DOI: 10.20514/2226-6704-2023-13-4-245-252
УДК 616.1/.9-085.212-06:616.831-009.7
EDN: AHXHPL

Г.А. Игнатенко, А.Э. Багрий, Т.С. Игнатенко, В.А. Толстой, И.С. Евтушенко, Е.С. Михайличенко*

ГОО ВПО «Донецкий национальный медицинский университет им. М. Горького», Донецк, Россия

ВОЗМОЖНОСТИ И ПЕРСПЕКТИВЫ ПРИМЕНЕНИЯ ГИПОКСИТЕРАПИИ В КАРДИОЛОГИИ

G.A. Ignatenko, A.E. Bagriy, T.S. Ignatenko, V.A. Tolstoy, I.S. Evtushenko, E.S. Mykhailichenko*

SEI HPE State Donetsk State Medical University named after M. Gorky, Donetsk, Russia

Possibilities and Prospects of Hypoxytherapy Application in Cardiology

Резюме

Несмотря на достижения современной кардиологии, заболеваемость и смертность от кардиоваскулярной патологии в большинстве стран мира остается высокой, что мотивирует более широкое использование дополнительных (альтернативных) профилактических и лечебных подходов, одним из которых является гипокситерапия. За несколько десятилетий использования этого метода накоплен обширный объем информации, позволяющий констатировать благоприятное воздействие различных режимов гипокситерапии на выраженность клинической картины сердечно-сосудистых заболеваний, что потенциально может улучшать их прогноз. Применение гипокситерапии ассоциируется с улучшением циркадного ритма артериального давления, поток-зависимой вазодилатации, со снижением инсулинорезистентности, уменьшением жесткости сосудистой стенки, улучшением реологии крови, функции эндотелия и системы оксида азота, снижением уровней провоспалительных и протромботических цитокинов. Ряд авторитетных экспертов рассматривают гипокситерапию в качестве доступного и перспективного метода профилактики и лечения сердечно-сосудистой патологии, эффективно дополняющего традиционные немедикаментозные и медикаментозные подходы. Накопленные данные свидетельствуют о серьезных перспективах расширенного изучения возможностей применения гипокситерапии у кардиологических больных, в том числе в рамках крупных государственных исследовательских программ. Настоящий обзор посвящен рассмотрению физиологических эффектов гипокситерапии, возможностей ее применения в кардиологической практике, в том числе с анализом собственных данных, а также мер предосторожности при ее проведении.

Ключевые слова: *гипокситерапия, сердечно-сосудистые заболевания, ишемическое прекондиционирование тканей, артериальная гипертония, ишемическая болезнь сердца*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 20.04.2023 г.

Принята к публикации 08.06.2023 г.

Для цитирования: Игнатенко Г.А., Багрий А.Э., Игнатенко Т.С. и др. ВОЗМОЖНОСТИ И ПЕРСПЕКТИВЫ ПРИМЕНЕНИЯ ГИПОКСИТЕРАПИИ В КАРДИОЛОГИИ. Архивъ внутренней медицины. 2023; 13(4): 245-252. DOI: 10.20514/2226-6704-2023-13-4-245-252. EDN: AHXHPL

Abstract

Despite the achievements of modern cardiology, the cardiovascular morbidity and mortality in most countries of the world remains high, which motivates the wider use of additional (alternative) preventive and therapeutic approaches, one of which is hypoxytherapy. Over several decades of

*Контакты: Евгения Сергеевна Михайличенко, e-mail: klassiki@inbox.ru
*Contacts: Eugenia S. Mykhailichenko, e-mail: klassiki@inbox.ru
ORCID ID: https://orcid.org/0000-0001-8625-1406

using this method, a large amount of data has been accumulated that allows us to state the beneficial effect of various hypoxytherapy regimens on the clinical course of cardiovascular diseases and can potentially improve prognosis of them. The use of hypoxytherapy is associated with an improvement in blood pressure circadian rhythm, flow-dependent vasodilation, an insulin resistance decrease, a vascular wall stiffness redaction, an improvement in blood rheology, endothelial function and nitric oxide system, a decrease of proinflammatory and prothrombotic cytokines levels. A number of modern experts consider hypoxytherapy as an affordable and perspective method of prevention and treatment of cardiovascular disease, effectively supporting traditional non-drug and drug-based approaches. Contemporary data indicate serious future perspectives for an expanded study of the hypoxytherapy possibilities in cardiac patients, including through the State research programmes. This review is devoted to the discussion of the physiological effects of hypoxytherapy, the possibilities of its application in cardiological practice, including with the analysis of own data, as well as precautions during its implementation.

