ORIGINAL ARTICLE

INFLUENCE OF INTERVAL NORMOBARIC HYPOXYTHERAPY ON THE PROCESSES OF ISCHEMIC PRECONDITIONING IN THE MYOCARDIUM OF PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

DOI: 10.36740/WLek202201211

Nadiia Masik, Sergiy Nechiporuk, Anastasiya-Aleksandra Fomina
NATIONAL PIROGOV MEMORIAL MEDICAL UNIVERSITY, VINNYTSIA, UKRAINE

ABSTRACT

The aim: Determination of cardioprotective effect of interval normobaric hypoxia in medical rehabilitation of patients with COPD.

Materials and methods: 123 patients with COPD who received basic drug therapy were examined and were divided into 2 groups. Patients of the main group (93 persons) additionally received 2 courses of 20 sessions of interval normobaric hypoxia. All patients underwent echocardiographic examination at the beginning and after 1 year of follow-up.

Results: Prior to treatment, all patients had changes in the myocardium of both ventricles, due mainly to hypoxic and inflammatory effects and to a lesser extent to increased pulmonary artery pressure. Interval normobaric hypoxytherapy caused adaptive-adaptive reactions of the cardiovascular system, which manifested a positive effect on the state of both left and right ventricles: increase in stroke volume and expulsion fraction, decrease in E-DV and E-SV of the left and right ventricular E-DS, elimination of myocardium. However, the result is more effective in patients with GOLD 1 and GOLD 2 compared to GOLD 3.

Conclusions: The use of interval normobaric hypoxytherapy in the rehabilitation of COPD, initiated by ischemic preconditioning, is pathogenetically justified because it triggers endogenous mechanisms of cardioprotection and metabolic adaptation.

KEY WORDS: COPD, interval normobaric hypoxytherapy, the phenomenon of ischemic preconditioning, cardioprotection

Wiad Lek. 2022;75(1 p.2):209-214

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) often coexists with other diseases that may develop as a result of or independently of COPD [1]. Thus, the association of COPD and cardiovascular pathology is primarily related to the presence of common risk factors such as smoking, age, hypodynamics, adverse environmental conditions, concomitant hypertension and diabetes, dyslipidemia, obesity, and similar pathogenetic mechanisms, such as systemic inflammation [2].

Medical rehabilitation of patients with COPD is one of the urgent problems of modern health care, and the presence of cardiovascular effects as a systemic manifestation of COPD involves the search for rehabilitation programs that take into account hemodynamics and external respiration and reflect the backup capabilities of the cardiorespiratory system [3] and increase the body's resilience to such "complex" patients.

An effective way to increase the body's resistance to damaging effects is the use of "conditioning" (from the English. Conditioning-stipulation), aimed at mobilizing endogenous defense mechanisms [4-6]. Preconditioning is a term that arose to describe the phenomenon of metabolic adaptation of an organism or its individual organs (myocardium, brain, etc.) to hypoxia and / or ischemia [5].

As a result of repeated short-term episodes of ischemia, conditions are created that allow the myocardium to adapt and better tolerate episodes of longer ischemia due to endogenous self-organizing cardioprotection, which is called ischemic preconditioning [7-9].

The cell survival program initiated by ischemic preconditioning is triggered by short episodes of non-lethal ischemia and is realized in most tissues and organs of different species of animals, as well as in humans [10]. The presence and severity of the phenomenon of ischemic preconditioning may depend on various factors - sex, age, the presence of certain diseases, changes in the structure and function of the myocardium, taking certain drugs [9, 11-13].

The mechanisms of formation of the protective effect of ischemic preconditioning are very similar to the processes that occur during the formation of adaptation to hypoxia (hypoxic preconditioning), they are associated with changes in intracellular metabolism with oxygen deficiency, but are accompanied by more powerful activation of the systems responsible for adaptation [14, 15].

