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Original Article

Effect of physical rehabilitation on the oxidative modification of proteins in patients with ischemic heart diseases

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Abstract
The article presents data on the characteristics of oxidative modification of proteins in patients with coronary heart disease based on a complex restorative treatment. The dynamics of oxidative modification of proteins at a high physical activity before and after the physical rehabilitation was studied. **The aim of the study.** Study the features of oxidative modification of proteins in patients with ischemic heart disease (IHD) on the background of treatment and assess the dynamic change of proteins at a high physical activity before and after the physical rehabilitation. **Materials and methods.** The study involved 65 men with ischemic heart disease, stable angina pectoris I-II class, age from 32 to 60 years, averaging 44,6 ± 1,39 years, and 30 men who made up the control group from 36 to 60 years, average 43,0 ± 2,54 years. **Results.** We found significant alteration index OMP at a high-level exercise in groups II and III, which amounted to respectively 0,9 ± 0,13 OOH ($p < 0.05$) and 0,6 ± 0,04 OOH ($p < 0.001$) compared with controls 0,7 ± 0,05 OOH, with a tendency to increase in the group and where the figure was 0,8 ± 0,20 OOH. **Conclusion.** 1. In patients with coronary artery disease detected increase in oxidative modification of proteins ($p < 0.001$) positive correlation with the content of creatinine ($r = 0,35$) ($p < 0.05$) and lactate dehydrogenase activity ($r = 0,42$) ($p < 0.05$), and negative - of the total activity of creatine phosphokinase ($r = -0,54$) ($p < 0.05$). After the physical rehabilitation according to our methodology of bicycle training reduced oxidative modification of proteins in the study group with a direct correlation with lactate dehydrogenase activity ($r = 0,35$) ($p < 0.05$), indicating a decrease in metabolic acidosis and improve cell.
Key words: Ischemic Heart Disease; Oxidation Modification of Proteins Physical Rehabilitation.

Introduction

Bioenergetic processes in the myocardium are optimal for the functioning of the heart muscle, and they are provided exclusively by adenosinetriphosphate (ATP), which is synthesized in the mitochondria due to the oxidative phosphorylation of oxygen molecular (Severyn, 2019). Under the conditions of sudden myocardial ischemia, the ATP synthesis stops in the mitochondria, and in the cells, a rapid reduction in creatine phosphate and subsequently, ATP occurs (Osypenko, 2018). The fundamentally important phenomenon in the early stages of myocardial ischemia is a sharp decrease in contractile function at a relatively moderate reduction in ATP and creatine phosphate levels.

Adaptive processes at the cellular level are accompanied by the change in the activity of energy-producing enzymes and the change in the cell membrane's functional state. This is because any stress effect on the body causes peroxide processes to be activated - oxidative stress. This results in the stimulation of oxidative modification of the membrane phospholipids and proteins, leading to changes in physical and chemical properties of cells (Ena, Khrystoforova,2014; Shumakov et al., 2019; Antunes et al., 2020; Tomanek, Lis, 2020; Diachenko-Bohun et al., 2019a; Hrytsai et al., 2019; Diachenko-Bohun et al., 2019b; Lavrin et al., 2019a; Lavrin et al., 2019b; Diachenko-Bohun et al., 2019c; Diachenko-Bohun et al., 2020; Sereda et al., 2020; Shevtsiv et al., 2020; Savliuk et al., 2020a; Kashuba et al., 2020a; Grygus et al., 2020; Hrytsai et al., 2020; Novopysmennyi et al., 2020; Nesterchuk et al., 2020; Kashuba et al., 2020b; Savliuk et al., 2020b; Momot et al., 2020; Kashuba et al., 2020c).

The aim of the study. Study the features of oxidative modification of proteins in patients with ischemic heart disease (IHD) on the background of treatment and assess the dynamic change of proteins at a high physical activitybefore and after the physical rehabilitation.