Key words: *hypoxytherapy, cardiovascular diseases, ischemic tissue preconditioning, arterial hypertension, ischemic heart disease*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 20.04.2023

Accepted for publication on 08.06.2023

For citation: Ignatenko G.A., Bagriy A.E., Ignatenko T.S. et al. Possibilities and Prospects of Hypoxi Therapy Application in Cardiology. The Russian Archives of Internal Medicine. 2023; 13(4): 245-252. DOI: 10.20514/2226-6704-2023-13-4-245-252. EDN: AHXHPL

AH — arterial hypertension, BP — blood pressure, HOT — hypoxytherapy, CAD — coronary artery disease, CVD — cardiovascular diseases, CHF — congestive heart failure, NO — nitrogen oxide

Arterial hypertesion (AH), coronary artery disease (CAD), congestive heart failure (CHF), cerebrovascular and peripheral vascular disorders are a cause of at least one third of all deaths globally, and their rate in mortality in developed countries is even higher [1, 2]. The leading role of these cardiovascular diseases (CVD) in the structure of causes of deaths globally forces to constantly improve the methods of prevention and treatment [2, 3].

An important achievement in cardiology and internal medicine in general is the widespread understanding of the need in adherence to recommendations to change the lifestyle, including low-salt healthy food, smoking cessation and cutting down on alcohol, moderate physical exercises, reduction of overweight, good sleeping habits and prevention of excessive emotional stress, regular monitoring and correction of blood pressure, blood sugar and lipids [3-6]. Solid achievements in cardiology during the past two decades also include introduction of advanced invasive and minimally invasive approaches (coronary revascularization, implants to control arrythmias and heart blocks, etc.), approval and wide use of statins for CVD, advances in anti-thrombotic therapy (dual anti-platelet therapy, novel oral anticoagulants), wider use of mineralocorticoid receptor antagonists in AH, use of dual neurohumoral blockade (valsartan plus sacubitril) and gliflozin in CHF [1, 3].

Unfortunately, despite impressive achievements in modern cardiology, desired reduction in CVD mortality and mortality has not yet been observed in a majority of countries all over the world [2]. Therefore, the interest in the use of additional (alternative) preventive and therapeutic approaches has been growing; one of such approaches is exposure to dosed and controlled hypoxia, commonly called hypoxytherapy (HOT). HOT variants (hypobaric, normobaric oxygenation with or without physical exercises, of various intensity and duration) have bee studied for decades [7–10]. Over this period, a lot of information has been gathered allowing to state that HOT has a number of favourable effects, which can reduce the intensity of clinical signs of CVD and has potential for improving the CVD prognosis [11–14]. A number of respectable experts see HOT as a convenient and promising approach to prevent and treat CVD, which is an efficient addition to conservative non-drug and drug methods [8, 15–17]. This literature review is dedicated to discussion of physiological effects of HOT, possible use of various HOT variants in CVD, and precautions for HOT procedures.

Physical Responses to Hypoxia

Exposure to controlled hypoxia causes formation of a complex of various physiological changes in the body [7, 12, 18-20]. A short period of hypoxia, especially intermittent, leads to development of a number of compensatory changes in respiratory and cardiovascular systems. They are designed to maintain sufficient oxygenation of peripheral tissues during hypoxia and potentially have cardiovascular protective effect [7, 10]. Respiratory changes are associated with exposure of carotid chemoreceptors to hypoxia and include hyperventilation, increase in the diffusive capacity of lungs (with an increase in the aero-hematic barrier permeability for respiratory gases — oxygen and carbon dioxide), increase in respiratory minute volume and ventilatory lung capacity, increase in respiratory response to physical activities [7, 12, 21]. Changes in the cardiovascular system during hypoxia are caused by sympathic nervous system activation and include increase in the heart rate at rest and during physical activities, increased cardiac output, increased endothelium-dependent and NO-mediated vasodilation, including arteriolar and venous vasodilation, improved endothelium function, reduced blood viscosity, reduced blood pressure (BP), increased hemoglobin oxygen affinity, increased expression of hypoxia-induced factor 1-α (HIF-α) and vascular endothelial growth factor (VEGF), as well as increased angiogenesis [7, 22]. These processes are closely associated with metabolic changes induced by short-term intermittent hypoxia, including reduced appetite (caused by a shift in hormones regulating food intake and energy balance, including leptin, ghrelin, glucagon-like peptide-1 (GLP-1), pancreatic polypeptide (PP), peptide YY (PYY), serotonin), increased activity of glycolysis enzymes and transmembrane glucose transporter GLUT4, reduced insulin resistance, body weight loss [11, 18, 19]. It was demonstrated that at least some of the above favourable effects of intermittent hypoxia can persist for 3 months after hypoxia termination [10, 21]. From the pathophysiological point of view, a number of authors believe that HOT variants that involve procedures of 20 to 60 minutes/day in sessions of at least 5 days (preferably 10–15 days), repeated once every 3–6 months, are optimal for steady cardiovascular protection [7, 8, 16, 21].

For some pathophysiologists and clinicians, intermittent hypoxia is a variant of hypoxic/ ischemic tissue preconditioning [7, 18]. This phenomenon comprises a set of biological reactions (changes in regulation of ion channels, ATP-sensitive potassium channels of mitochondria, mitochondria membrane permeability, formation of active oxygen radicals) to increase tissue resistance to effects of hypoxia and ischemia by means of hypoxic training [17]. Metabolic adaptation to mild intermittent ischemic events has been studied mostly for myocardium (and is used for its protection against ischemic/reperfused events during revascularisation); there are some evidences of this phenomenon in brain tissue as well (later it can be useful for brain protection against ischemia) [17, 20, 22]. Interpretation of effects of HOT as a variant of hypoxic/ischemic tissue preconditioning seems promising for the assessment of perspective clinical use of this metod, especially in cardiology and neurology [8, 12, 13, 20].