An integral feature of preconditioned tissues is the ability of mitochondria to effectively restore their ATP-synthesizing function after prolonged ischemia, as well as a significant decrease in the production of reactive oxygen species during reoxygenation compared to non-conditioned mitochondria [6, 16, 17]. A special role is played by uncoupling proteins (UCPs), which are localized in the inner membrane of mitochondria and

regulate the functioning of the electron transport chain [18]. It has been shown that these proteins may be one of the end effects of cell survival and ischemia adaptation. Moderate separation of oxidative phosphorylation mediated by UCP can reduce the production of reactive oxygen species by the respiratory chain, provide a quick restoration of the energy function of mitochondria in the early postischemic period and significantly increase the percentage of surviving cardiomyocytes and, accordingly, contribute to the rapid restoration of myocardial functions.

Ischemia also induces a hypoxia-inducible factor (HIF), which activates a wide range of responses aimed at protecting cells from hypoxic damage or promoting reoxygenation of affected tissue [19, 20]. Activators of HIF-1α and genes, the expression of which increases upon stabilization of HIF-1α, trigger adaptation reactions to hypoxia. HIF-1α is defined as a critical regulator of the response to ischemic damage in patients with microcirculatory disorders [21].

Based on the described mechanisms of ischemic preconditioning, it becomes obvious that there is the need to search for tools and methods that can simulate signal cascades of preconditioning. The experiment proved the "training" effect of periodic hypoxia, which adapts the animal's body to conditions of oxygen deficiency.

Under conditions of intermittent hypoxia, the damaging factor does not act continuously, there is an alternation of normoxia with lack of oxygen, this is a kind of "ischemia / reperfusion" [22].

An important role in the mechanism of this adaptation is played by reactions at the level of the body (hyperventilation, activation of the heart, increased erythropoiesis, etc.), and a modification of cellular metabolism (activation of glycolysis, increased ability to utilize oxygen at its low content, increased power of the antioxidant cellular defense system and others) [15]. As a result, hypoxic training leads to better tolerance of oxygen deficiency by the cells [23], i.e. adaptation occurs, as a result of which myocardial metabolism changes, adapting to a reduced supply of oxygen.

From a clinical point of view, the development of new rehabilitation programs based on the use of the phenomenon of ischemic preconditioning is a promising direction in the treatment of patients with the presence of myocardial damage with COPD. Since there are currently few studies on the development of non-drug rehabilitation techniques using the preconditioning effect in such patients, the question of the practical use of the preconditioning phenomenon requires further clinical study.

THE AIM

Based on this, the aim of the study was to determine the cardioprotective effect of the use of interval normobaric hypoxia in rehabilitation and prevention programs for patients with COPD by launching the phenomenon of myocardial preconditioning.

MATERIALS AND METHODS

The study included 123 patients diagnosed with COPD at least 6 months before the study, in whom the disease was in remission. Participation in the study was voluntary, all subjects received detailed information about the study and signed an informed consent.

The diagnosis of COPD was established in accordance with the recommendations of GOLD and the order of the Ministry of Health of Ukraine № 555 from 27.06.2013 [1, 24, 25].

Among the examined patients there were 58 men (47.15%) and 65 women (52.85%). The middle age was 43.7±14.8 years. The duration of the disease averaged 13.63±2.06 years. Characteristics of patients by age are presented in table I.

The diagnosis of mild COPD (GOLD 1) was established in 41 (33.33%) patients, moderate (GOLD 2) - in 54 (43.90%) patients, severe (GOLD 3) - in 28 (22.77 %) persons. In 37 (30.08%) patients with COPD signs were found of pulmonary insufficiency (LN) of I degree, in 32 (26.02%) patients - signs of LN of II degree, and in 7 (5.69%) - signs of LN III degree.

The patients examined by us were divided into 2 groups, representative by age, sex, clinical course of COPD (table II).

