sensitivity ↓ fasting glycemia ↑ tolerance to hypoxia ↑ HIF-1a mRNA in blood leukocytes Maximum effect one month after the completion of the course
Neuhoff CG, 2018 [29]	Diabetes mellitus	SR	4 RCT	Hypoxic Exposure and IHT at rest	conflicting data on lowering fasting glucose levels
Kim SW, 2021 [30]	Diabetes mellitus	Descriptive review	4 RCT	PE under hypoxic condition	improved glucose uptake and insulin sensitivity
Ignatenko GA, 2018 [31]	IHD: stable angina NYHA II-III + COPD	RCT	90	IHHT at rest	↓frequency of non-permanent/persistent cough, ↓ frequency of dyspnea at rest/after exercise reclassification to less heavy NYHA class ↑ tolerance to PE
Borukaeva IK, 2019 [32]	Bronchial asthma mild to moderate	RCT	46	IHT at rest	↑ tidal volume, alveolar ventilation ↑ efficiency of gas exchange between alveolar air and venous blood
Bayer U, 2017 [33]	Dementia + IHD, CHF, AH	RCT	34	IHHT at rest	↑ 6 MWT distance ↑ cognitive functions
Wang H, 2020 [34]	Mild Cognitive Impairment + IHD, AH, DM	Pilot study	7	IHT at rest	↑ cognitive functions ↓SBP, DBP
Jung M, 2020 [35]	Dementia Multimorbidity patients Healthy	SR with meta-analysis	18	PE under hypoxic condition	↑ cognitive functions

Note: *IHD – Ischemic Heart Disease, CHF – Chronic Heart Failure, AH – Arterial Hypertension, COPD – Chronic Obstructive Pulmonary Disease, RCT – randomized clinical trial, IHT/IHHT – Interval Hypoxia Treatment/– Interval Hypoxia Hyperoxia Treatment, PE – physical exercise, CHE – Continuous Hypoxia Exposure, SR – systematic review, CT – clinical trial, HR – Heart Rate, SBP/DBP – Systolic/Diastolic Blood Pressure, LDL – low density lipid, ALT – alanine aminotransferase, AST – aspartate aminotransferase*