Stable and long-term exposure to hypoxia (e.g., living in high mountain regions) is associated with increased erythropoiesis and reduced cardiac output to the level close to the normoxia [23].

Available hypoxia variants used in clinical settings, including intermittent variants of exposure to normobaric and hypobaric dosed hypoxia as well as physical activities during controlled hypoxia lead to similar positive respiratory, cardiovascular and metabolic changes; and it is assumed that their intensity can be higher in hypobaric HOT as compared to normobaric conditions and in HOT with physical activities as compared to HOT without any exercises [19, 23]. Favourable HOT-associated effects can be used for CVD both for prevention and treatment [9, 14, 21, 24].

Clinical Effects of HOT

HOT is promoted as a method of alternative medicine, the advantage of which adds to the possibilities of conventional methods of CVD prevention and treatment [22, 24]. Two HOT variants are worth noting — these are procedures with exposure to various types of dosed hypoxia and physical activities during controlled hypoxia. Both these variants demonstrate a number of positive effects for cardiovascular system and CVD pathophysiology. Let's discuss the possibilities of both these variants of HOT in CVD.

Exposure to dosed hypoxia. The assumption of possible favourable effect of oxygen-deficient air inhalation on CVD is based on the information from epidemiological studies comparing cardiovascular characteristics of those living in high mountain regions and flat-bottom land. The information in such analyses is often ambiguous because of significant diversity of the studied populations in ethnicity, race, gender, physical activity and diet. At the same time, the largest and most respected epidemiological papers evidence reduction in the cardiovascular risk in people living in high mountain regions vs. those living in flat-bottom land. A series of papers by Faeh D. et al. (2009, 2016) assessed the impact of the altitude above sea level on CVD first in 1.64 million, then in 4.2 million of people from various regions in Germany and Switzerland (using the Swiss National Cohort Study Group register) [25, 26]. Results of such large studies quite definitely demonstrated (1) marked favourable effect of living in mountain regions on the risk and progression of CAD; (2) independent protective effect of being born in a high mountain region regarding the risk of CAD; (3) linear dependence of the cardiovascular mortality on the increase of the altitude above sea level. Similar evidence of positive effects of living in a mountain region on the cardiovascular risk was observed in other population studies (Ezzati M. et al., 2012), where analysis was performed by such respected epidemiological sources in the USA as the National Center for Health Statistics, he National Elevation Dataset and the U.S. Census Estimates [27]. The paper by Winkelmayer W.C. et al. (2012) which analysed a US dialysis population also showed a significantly lower rate of myocardial infarction, cerebral strokes and cardiovascular complications among people living in mountains as compared to people living in flat regions [28].

These promising information from epidemiological registers was used to plan a number of studies where exposure to dosed hypoxia was used for prevention and therapy in various categories of people — healthy people and CVD patients [29-34]. Vedam H. et al. (2009) evaluated the cardiovascular effects of hypoxia with controlled reduction in oxygen saturation to 80 % for 20 minutes in a group of healthy male volunteers [29]. The authors proved that inhalation of an oxygen-deficient air mix results in endothelium-dependent and NO-mediated arterial vasodilation with increased blood flow in skeletal muscles. Leuenberger U.A., et al. (2008) created hypobaric hypoxia conditions in a group of healthy male volunteers; these conditions were similar to those at an altitude of 2438–4877 m above sea level during 20 minutes [30]. They demonstrated that this hypoxia regimen is associated with increased NO production in venous endothelium of skeleton muscles and development of marked hypoxia-induced vasodilation in this blood flow. Another study by Tremblay J.C., et al. (2020) confirmed favourable effects of hypobaric hypoxia on endothelial function in healthy males, including after induced increased in circulating plasma during this study [31].

Cardiovascular effects of HOT were assessed in a number of studies in patients with various CVD. Patients with stage 1 AH demonstrated favourable clinical and pathophysiological effects from 20-day use of intermittent normobaric HOT, presenting as BP reduction and increased NO production [32]. It is worth mentioning that the achieved BP reduction was maintained for over 3 months in 28 out of 33 studied patients. A double-blind study by Burtscher M., et al. (2004) assessed effects of 3-week intermittent HOT (with inspired oxygen fraction (FiO_2) = 0.10–0.14) in 16 males aged 50–70 years, including 8 post-infarct patients and the other 8 patients who did not have myocardial infarction [33]. The authors demonstrated that the use of HOT was associated with improved aerobic capacity and improved tolerance to physical activities in elderly people, both post-infarction patients and those who did not have myocardial infarction. According to another report by del Pilar Valle M., et al. (2006), intermittent hypobaric HOT in patients with severe chronic coronary disorders was associated with marked improvement in miocardial perfusion [34]. The authors used this information to conclude that this method can be a useful addition to conventional management of patients with chronic CAD.