All patients received basic drug therapy according to the order for 3 or more months before inclusion in the study. Patients in the main group (93 people) additionally received sessions of interval normobaric hypoxia. For 30 minutes, patients breathed a gas hypoxic mixture consisting of 10% oxygen and 90% nitrogen, corresponding to an altitude of 5,000 meters above sea level. Each session consisted of six cycles of breathing a hypoxic gas mixture with intervals during which the patient breathed atmospheric air. Modeling of "mountain air" was carried out with the help of the device-hypoxicator "Borey-2" (the device of the Borey type, manufactured by the scientific medical-engineering center NORT NAS of Ukraine, Kyiv). The hypoxicator allows dosing both the level of hypoxia and the training mode that provides the greatest efficiency and safety [26]. The course of treatment was 20 sessions. Repeated course of hypoxytherapy was performed after 6 months. During the study period, 2 courses of hypoxytherapy were performed.

All patients underwent echocardiographic examination on the device "Sim-5000" (made in Japan) in M-mode and B-mode at the beginning of the study and after 1 year of observation. This evaluated the structural and functional parameters of the heart: the thickness of the anterior wall of the right ventricle (RV), end-diastolic size (E-DS) of the right ventricle, end-diastolic size of the left ventricle (LV), end-systolic size of the left ventricle, the thickness of the interventricular septum (T IVS) and the posterior wall (PW) of the left ventricle in diastole calculated indicators of intracardiac hemodynamics by conventional methods: end-diastolic (E-D), end-systolic (E-S) and stroke volume (SV), LV, minute volume (MV), expulsion fraction (EF), anterior-posterior contraction fraction the size of the left ventricle during systole (CF). Assessment of LV diastolic function was performed on the basis of determining the dependence of the movement of the anterior mitral valve on the speed of mitral blood flow. The dynamics of the pressure gradient between the right ventricle and the pulmonary artery were studied.

The data obtained were processed by methods of variation statistics using the computer program "Statistica 6.0 for Windows" [27].

RESULTS

For patients of both groups before treatment deterioration of contractile ability of a myocardium of a right and left ventricles was defined. Thus, there was an increase in the E-DS of the RV, which was 2.50±0.04 cm in patients of the main and 2.55±0.05 cm in patients of the control groups. Along with this, there was hypertrophy of the anterior wall of the RV – its thickness at the end of diastole was 0.57±0.02 cm. Similar changes were observed in the structural state of the left ventricle (LV). E-DV and E-SV of the left ventricle (LV) were 128.6±1.40 ml and 55.3±0.99 ml, respectively, in patients of the main group and 129.0±2.10 ml and 54.1±1.97 ml in patients of the control group.

Changes in the functional state of the left ventricle coincided with structural adjustment. In both groups of the study, the expulsion fraction (EF) was reduced and was 57.2±0.43% in the main and 58.3±0.98% in the control groups. There was no significant difference in the performance of both groups before treatment (p> 0.05) (table III).

The presence of diastolic myocardial dysfunction (DMD) in patients with COPD before treatment was observed in 36.6% of

Table I. Distribution of patients by age

Age	Number of respondents	
	Absolute	% ratio
Up to 35 years	31	25.2
36-45	31	25.2
46-55	31	25.2
56 and older	30	24.4
Total	123	100

Table II. Distribution of patients by severity of the clinical course of COPD

Observation groups	n	GOLD 1	GOLD 2	GOLD 3
Basic	93	30 (32,3%)	40 (43,0%)	23 (24,7%)
Control	30	11 (36,7%)	14 (46,6%)	5 (16,6%)
Total	123	41 (33,3%)	54 (43,9%)	28 (22,8%)

Table III. Structural and functional indicators of the heart of patients with COPD before treatment (M ± m)

Indicators	Main group n=93	Control group n=30
E-DS of the right ventricle, cm	2,50±0,04	2,55±0,05
The thickness of the anterior wall of the right ventricle, cm	0,57±0,02	0,56 ± 0,03
E-DVof the left ventricle, ml	128,6 ± 1,40	129,0 ± 2,10
E-SV of the left ventricle, ml	55,3 ± 0,99	54,1 ± 1,97
EF, %	57,2 ± 0,43	58,3 ± 0,98
CF, %	30,4 ± 0,27	31,2 ± 0,65
SV of the LV, ml	73,3 ± 0,62	74,9 ± 0,88
Heart rate, beats / min	72,1 ± 0,59	73,2 ± 1,70
End-diastolic pressure between the right ventricle and the pulmonary artery, mm. Hg.	3,57 ± 0,08	3,56 ± 0,11

Note. A significant difference in the indicators before treatment compared with the control group was not found (p>0.05).