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Materials and methods

Participants. The study involved 65 men with ischemic heart disease, stable angina pectoris I-II class, age from 32 to 60 years, averaging 44,6 ± 1,39 years, and 30 men who made up the control group 36 to 60 years, average 43,0 ± 2,54 years. Diagnosis is established based on the clinic, ECG, and laboratory examination following the European Society of Cardiology's standard criteria.

Procedure/Test protocol/Skill test trial/Measure/Instruments. Among examined patients, the groups were divided depending on the purpose of the rehabilitation program. All patients took citrulline malate at a dose of 2 g 3 times a day. The first group consisted of patients who took citrulline malate alone, and the second group consisted of patients who additionally conducted a standard set of therapeutic exercises (Mysiura et al., 2016), the third group consisted of patients who, while taking the drug was conducted by bicycle developed technique (Polianska, Kurtian,2006).

Data collection and analysis / Statistical analysis. Determination of the oxidative modification intensity of proteins in blood serum was determined by O.U. Dubinin method as modified by prof. I.F. Meschyshena Bukovinian State Medical University. The principle of the method is based on the relation of reaction between amino acid residues oxidized proteins and 2,4-Dinitrophenylhydrazine and the formation of aldehyde- and keton dinitrofenilhidrazin. Statistical analysis of the research results carried out on a personal computer using the application package Statistica 6,0 for Windows by StatSoft (USA) Excel 2000 within Microsoft Office 2000 Professional (USA) by the definition of averages, standard deviation, Student's t-test, and correlation analysis.Analysis of the distribution of values obtained wasperformed using the Kolmogorov-Smirnov test. The Kruskal-WallisH test was used to compare medians among three comparisongroups. Spearman's correlation coefficient (rs) was used todetermine the strength and direction of the association betweentwo variables. A probability value of $p<0.05$ was consideredstatistically significant.

Results

Index of oxidative modification of proteins (OMP) was higher in I, II, and III groups, accounting in accordance 1,2±0,26 OOH ($p<0,001$), 0,9±0,07 OOH ($p<0.001$), and 0.7±0,07 OOH compared with the control group 0,6±0,04 OOH(Table 1).

Thus, the observed increase in the OMP process indicates the presence of cell membrane destruction and tensions in the metabolic of cardiomyocytes, evidenced by a positive correlation to the OMP the first group containing creatinine ($r=0,35$) ($p<0.05$) and lactate dehydrogenase activity (LDH) ($r=0,42$) ($p<0.05$) in the second group of LDH ($r=0,35$) ($p<0.05$) and negative correlation with the total activity of creatine phosphokinase (CPK) ($r=-0,54$) ($p<0.05$).

Table 1.Features of oxidative modification of proteins in patients with ischemic heart disease

Index	Control (n=30)	I group (n=20)	II group (n=20)	III group (n=25)
OMP (OOH)	0,6±0,04	1,2±0,26***	0,9±0,07***	0,7±0,07

Note: The probability coefficient compared with the control group: *p<0,05,**p<0,01,*** p<0,001.

The leading role in the progression of the disease is played by mitochondrial changes. As a result of such processes, there is an increase in the number of reactive oxygen species (ROS). The main route of molecular oxygen activation in a cell is to restore it to the active centers of enzymes - oxidase and oxygenase. The high reactivity makes them highly toxic to biological systems at all levels of existence. The primary sources of the formation of superoxide anion radical, hydrogen peroxide, and hydroxyl radicals are the enzyme system: NADPH - oxidase, xanthine oxidase, mitochondrial cytochrome oxidase, and microsomal monooxygenases (cytochrome P-450) (Severyn,2019; Krzesiak et al., 2017).

Oxidase path of oxygen associated with the oxidation of energy substrates (lipids, carbohydrates, amino acid carbon skeletons) and realized by the final link of the respiratory chain cytochrome. This path of oxidation conjugate of oxidative phosphorylation (formation of ATP from ADP and inorganic phosphorus by the energy protons and electrons) is the main energy source. The mitochondrial respiratory chain can act as a hydrogen peroxide source (Ostapchenko et al. 2018; Shumakov et al., 2020).