A lot of studies with various HOT variants in CVD (mostly intermittent normobaric HOT) were published in Russian sources [8, 20, 24, 35]. These papers are based on relatively small cohorts of patients with CVD and generally positive HOT effects and good tolerability. At the same time, patients with arterial hypertension and chronic CAD demonstrated favourable effects of HOT on BP and NO-dependent vasodilation of arterial and venous blood flows. Besides, there were positive effects of HOT on insulin resistance, pro-inflammatory and prothrombotic cytokines, as well as clinical parameters (better physical activity tolerability, reduction in angina functional class) [8, 20, 24, 35].

Numerous studies led by Prof. G. A. Ignatenko are dedicated to the use of normobaric hypoxytherapy as a part of therapy and prevention of arterial hypertension, chronic heart disease, microvascular angina, metabolic syndrome, ischemic pre-conditioning, etc. [24, 36, 37]. Hypoxytherapy addition to a comprehensive therapeutic program for young patients with genetically induced hypertension vs. patients who were treated only with medications allowed reducing the number of complaints (headache, palpitation, irregular heart rate), the rate of uncomplicated and complicated hypertensic crises, extrasystolic arrhythmia and paroxysmal atrial fibrillation, daily average systolic and diastolic blood pressure (BP), total peripheral vascular resistance. Reduction in night-peacker circadian variability with a corresponding increase in the dipper type makes it possible to bring daily pressure fluctuations to physiological values and to minimise night risks associated with cardiac and cerebral blood flow disorders [37]. High efficiency of hypoxytherapy was observed in comorbidities (cardiac pathology and bronchopulmonary, endocrine, renal, prostate gland diseases, etc.). The results of the use of hypoxytherapy in cardiopulmonary disorders observed by the authors make it possible to treat hypoxytherapy as a universal pathogenic therapy which can optimise coronary blood flow, reduce manifestations of bronchial obstruction, cardiac and respiratory insufficiency and improve physical activity tolerability [38]. Hypoxytherapy, a non-drug component of a long-term comprehensive treatment program, can help in improving some parameters that characterise the quality of life (physical functioning, viability, social functioning, role emotional functioning) to the level of healthy people [39].

Physical Activities During Controlled Hypoxia. A combination of dosed physical activity with exposure to hypoxia leads to the development of marked compensatory arterial vasodilation aimed at maintenance of sufficient oxygen supply to skeletal muscles during oxyhemoglobin deficiency in blood [23, 41]. Physical activities themselves are a potent factor affecting metabolism [16, 40, 41]. During hypoxia, physical activities are associated with reduced oxygen supply to skeletal muscles and increased oxygen demand, resulting in marked reduction of partial oxygen pressure in mitochondria of engaged muscles [42]. In turn, it is associated with increased NO production by vascular endothelial cells and compensatory vasodilation mobilisation [9, 40, 42]. This process underlines potential vaso- and cardioprotection by load HOT in CVD prevention and treatment.

Cardiovascular effects of a combination of physical activity and hypoxia were studied both in healthy volunteers and patients with CVD. The population of healthy female volunteers studied by Jung K., et al. (2020) demonstrated that pilates during hypobaric hypoxia (FiO_2 = 0.145) vs. normoxia was associated with development of more marked metabolic response (carbon dioxide excretion, carbohydrates oxidation) and more significant vasodilation [43]. Similarly, in the study by Katayama K., et al. (2013), physical activity during hypoxia (FiO_2 = 0.12) in healthy male subjects resulted in more marked endothelium-dependent vasodilation as compared to similar activities during normoxia [44].

There are numerous reports where load HOT was used in post-menopausal women (Nishiwaki M., et al. (2011), hypobaric hypoxia similar to an altitude of approx. 2000 m above sea level [45]), elderly men (Park H., et al. (2019), normobaric hypoxia, FiO_2 = 0.145 [46]), obese women (Jung K., et al. (2020), hypobaric hypoxia [47]), in sportsmen (Zembron-Lacny A., et al. (2020), intermittent hypoxia for 6 days at FiO_2 = 0.135–0.12 in combination with intensive physical activities [48]). These and some other similar papers (Wee J., et al. (2015) demonstrated that physical activities in combination with HOT are associated with vasodilation, BP reduction, improved functioning of vegetative nervous system, blood rheology, functions of endothelium, lipid profile and glucose tolerability, as well as reduced levels of pro-inflammatory mediators; and all these valuable biological effects were much more marked compared to absence of hypoxia [15].