Table IV. Structural and functional parameters of the heart of patients with COPD after treatment (M±m)

Indicators	Main group n=93	Control group n=30
E-DS of the right ventricle, cm	2,34 ± 0,04**	2,57 ± 0,06*
The thickness of the anterior wall of the right ventricle, cm	0,49 ± 0,02**	0,56 ± 0,03*
E-DVof the left ventricle, ml	123,3 ± 1,30*	129,4 ± 2,20*
E-SV of the left ventricle, ml	44,4 ± 0,99**	54,6 ± 1,93*
EF, %	64,3 ± 0,52**	57,9 ± 0,98*
CF, %	35,3 ± 0,37**	30,9 ± 0,62*
SV of the LV, ml	79,0 ± 0,70**	74,8 ± 1,15*
Heart rate, beats / min	67,3 ± 0,56**	74,5 ± 1,57*
End-diastolic pressure between the right ventricle and the pulmonary artery, mm. Hg.	2,52 ± 0,07	3,60 ± 0,11

Note. 1) The sign * indicates a probable difference in the indicators (p<0.05) in comparison with the indicators of the control group;
2) The sign ** indicates a probable difference in indicators (p<0.05) in comparison with patients before treatment.

Table V. Dynamics of structural and functional parameters of the heart of patients with COPD depending on the severity of treatment (M±m)

Indicators		GOLD 1 n=30	GOLD 2 n=40	GOLD 3 n=23	Control group n=30
E-DS of the right ventricle, cm	before	2,35 ± 0,07	2,55 ± 0,04	2,54 ± 0,05	2,55±0,05
	after	2,19 ± 0,05	2,39 ± 0,06 *	2,42 ± 0,07	2,57 ± 0,06
E-DV of the left ventricle, ml	before	123,9 ± 2,8	133,5 ± 1,7	139,2 ± 0,22	129,0 ± 2,10
	after	119,2 ± 2,6	125,4 ± 1,6 *	135,8 ± 0,24	129,4 ± 2,20
E-SV of the left ventricle, ml	before	51,4 ± 1,93	57,4 ± 1,28	64,8 ± 0,26	54,1 ± 1,97
	after	51,2 ± 1,91	45,1 ± 1,25 *	60,7 ± 0,31 *	54,6 ± 1,93

Note. The sign * indicates a probable difference in indicators ($p<0.05$) in comparison with the control group.

the main and 33.3% of the control groups. In patients of both groups, the end-diastolic pressure between the RV and the pulmonary artery did not exceed the norm and was, respectively, 3.57±0.08 mm. Hg. and 3.56±0.11 mm. Hg.

Analyzing the set of obtained indicators of the structural and functional state of the myocardium, it can be noted that before treatment in patients of both groups there were changes due mainly to hypoxic and inflammatory effects on the myocardium and to a lesser extent to increased pulmonary artery pressure.

After a course of complex treatment with the inclusion of the method of normobaric hypoxytherapy (twice a year), there was a positive dynamics of structural and functional status of the heart. Thus, the thickness of the anterior wall of the RV decreased by 16.33% in patients of the main group, while in the control remained unchanged. Indices of E-DS of the RV decreased by 6.84% and the right atrium from 4.7±0.05 cm to 4.55±0.05 cm, respectively. The decrease in the degree of hypertrophy and the size of the RV occurred simultaneously with the decrease in the level of end-diastolic pressure between the RV and the pulmonary artery by 41.67%. No dynamic pressure changes were observed in the control group. Along with structural changes in the right heart, similar changes occurred in the left ventricle. In patients of the main group under the influence of complex treatment there was a decrease in E-DV and E-SV of the left ventricle by 4.29% and 24.44%, respectively. These structural changes led to an increase SV of LV by 7.78%. There were no statistically significant changes in LV in patients of the control group. Comparative data of patients of both groups are shown in table IV.