Oxygenase way allows for the inclusion of one or two oxygen atoms in the substrate molecule by oxygenase enzymes. It is possible to restore the electrons of oxygen to form superoxide anion radicals and hydrogen peroxide. Oxygenase pathway is one of the main ways of formation of ROS (Osypenko,2018; Skliarov et al., 2015).

Today The main factors that contribute to the switching of the use of oxygen from oxidase to oxygenase: the excess of catecholamines and their products of incomplete oxidation under stress, a lot of restored pyridine nucleotide (NADH, NADPH) - donors of electrons, inactivation of the enzymatic and nonenzymatic antioxidant systems in a variety of diseases and avitaminosis E, accumulation of polyene nonsaturated lipids, which are exposed to ROS (in obesity). Switching the use of oxygen from the oxidase way to the oxygenase promotes

ROS's enhanced formation, and therefore, their negative impact on the phospholipids and biopolymers (proteins and nucleic acids). OMP increases under oxidative stress (Osypenko,2018; Shumakov et al., 2019; Krylatov et al., 2018).

Given that under hypoxia, there is a violation in the process of oxidative phosphorylation and action of the respiratory chain in the mitochondria, it should be noted the possibility of an increase of ROS, to which there is sensitive proteins membrane. OMP may include a direct cause of protein fragmentation or protein denaturation. Fragmented and denatured proteins are substrates for intracellular proteases (Skliarov et al., 2015).

After the oxidative modification, the proteins begin to be highly sensitive to proteolysis. In enzymes' case, the latest move in catalytically inactive or less active and more thermally labile forms (Osypenko, H. (2018; Ostapchenko et al., 2018).

We found significant alteration index OMP at a high-level exercise in groups II and III, which amounted to respectively 0,9±0,13 OOH ($p<0.05$) and 0,6±0,04 OOH ($p<0.001$) compared with controls 0,7±0,05 OOH, with a tendency to increase in the group and where the figure was 0,8±0,20 OOH (Table 2).

Table 2.Features of oxidative modification of proteins in patientswith ischemic heart disease at a high level exercise

Index	Control (n=30)	I group (n=20)	II group (n=20)	III group (n=25)
OMP (OOH)	0,7±0,05	0,8±0,20	0,9±0,13*	0,6±0,04***

Note: The probability coefficient compared with the control group: * p<0,05, ** p<0,01, *** p<0,001.

The observed increase in OMP may indicate that in patients began the destruction of cell membranes, which manifests itself in a violation of the integrity of the protein-membrane structures at high physical activity, as evidenced by the direct correlation of OMP index with the general action of the creatine kinase (r=0,32) ($p<0.05$).

Such changes show that under conditions of oxidative stress and non-controlled reactions of ROS, the superior processes become the unregulated proteins' modifications, which leads eventually to the loss of their biological activity. OMP generates new antigens and provokes an immune response that can cause secondary damage to other biomolecules (Severyn,2019; Skliarovet al., 2015; Shumakov et al., 2020).

The treatment in patients with ischemic heart disease index OMP did not change significantly, forming in the first group 1,2±0,26 OOH, in the second group 0,8±0,10 OOH, and the third group 0,9±0, 44 OOH (Fig. 1).