Effects of load HOT on cardiovascular parameters were studied also in persons with CVD. Muangritdech N., et al. (2020), who analysed the results of the use of intermittent normobaric hypoxia (FiO_2 = 0.14) in combination with dosed physical load in patients with AH and found out that this method results in marked reduction of arterial hypertension, presumably due to such favourable metabolic effects as increased NO metabolite levels and increased HIF-α production [17]. Significant contribution to the study of effects of HOT in patients with CVD was made by outstanding Russian specialists, in particular by the study team led by Academician O. V. Korkushko [49]. These studies demonstrated that, in elderly persons with CAD, intermittent normobaric hypoxia in combination with dosed physical activities resulted in reduction in angina intensity; according to the authors, this positive effect is due to an improved function of coronary artery endothelium, normalised miocardial microcirculation and optimised oxygen consumption by myocardium. In a series of papers dedicated to HOT and in an analysis summarising data from numerous sources published over the last 50 years, T. V. Serebrovskaya et al. (2014, 2016) defend for a good reason the viewpoint that load HOT can be a very useful therapy complementing modern treatments of most common CVD, including AH, CAD and CHF [8, 35].

Precautions for HOT

For HOT, there are some evidence of a certain favourable potential for the clinical manifestation and course of CVD [29, 31, 33-35, 63]. The two recent decades are remarkable for active studies of the therapeutic effects of HOT, which allowed confirming a number of useful pathophysiological and clinical characteristics of this method and its good tolerability. However, the development of HOT is hindered by the lack of standardisation of the equipment used and hypoxia regimens; therefore, it is not possible to conduct large multicenter studies under an advanced protocol (preferably randomised controlled studies) and this method cannot be added to the Russian and international guidelines for the management of CVD [8, 9, 22].

HOT procedures in persons with CVD require certain precautions [9]. Experts claim that persons undergoing HOT should have stable CVD, without exacerbations and decompensation, because otherwise clinical signs of CVD can increase even in dosed and controlled hypoxia [8, 9]. According to some authors, before HOT a number of tests should be conducted with dosed physical activity with normoxia in order to assess HOT safety [8, 9]. It is essential to keep taking all medications prescribed by the attending physician during HOT, especially statins and antithrombotic agents, without any breaks. During therapy with HOT, it is advised to avoid such potentially unfavourable factors as physical overwork, dehydration, marked changes in the diet and temperature regimen (including overheating, e.g., baths, or hypothermia, e.g., cold training); it is also important to reduce emotional stress (at home, at work, including stress from smoking cessation, etc.). For an optimal result, it is useful to create positive motivation for the patient and their relatives for HOT, to explain positive effects of the procedure and precautions and make sure they comply with a course of at least 5 days long [50]. A decision to initiate HOT should be taken by the doctor; the room where the procedure is performed should be equipped with a CVD first aid kit.

Conclusion

HOT including procedures with exposure to dosed intermittent hypoxia ans physical activities during controlled hypoxia are characterised by the development of various favourable pathophysiological and clinical effects in chronic CVD and can be a valuable component of a comprehensive therapy. Positive effects of HOT demonstrated in healthy subjects and CVD patients include improved circadian AH rhythm and flow-associated vasodilation, reduced insulin resistance, reduced vascular wall rigidity, improved blood rheology, endothelial and NO system function, reduced levels of pro-inflammatory and prothrombotic cytokines. This information shows sound perspectives of a deeper study of HOT capabilities in CVD patients, including during large state research programs.

Вклад авторов:

Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

Игнатенко Г.А. (ORCID ID: https://orcid.org/0000-0003-3611-1186): создание идеи и концепции рукописи, утверждение окончательного варианта

Багрий А.Э. (ORCID ID: https://orcid.org/0000-0003-2592-0906): написание актуальности, раздела, посвященного физиологическим эффектам гипокситерапии, критический обзор материала, окончательное редактирование рукописи

Игнатенко Т.С. (ORCID ID: https://orcid.org/0009–0001–2138–2277): сбор и анализ литературных данных, написание раздела о клинических эффектах гипокситерапии, редактирование рукописи

Толстой В.А. (ORCID ID: https://orcid.org/0009–0002–4586-3718): сбор и анализ литературных данных, написание раздела «Физические нагрузки в условиях контролируемой гипоксии»

Евтушенко И.С. (ORCID ID: https://orcid.org/0009-0008–5989–7891): сбор и анализ литературных данных, написание заключения, редактирование рукописи

Михайличенко Е.С. (ORCID ID: https://orcid.org/0000-0001-8625-1406): сбор, анализ и обобщение литературных данных, написание резюме, подготовка рукописи к публикации

Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

Ignatenko G.A. (ORCID ID: https://orcid.org/0000-0003–3611–1186): generating the idea and the concept of the manuscript, approval of the final version

Bagriy A.E. (ORCID ID: https://orcid.org/0000-0003-2592-0906): writing the relevance, the section devoted to the physiological effects of hypoxytherapy, critical review of the material, final editing of the manuscript.

Ignatenko T.S. (ORCID ID: https://orcid.org/0009-0001–2138–2277): collection and analysis of literature data, writing a section devoted to the clinical effects of hypoxytherapy, editing the manuscript.

Tolstoy V.A. (ORCID ID: https://orcid.org/0009–0002–4586–3718): collection and analysis of literature data, writing the section "Physical activity in conditions of controlled hypoxia".

Evtushenko I.S. (ORCID ID: https://orcid.org/0009–0008–5989–7891): collection and analysis of literary data, writing a conclusion, editing a manuscript.