During adaptation to normobaric hypoxia, an adaptive response of the cardiovascular system was observed, while the minute volume (MV) remained unchanged (5.29±0.07 l / min before treatment and 5.33±0.07 l / min after) at increase in stroke volume (SV). Myocardial contractility increased, as evidenced by an increase in EF by 12.41% and CF by 16.12% and the elimination of manifestations of diastolic myocardial dysfunction from 36.6% to 11.8% in patients of the main group (from 33.3% to 26.7% - in the control).

The dependence of dynamics of the indicators of the structural and functional state of the heart in the examined patients with varying severity of COPD on the chosen treatment regimen deserves attention. Under the influence of complex treatment, an improvement in the functional state of the left ventricle was observed depending on the severity of COPD. Thus, in patients with GOLD 1 before treatment, changes in E-DV and E-SV did not go beyond the physiological corridor. After comprehensive treatment, E-DV decreased by 3.9%, in the absence of E-SV changes. At GOLD 2 E-DV and E-SV, which before treatment did not differ from the control group, under the influence of treatment significantly decreased by 6.46% and 27.27%, respectively. In patients with GOLD 3, E-DV and E-SV decreased by 2.5% and 6.75%, respectively. Changes in E-DV and E-SV in patients of the control group were not statistically significant (table V). Analyzing the data obtained, we can conclude that the use of comprehensive treatment is more effective in patients with GOLD 1 and GOLD 2.

The expediency of prescribing normobaric hypoxytherapy for the prevention of heart failure in the early stages of the disease is also indicated by the dynamics of E-SV - of the left ventricle depending on the presence of complications. In patients with signs of pulmonary insufficiency (PI) I, E-SV decreased by 20.4%, with manifestations of PI II - by 21.4%, in patients with PI III - by 6.3%.

According to the results of the study, the right ventricle, which, in addition to hypoxic and toxic factors, is affected by resistance load due to pulmonary hypertension, which occurs during exercise, responds earlier than the left. In patients with GOLD 1, the E-DS of the RV was 2.35±0.07 cm before treatment, while in patients with manifestations of GOLD 2 and GOLD 3, dilatation of the RV was observed: the E-DS was 2.55±0.04 cm and 2.54±0.05 cm, respectively. Under the influence of treatment, E-DS of the RV decreased in patients of the main group: with signs of GOLD 1 - by 6.8%, with GOLD 2 - by 6.3% and with GOLD 3 - by 4.8%. In patients of the control group there were no statistically significant changes in the structure of the RV, but, on the contrary, there was a tendency to increase its E-DS. The most effective comprehensive treatment is in patients with mild or moderate course of the disease. The level of E-DP between the right ventricle and the pulmonary artery confirms the point of view of most authors that the occurrence of edema of the lower extremities is more due to blood deposition in the inferior vena cava than to true right ventricular failure [28].

DISCUSSION

It is supposed that the mechanisms of ischemic preconditioning are largely similar to the body's adaptation to intermittent hypoxia [29, 30]. In contrast to ischemic preconditioning models, which are always local in nature (ischemia of a specific site or organ), the whole organism is exposed to hypoxic preconditioning [31]. Oxygen deficiency in conditions of hypoxia / ischemia requires maximum mobilization and tension of the potential adaptive capabilities of the body. This leads to an increase in the

efficiency of functioning of oxygen transport at various levels: respiration and systemic blood flow are activated, microcirculation is improved, the activity of respiratory enzymes and antioxidant systems is increased, lipid peroxidation processes are inhibited [32-34].

There is an opinion that hypoxic preconditioning reduces the anti-inflammatory effect of ischemia / reperfusion in the myocardium, affecting the lipoxygenase pathway of arachidonic acid metabolism, leading it to a state of "readiness" for a possible ischemic attack, thereby reducing damage to cardiomyocytes [14].

Thus, sessions of interval hypoxia are accompanied by successive adaptation-maladaptation stages. According to [35], these stages are combined or separated in time: metabolic adaptation - "ischemic preconditioning" (implementation of various intracellular metabolism pathways), functional adaptation - "myocardial hibernation" (reduction of myocardial contractile function according to the level of energy phosphates), biological rehabilitation - «stunned myocardium» (restoration of contractile function) or death of myocardial cells (apoptosis).