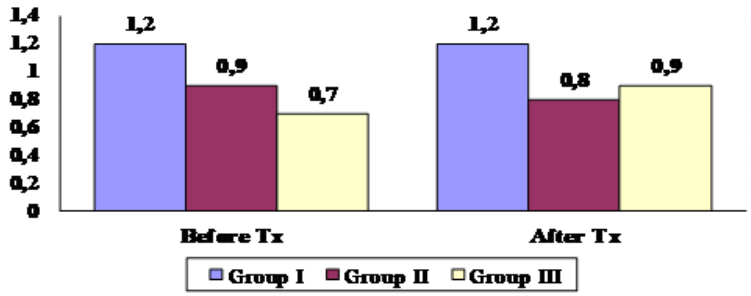

Fig. 1. Dynamics of oxidative modification of proteinsin patients with a background of Rehabilitation

Confirmation of improvement in metabolic and reduction in cells acidosis is a direct correlation detection of OMP with the activity of LDH in first group (r = 0,35) ($p <0.05$) in the second group (r = 0,54) ($p < 0.05$) in the third group (r = 0,34) ($p <0.05$). However, the resistance of mechanism of destruction of cell membranes proves to establish a negative correlation with OMP with the activity of total creatinine kinase, and the content of creatine, where the coefficient corresponds to the first and second group respectively (r = -0,42) ($p <0.05$) and (r = -0,44) ($p <0.05$), which lead to high sensitivity of creatinine phosphokinase way and resynthesis of ATP and its enzymes.

According to recent studies (Osypenko,2018; Severyn,2019; Skliarov et al., 2015; Krylatov et al., 2018; Rengo et al., 2017), oxidation modified proteins, in general, is not restored and must be removed by proteolytic degradation there for a reduction in proteolysis can lead to increased cellular content of altered redox proteins as studies have shown that oxidative stress causes many intracellular changes, including apoptosis. The combination of modification and degradation of chemically modified protein is in the range of normal metabolic reactions of proteins in vivo. It causes chemical apoptosis (Christiansen et al., 2018), which is one of the manifestations of programmed cell death.

Oxidative stress is formed in the uncontrolled generation of ROS, which is involved in the pathogenesis of many pathological processes. Generating in terms of oxidative stress, ROS exert a damaging effect on all

biological structures. The level of such exposure and its functional consequences depend on the nature of ROS molecules and targets (Krylatov et al., 2018; Krzesiak et al., 2017).After treatment at a high level of exercise OMP index in all groups did not change significantly, accounting for 1,1 ± 0,18 OOH (I group), 0,9 ± 0,15 OOH (II group), and 0,7 ± 0,04 OOH (group III) (Table 3).

Table 3. Features of oxidative modification of proteins in patients with ischemic heart disease on the background of rehabilitation at a high level of exercise

Index	I Group (n=20)		II Group (n=20)		III Group (n=25)	
	Before Tx	After Tx	Before Tx	After Tx	Before Tx	After Tx
OMP (OOH)	0,8±0,20	1,1±0,18	0,9±0,13	0,9±0,15	0,6±0,04	0,7±0,04

Note: The probability coefficient compared with the control group:* p<0,05, **p<0,01, *** p<0,001.

However, at a high level of exercise, we found in the first group a direct correlation of OMP with a decrease in activity OMB-MB fraction CK (r = 0,35) (p <0.05) and negatively with the content of creatinine (r = -0,35) (p <0.05) and total CK (r = -0,34) (p <0.05), suggesting the destruction of membranes of cardiomyocytes and an imbalance between energy synthesis and excretion of metabolic products of cells. In the second group, a direct correlation OMP containing creatinine (r = 0,53) (p <0.05) and negatively with increasing creatine (r = -0,54) (p <0.05), which proves normalization of energy supply material for the synthesis and excretion of metabolic products of energy at the cellular level. In the third group index OMP had a direct correlation with an increase in creatine content (r = 0,54) (p <0.05) and total CK (r = 0,53) (p <0.05), confirming normalization of admission plastic material creatinine phosphokinase way to activate ATP resynthesis process optimization and energy cells.

Discussion

Thus, applying the treatment combination malate citrulline, which stimulates the reduction of acidosis and speed of rotation of the Krebs cycle, and physical exercise aerobic direction can be achieved by the inclusion of mechanisms for energy, which is more easily formed by oxidation (in the Krebs cycle) decay products of carbohydrates and other substrates tissue breathing, especially fatty acids and acetate (Osypenko,2018; Skliarov et al., 2015).