Mykhailichenko E.S. (ORCID ID: https://orcid.org/0000-0001-8625-1406): collection, analysis and generalization of literary data, writing a summary, manuscript preparation

Список литературы/ References:

1. Mc Namara K., Alzubaidi H., Jackson J.K. Cardiovascular disease as a leading cause of death: how are pharmacists getting involved? Integrated pharmacy research and practice. 2019: 1-11. doi: 10.2147/IPRP.S133088.
2. Timmis A., Vardas P., Townsend N. et al. European Society of Cardiology: cardiovascular disease statistics 2021. European Heart Journal. 2022; 43(8): 716-799. doi: 10.1093/eurheartj/ehab892.
3. Mendis S. Global progress in prevention of cardiovascular disease. Cardiovascular Diagnosis and Therapy. 2017; 67: S32-S38. doi: 10.21037/cdt.2017.03.06.
4. Rippe J.M. Lifestyle Strategies for Risk Factor Reduction, Prevention, and Treatment of Cardiovascular Disease. American Journal of Lifestyle Medicine. 2019; 13: 204–212. doi: 10.1177/1559827618812395.
5. Moore S.C., Patel A.V., Matthews C.E. et al. Leisure time physical activity of moderate to vigorous intensity and mortality: A large pooled cohort analysis. PLoS Medicine. 2012; 9: e1001335. doi:10.1371/journal.pmed.1001335.
6. Piercy K.L., Troiano R.P., Ballard R.M. et al. The physical activity guidelines for Americans. JAMA. 2018; 320: 2020–2028. doi: 10.1001/jama.2018.14854.
7. Verges S., Chacaroun S., Godin-Ribuot D. et al. Hypoxic Conditioning as a New Therapeutic Modality. Frontiers in Pediatrics. 2015; 3: 58. doi: 10.3389/fped.2015.00058.
8. Serebrovskaya T.V., Xi L. Intermittent hypoxia training as nonpharmacologic therapy for cardiovascular diseases: Practical analysis on methods and equipment. Experimental Biology and Medicine. 2016; 241: 1708–1723. doi:10.1177/1535370216657614.
9. Millet G.P., Debevec T., Brocherie F. et al. Therapeutic Use of Exercising in Hypoxia: Promises and Limitations. Frontiers in Physiology. 2016; 7: 224. doi: 10.3389/fphys.2016.00224.
10. Neubauer J.A. Invited Review: Physiological and pathophysiological responses to intermittent hypoxia. Journal of Applied Physiology. 2001; 90: 1593–1599. doi: 10.1152/jappl.2001.90.4.1593.
11. Behrendt T., Bielitzki R., Behrens M. et al. Effects of intermittent hypoxia–hyperoxia on performance-and health-related outcomes in humans: A systematic review. Sports Medicine-Open. 2022; 8(1): 1-28. doi: 10.1186/s40798-022-00450-x.
12. Riley C.J., Gavin M. Physiological Changes to the Cardiovascular System at High Altitude and its Effects on Cardiovascular Disease. High Altitude Medicine & Biology. 2017; 18: 102–113. doi: 10.1089/ham.2016.0112.