The phenomenon of preconditioning is essentially a way of physiological training for oxygen deficiency and is a promising scientific direction for the formation of ischemic and hypoxic tolerance of the body. Assessing in the complex indicators of structural and functional state of the heart in patients of the main and control groups before and after treatment, we can conclude that the inclusion in the complex treatment of interval normobaric hypoxia has a positive effect on both left and right ventricles. The use of the phenomenon of ischemic preconditioning in rehabilitation programs is pathogenetically justified, as its initiation triggers endogenous mechanisms of cardioprotection and metabolic adaptation to non-lethal ischemia. Thus, the use of normobaric hypoxytherapy can increase the contractility of the myocardium, reduce the degree of hypertrophy of the muscles of the wall and ventricular dilatation, eliminate the manifestations of diastolic myocardial dysfunction. These changes are due to the activation of the energy supply of the heart, reducing infectious and toxic effects on the myocardium, as well as increasing the efficiency of pulmonary gas exchange, which determines normobaric hypoxia as an effective tool to eliminate bronchial obstruction in COPD. Therefore, the implementation of approaches that promote the activation and prolongation of this natural defense mechanism (preconditioning) will significantly reduce cardiovascular morbidity and mortality.

CONCLUSIONS

1. The process of heart remodeling in patients with COPD covers the entire myocardium, which is confirmed by an increase in the size of the right ventricle (E-DS - 2.52±0.04 cm) and a decrease in the contractile capacity of myocardium of the left ventricle (EF - 57.75±0.71%). These changes are mainly due to hypoxic and inflammatory effects on the myocardium and to a lesser extent to an increase in pulmonary artery pressure, as the end-diastolic pressure between the right ventricle and the pulmonary artery did not exceed normal.
2. The use of interval normobaric hypoxia in the rehabilitation treatment of patients with COPD has a positive effect on the structural and functional state of the myocardium of the right heart. Thus, the degree of right ventricular hypertrophy decreased by 16.33% and the level of end-diastolic pressure between the right ventricle and the pulmonary artery by 41.67%.
3. The positive effect of normobaric hypoxytherapy was noted on the condition of the left ventricle, which was confirmed by a decrease E-DV and E-SV of the left ventricle by 4.29% and 24.44%, respectively, an increase SV by 7.78%, an increase EF by 12.41% and CF by 16.12%.
4. The course of normobaric hypoxytherapy is more effective in patients with GOLD 1 and GOLD 2, which allows it to be recommend as an effective and safe addition or alternative to traditional methods of rehabilitation compared to traditional schemes, which will reduce the financial costs of treatment and sustainable remission.