ROS Attack of the proteins leads to the formation of primary amino radicals that enter into the secondary interactions with adjacent amino acid residues, which generally creates a very complex picture of ROS's damaging effect on protein macromolecules (Krylatovet al., 2018).

Modification of amino acid residues in proteins (i.e., conversion of the primary structure level) leads to these profound protein structure changes. This is reflected in the fragmentation and aggregation of proteins exposed to ROS. The consequence of such structure injuries leads to increased sensitivity to proteolytic degradation of proteins. Damage to the lipid matrix of biomembranes due to the formation of peroxide molecular products of polyunsaturated acyl accompanied by OMP and violation of biophysical properties of membrane proteins, which leads to profound changes enzymatic and ion transport properties of membranes (Skliarov et al., 2015; Rengo et al., 2017).

According to the literature, an essential mechanism in modifying proteins under oxidative stress is the formation of adducts of LPO with the enzymatic complex. It was noted the presence of peroxide lipid-modified proteins in human atherosclerotic plaques formed by the direct interaction of lysine residues with products of lipid peroxidation (Ostapchenko et al., 2018; Skliarov et al., 2015; Christiansen et al., 2018).

There is a perception of the possibility of the formation of autoantibodies to various types of adducts OMP, which has a pathogenic role in atherosclerosis and various inflammatory infect diseases (Ena, Khrystoforova,2014; Krzesiak et al., 2017).

Thus, various alcohols, aldehydes, hydrocarbons, and lipid peroxidation products may impair protein synthesis, vascular permeability changes, and the nature of the inflammatory response. According to some authors, it should be noted in a state of oxidative stress by ROS attack exposed not primarily by lipids, proteins, and plasma membranes, leading to their depolymerization and cell lysis. Proved that phospholipid-esterified isoketanol quickly damages the membrane proteins. The authors noted a high correlation between the synthesis of aberrant proteins and their oxidative modification (Ena, Khrystoforova,2014; Skliarov et al., 2015;Christiansen et al., 2018; Krylatov et al., 2018).

Thus, the process of oxidative modification of proteins associated with oxidized lipids peroxidation and destruction of cell membranes, which leads to a violation of their metabolism and eventually to a breach of the ion gradient of cells, in turn deepening the dysfunction of cardiomyocytes, which are extremely sensitive to changes in these mechanisms. Early work on these links and reducing the pathogenic process lysis of cell membranes help improve metabolic rate and decrease the progression of ischemic heart disease.

Conclusion

1. In patients with coronary artery disease, detected increase in oxidative modification of proteins ($p<0.001$) positive correlation with the content of creatinine ($r=0,35$) ($p<0.05$) and lactate dehydrogenase activity ($r=0,42$) ($p<0.05$), and negative - of the total activity of creatine phosphokinase ($r=-0,54$) ($p<0.05$). After the physical rehabilitation according to our methodology of bicycle training reduced oxidative modification of proteins in the study group with a direct correlation with lactate dehydrogenase activity ($r=0,35$) ($p<0.05$), indicating a decrease in metabolic acidosis and improve cell. 2. At a high physical activity in the dynamics of the treatment of ischemic heart disease revealed a direct correlation index of oxidative modification of proteins containing creatine ($r=0,54$) ($p<0.05$) and total creatine kinase activity ($r=0,53$) ($p<0.05$), confirming receipt of the normalization process energy material to activate creatine phosphokinase way resynthesis of ATP and energy optimization cells.

Prospects for further research. Investigation of oxidative modification of proteins in patients with ischemic heart disease on the background of physical rehabilitation in conjunction with taking proteolytic drugs.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the institutional and / or national research committee's ethical standards and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed Consent Informed consent was obtained from all individual participants included in the study. All subjects of the institutional survey gave consent for anonymized data to be used for publication purposes.

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