13. Rimoldi S.F., Sartori C., Seiler C. et al. High-altitude exposure in patients with cardiovascular disease: risk assessment and practical recommendations. Progress in Cardiovascular Diseases. 2010; 52: 512–524. doi: 10.1016/j.pcad.2010.03.005.
14. Savla J.J., Levine B.D., Sadek H.A. The Effect of Hypoxia on Cardiovascular Disease: Friend or Foe? High Altitude Medicine & Biology. 2018; 19: 124–130. doi: 10.1089/ham.2018.0044.
15. Wee J., Climstein M. Hypoxic training: Clinical benefits on cardiometabolic risk factors. Journal of Science and Medicine in Sport. 2015; 18: 56–61. doi: 10.1016/j.jsams.2013.10.247.
16. Bailey D.M., Davies B., Baker J. Training in hypoxia: modulation of metabolic and cardiovascular risk factors in men. Medicine and Science in Sports and Exercise. 2000; 32: 1058–1066.
17. Muangritdech N., Hamlin M.J., Sawanyawisuth K. et al. Hypoxic training improves blood pressure, nitric oxide and hypoxia-inducible 7 factor-1 alpha in hypertensive patients. European Journal of Applied Physiology. 2020; 120: 1815–1826. doi: 10.1007/s00421-020-04410-9.
18. Park H., Kim J., Park M. et al. Exposure and Exercise Training in Hypoxic Conditions as a New Obesity Therapeutic Modality: A Mini Review. Journal of Obesity & Metabolic Syndrome. 2018; 27: 93–101. doi: 10.7570/jomes.2018.27.2.93.
19. Urdampilleta A., González-Muniesa P., Portillo M.P. et al. Usefulness of combining intermittent hypoxia and physical exercise in the treatment of obesity. Journal of Physiology and Biochemistry. 2012; 68: 289–304. doi: 10.1007/s13105-011-0115-1.
20. Rybnikova E.A., Nalivaeva N.N., Zenko M.Y. et al. Intermittent Hypoxic Training as an Effective Tool for Increasing the Adaptive Potential, Endurance and Working Capacity of the Brain. Front. Neurosci. 2022; 16: 941740. doi: 10.3389/fnins.2022.941740.
21. Prabhakar N.R., Peng Y., Kumar G.K. et al. Peripheral chemoreception and arterial pressure responses to intermittent hypoxia. Comprehensive Physiology. 2015; 5: 561–577. doi: 10.1002/cphy.c140039.
22. Park H.Y., Kim S.W., Jung W.S. et al. Hypoxic Therapy as a New Therapeutic Modality for Cardiovascular Benefit: A Mini Review. Rev. Cardiovasc. Med. 2022; 23(5): 161. doi: 10.31083/j.rcm2305161.
23. Sinex J.A., Chapman R.F. Hypoxic training methods for improving endurance exercise performance. Journal of Sport and Health Science. 2015: 4(4): 325-332. doi: 10.1016/j.jshs.2015.07.005.
24. Игнатенко Г.А., Дубовая А.В., Науменко Ю.В. Возможности применения нормобарической гипокси-терапии в терапевтической и педиатрической практиках. Российский вестник перинатологии и педиатрии. 2022; 67(6): 46-53. doi: 10.21508/1027-4065-2022-67-6-46-53.
Ignatenko G.A., Dubovaya A.V., Naumenko Yu.V. Treatment potential of normobaric hypoxic therapy in therapeutic and pediatric practice. Rossiyskiy Vestnik Perinatologii i Pediatrii (Russian Bulletin of Perinatology and Pediatrics). 2022; 67(6): 46-53. doi: 10.21508/1027-4065-2022-67-6-46-53 [In Russian].
25. Faeh D., Gutzwiller F., Bopp M. Lower Mortality from Coronary Heart Disease and Stroke at Higher Altitudes in Switzerland. Circulation. 2009; 120: 495–501. doi: 10.1161/CIRCULATIONAHA.108.819250.
26. Faeh D., Moser A., Panczak R. et al. Independent at heart: persistent association of altitude with ischaemic heart disease mortality after consideration of climate, topography and built environment. Journal of Epidemiology and Community Health. 2016; 70: 798–806. doi: 10.1136/jech-2015-206210.
27. Ezzati M., Horwitz M.E., Thomas D.S. et al. Altitude, life expectancy and mortality from ischaemic heart disease, stroke, COPD and cancers: national population-based analysis of us counties. Journal of Epidemiology and Community Health. 2012; 66: e17. doi: 10.1136/jech.2010.112938.
28. Winkelmayer W.C., Hurley M.P., Liu J. et al. Altitude and the risk of cardiovascular events in incident us dialysis paients. Nephrology, Dialysis, Transplantation. 2012; 27: 2411– 2417. doi: 10.1093/ndt/gfr681.
29. Vedam H, Phillips CL, Wang D, Barnes DJ, Hedner JA, Unger G, et al. Short-term hypoxia reduces arterial stiffness in healthy men. European Journal of Applied Physiology. 2009; 105: 19– 8 25.
30. Leuenberger U.A., Johnson D., Loomis J. et al. Venous but not skeletal muscle interstitial nitric oxide is increased during hypobaric hypoxia. European Journal of Applied Physiology. 2008; 102: 457–461. doi: 10.1007/s00421-007-0601-x.
31. Tremblay J.C., Ainslie P.N., Turner R. et al. Endothelial function and shear stress in hypobaric hypoxia: time course and impact of plasma volume expansion in men. American Journal of Physiology-Heart and Circulatory Physiology. 2020; 319: H980–H994. doi: 10.1152/ajpheart.00597.2020.
32. Lyamina N.P., Lyamina S.V., Senchiknin V.N. et al. Normobaric hypoxia conditioning reduces blood pressure and normalizes nitric oxide synthesis in patients with arterial hypertension. Journal of Hypertension. 2011; 29: 2265–2272. doi: 10.1097/HJH.0b013e32834b5846.
33. Burtscher M., Pachinger O., Ehrenbourg I. et al. Intermittent hypoxia increases exercise tolerance in elderly men with and without coronary artery disease. International Journal of Cardiology. 2004; 96: 247–254. doi: 10.1016/j.ijcard.2003.07.021.
34. Valle M.D.P., García-Godos F., Woolcott O.O. et al. Improvement of myocardial perfusion in coronary patients after intermittent hypobaric hypoxia. Journal of Nuclear Cardiology. 2006; 13: 69–74. doi: 10.1016/j.nuclcard.2005.11.008.
35. Серебровская Т.В., Шатило В.Б. Опыт использования интервальной гипоксии для предупреждения и лечения заболеваний сердечно-сосудистой системы. Обзор. Кровообіг та гемостаз. 2014; 1-2: 16-33.
Serebrovskaja T.V., Shatilo V.B. Experience in the use of interval hypoxia for the prevention and treatment of diseases of the cardiovascular system. Review. Krovoobig ta gemostaz. 2014; 1-2: 16-33. [In Russian].
36. Игнатенко Г.А., Денисова Е.М., Сергиенко Н.В. Гипокситерапия как перспективный метод повышения эффективности комплексного лечения коморбидной патологии. Вестник неотложной и восстановительной хирургии. 2021; 6(4): 73-80.
Ignatenko G.A, Denisova E.M., Sergienko N.V. Hypoxytherapy as a promising method of increasing the effectiveness of complex

treatment of comorbid pathology. Bulletin of urgent and recovery surgery. 2021; 6(4): 73-80. [In Russian].