REFERENCES

1. Feshchenko Y.I., Gavrysyuk V.K., Dziublyk A.Y. et al. Adapted clinical guideline: chronic obstructive pulmonary disease (part 1). Ukr. Pulmonol. J. 2019;2:5–18. doi: 10.31215/2306-4927-2019-104-2-5-18.
2. Krakhmalova O.O., Getman O.A., Kolesnikova O.N. et al. Peculiarities of COPD and IHD co-morbidity in patients with frequent and rare exacerbations of COPD Ukr. Pulmonol. J. 2018; 2:19-24. doi: 10.31215/2306-4927-2018-100-2-19-24.
3. Krakhmalova O.O., Hetman O.A., Kharchenko Yu.Y., Izmailova O.V. Dynamics of ultrasound parameters of diastolic and systolic cardiac function in COPD patients with concomitant coronary heart disease, depending on maintenance therapy of COPD and the presence of pulmonary rehabilitation. Ukr. Pulmonol. J. 2017; 4:30–34. (In Ukrainian).
4. Baranova K.A. Remote ischemic brain conditioning: phenomena and mechanisms. Neurochemistry. 2017,34(3):1-6. doi: 10.7868/S1027813317030025.
5. Levchenkova O.S., Novikov V.E. Possibilities of Pharmacological Preconditioning. Annals of the Russian Academy of Medical Sciences. 2016;71(1):16–24. doi: 10.15690/vramn626).
6. Bautin A.E., Karpova L.I., Marichev A.O. et al. Cardioprotective effects of ischemic conditioning. Up-to-date information in physiology, experimental evidences and clinical applications. Translational Medicine. 2016;3(1): 50–62. (In Russian).
7. Khetsuriani M., Ioffe N., Rudenko M. et al. Remote Ischemic Preconditioning Contributes to the Expression of Long Non-Coding RNA H19 and Hypoxia-Inducible Factor-1α during Isolated Coronary Artery Bypass Graft Surgery in Patients with Ischemic Heart Disease. Ukrainian Journal of Cardiovascular Surgery. 2020;3(40):49-54.
8. Randhawa P.K., Bali A., Virdi J.K., Jaggi A.S. Conditioning-induced cardioprotection: Aging as a confounding factor. Korean J Physiol Pharmacol. 2018;22(5):467-479. doi:10.4196/kjpp.2....
9. Macovei L., Anghel L. Pre-conditioning and post-conditioning in myocardial infarction. J Invasive Noninvasive Cardiol. 2017;1(1):4-5. doi: 10.35841/invasive-cardiology.1.1.4-5.
10. Casós K., Ferrer-Curriu G., Soler-Ferrer P. et al. Response of the human myocardium to ischemic injury and preconditioning: The role of cardiac and comorbid conditions, medical treatment, and basal redox status. PLoS ONE. 2017;12(4): e0174588. doi:10.1371/journa....
11. Zhou D., Ding J., Ya J. et al. Remote ischemic conditioning: a promising therapeutic intervention for multi-organ protection. Aging (Albany NY). 2018;10(8):1825–1855. doi: 10.18632/aging.101527.

12. Ahmadabad A.R.., Ghadiri M.K., Gorji A. The role of Toll-like receptor signaling pathways in cerebrovascular disorders: the impact of spreading depolarization. J Neuroinflammation. 2020;17:108. doi:10.1186/s12974....
13. Feige K., Raupach A., Torregroza C. et al. Effluent from ischemic preconditioned hearts confers cardioprotection independent of the number of preconditioning cycles. PLoS ONE. 2020;15(12): e0243220. doi:10.1371/journa....
14. Serebrovska T.V., Portnychenko A.G., Portnichenko V.I. et al. Effects of intermittent hypoxia training on leukocyte pyruvate dehydrogenase kinase 1 (PDK-1) mRNA expression and blood insulin level in prediabetes patients. Eur J Appl Physiol. 2019;119: 813–823. doi:10.1007/s00421....
15. Liamina N.P., Kotel'nikova E.V., Karpova E.S. Adaptation to hypoxia and ischemic preconditioning: pathophysiologic and clinical aspects of cardioprotection in patients with coronary disease. Cardiosomatics. 2015; 3:27-32.
16. Kuznetsov A.V., Javadov S., Margreiter R. et al. The Role of Mitochondria in the Mechanisms of Cardiac Ischemia-Reperfusion Injury. Antioxidants (Basel). 2019;8(10):454. doi: 10.3390/antiox8100454.
17. Hoshovs'ka Iu.V. The role of uncoupling proteins in mechanisms of protection from oxidative stress. Physiol. J. 2015;61(1):91-101.
18. Busiello R.A., Savarese S., Lombardi A. Mitochondrial uncoupling proteins and energy metabolism Front. Physiol. 2015;6:36. doi: 10.3389/fphys.2015.00036.
19. Aitbaev K.A., Murkamilov I.T., Fomin V.V. Inhibition of HIF-prolyl 4-hydroxylases as a promising approach to the therapy of cardiometabolic diseases. Therap. arch. 2018,8:86-94. doi:10.26442/terar....
20. He X.R., Huang J.C., Chen G.P., Lin Q.C. MicroRNA-1249 regulates the apoptosis of myocardial cells in rats with chronic intermittent hypoxia by autophagy. Zhonghua Yi Xue Za Zhi. 2018;98(36):2937-2941. doi: 10.3760/cma.j.issn.0376-2491.2018.36.013.
21. Duscher D., Maan Z.N., Whittam A.J. et al. Fibroblastspecific deletion of hypoxia inducible factor-1 critically impairs murine cutaneous neovascularization and wound healing. Plast Reconstr Surg. 2015,136(5):1004. doi: 10.1097/PRS.0000000000001699.26.
22. Pena E., Brito J., El Alam S., Siques P. Oxidative Stress, Kinase Activity and Inflammatory Implications in Right Ventricular Hypertrophy and Heart Failure under Hypobaric Hypoxia. Int J Mol Sci. 2020;21(17):6421. doi:10.3390/ijms21176421.
23. Weng X., Chen H., Yu Q. et al. Intermittent Hypoxia Exposure Can Prevent Reductions in Hemoglobin Concentration After Intense Exercise Training in Rats. Front. Physiol. 2021; 12:627708. doi:10.3389/fphys....
24. Ministry of Health Order No. 555 of June 27, 2013 «Unified clinical protocol of primary, secondary (specialized), tertiary (highly specialized) medical care and medical rehabilitation. Chronic obstructive pulmonary disease». http://mtd.dec.gov.ua/images/d.... [date access 12.01.2021] (In Ukrainian).
25. Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease: 2017 Report. 2017. http://goldcopd.org/gold-2017-... [date access 12.01.2021]
26. Poliahushko L.H., Slipchenko V.H., Kotunov V.O. Udoskonalennia aparatno-prohramnoho kompleksu. Hipoksiia yak metod pidvyshchennia adaptatsiinoi zdatnosti orhanizmu. Kyiv:NTUU «KPI». 2015, 233p. (In Ukrainian).
27. Nieminen P. Applications of Medical Informatics and Data Analysis Methods. Appl. Sci. 2020;10:7359.
28. Gavrisiuk V.K., Yachnik A.I., Merenkova E.A. Cor pulmonle in light of international NICE-COPD and GOLD. Ukr. Pulmonol. J. 2014; 2:17-19.
29. Morand J., Arnaud C., Pepin JL. et al. Chronic intermittent hypoxia promotes myocardial ischemia-related ventricular arrhythmias and sudden cardiac death. Sci Rep. 2018;8:2997.
30. Serebrovskaya T.V., Shatilo V.B. Experience of using interval hypoxia in prevention and treatment of cardiovascular diseases: Review. Circulation and haemostasis. 2014;1:16-33.
31. Novikov V.E., Levchenkova O.S., Pozhilova E.V. Preconditioning as a method of metabolic adaptation to hypoxia and ischemia. Bulletin of the Smolensk State Medical Academy. 2018;17(1):69-79.
32. Asanov E.O., Svintsytskyi A.S., Polyagushko L.G. et al. Influence of hypoxic training on autonomic nervous system in elderly patients with COPD. Ukr. Pulmonol. J. 2017;1:31-36.
33. Mateika J.H., El-Chami M., Shaheen D., Ivers B. Intermittent hypoxia: a low-risk research tool with therapeutic value in humans J Appl Physiol. 2015;118:520–532. doi:10.1152/japplphysiol.00564.2.
34. Bernardi L. Interval hypoxic training. Adv. Exp. Med. Biol. 2001;502:377-399.
35. Yakovleva L.N. Special conditions of myocardium with ischemia. Medicine of Ukraine. 2018;2(218):43-48.

ORCID and contributionship:
Nadiia Masik: 0000-0002-6552-2470 [A,B,D-F]
Sergiy Nechiporuk: 0000-0003-3860-1189 [A-C,F]
Anastasiya-Aleksandra Fomina: 0000-0002-8544-596X [C,D]

Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR
Nadiia Masik
National Pirogov Memorial Medical University
56 Pirogov St,. 210018 Vinnytsia, Ukraine
tel: +308-97-6962631
e-mail: MasikOl@i.ua

Received: 08.01.2021
Accepted: 28.08.2021

A - Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article