37. Игнатенко Г.А., Мухин И.В., Джоджуа Р.А. Влияние разных режимов терапии на частоту гипертензивных кризов и суточные профили артериального давления у молодых больных генетически индуцированной гипертонической болезнью. Вестник гигиены и эпидемиологии. 2020; 24(2): 159-163.
Ignatenko G.A., Muhin I.V., Dzhodzhua R.A. The effect of different therapy regimens on the frequency of hypertensive crises and daily blood pressure profiles in young patients with genetically induced hypertension. Vestnik of hygiene and epidemiology. 2020; 24(2): 159-163. [In Russian].
38. Игнатенко Г.А., Контовский Е.А., Дубовик А.В. и др. Применение интервальной нормобарической гипокситерапии у больных с кардиопульмональной патологией. Вестник гигиены и эпидемиологии. 2018;22(4):22-25.
Ignatenko G.A., Kontovskij E.A., Dubovik A.V. et al. The use of interval normobaric hypoxytherapy in patients with cardiopulmonary pathology. Vestnik of hygiene and epidemiology. 2018;22(4):22-25. [In Russian].
39. Игнатенко Г.А., Мухин И.В., Паниева Н.Ю. Качество жизни у гипертензивных больных гипотиреозом на фоне разных режимов терапии. Вестник гигиены и эпидемиологии. 2020; 24(2): 185-188.
Ignatenko G.A., Muhin I.V., Panieva N.Ju. Quality of life in hypertensive patients with hypothyroidism against the background of different therapy regimens. Vestnik of hygiene and epidemiology. 2020; 24(2): 185-188. [In Russian].
40. Montero D., Lundby C. Effects of Exercise Training in Hypoxia Versus Normoxia on Vascular Health. Sports Med. 2016; 46: 1725–1736. doi: 10.1007/s40279-016-0570-5.
41. Casey D.P., Joyner M.J. Local control of skeletal muscle blood flow during exercise: influence of available oxygen. Journal of Applied Physiology. 2011; 111: 1527–1538. doi: 10.1152/japplphysiol.00895.2011.
42. Wang J., Wu M., Mao T. et al. Effects of normoxic and hypoxic exercise regimens on cardiac, muscular, and cerebral hemodynamics suppressed by severe hypoxia in humans. Journal of Applied Physiology. 2010; 109: 219–229. doi: 10.1152/japplphysiol.00138.2010.
43. Jung K., Seo J., Jung W.S. et al. Effects of an Acute Pilates Program under Hypoxic Conditions on Vascular Endothelial Function in Pilates Participants: A Randomized Crossover Trial. International Journal of Environmental Research and Public Health. 2020; 17: 258. doi: 10.3390/ijerph17072584.
44. Katayama K., Fujita O., Iemitsu M. et al. The effect of acute exercise in hypoxia on flowmediated vasodilation. European Journal of Applied Physiology. 2013; 113: 349–357. doi: 10.1007/s00421-012-2442-5.
45. Nishiwaki M., Kawakami R., Saito K. et al. Vascular adaptations to hypobaric hypoxic training in postmenopausal women. The Journal of Physiological Sciences. 2011; 61: 83–91. doi: 10.1007/s12576-010-0126-7.
46. Park H., Jung W., Kim J. et al. Twelve weeks of exercise modality in hypoxia enhances health-related function in obese older Korean men: a randomized controlled trial. Geriatrics & Gerontology International. 2019; 19: 311–316. doi: 10.1111/ggi.13625.
47. Jung K., Kim J., Park H. et al. Hypoxic Pilates Intervention for Obesity: A Randomized Controlled Trial. International Journal of Environmental Research and Public Health. 2020; 17: 7186. doi: 10.3390/ijerph17197186.
48. Zembron-Lacny A., Tylutka A., Wacka E. et al. Intermittent Hypoxic Exposure Reduces Endothelial Dysfunction. Biomed Res Int. 2020; 2020: 6479630. doi: 10.1155/2020/6479630.
49. Korkushko O.V., Shatilo V.B., Ishchuk V.A. Effectiveness of intermittent normabaric hypoxic trainings in elderly patients with coronary artery disease Advances in Gerontology. 2010;23:476–482.
50. Levine B.D. Going High with Heart Disease: The Effect of High-Altitude Exposure in Older Individuals and Patients with Coronary Artery Disease. High Altitude Medicine & Biology. 2015; 16: 89–96. doi: 10.1089/ham.2015.0043.