The effectiveness of metabolic therapy in patients with coronary heart disease and arrhythmias

G.M. Tulaboeva, A.A. Khalimov, X.M. Sagatova, Yu.Sh. Talipova, N.M. Abdukadirova, A.A. Khusanov, S.Dj. Mominov.

Center for the development of professional qualifications of medical workers, Department of cardtology and gerontology, interventional cardiology and arrhythmia

Abstract. The main pathological condition that occurs in many diseases of the cardiovascular system, in particular in coronary heart disease, is hypoxia. Clinical data indicate that a promising direction in the fight against hypoxia is the use of pharmacological agents that reduce hypoxia and increase the body's resistance to oxygen deficiency. Of particular interest are metabolic drugs that purposefully affect metabolic processes during hypoxia. These are drugs of various chemical classes, their action is mediated by various mechanisms: improving the oxygen transport function of the blood, maintaining the energy balance of cells, correcting the function of the respiratory chain and metabolic disorders of tissue and organ cells. Similar properties are possessed by antihypoxants, antioxidants and cytoprotectors, which are widely used in clinical practice. This article presents data from a clinical study of the drug gluthione, which open up additional therapeutic possibilities for the pharmacotherapy of coronary artery disease. Due to the original mechanism of action aimed at optimizing the energy metabolism of the myocardium, this drug should be used in combination therapy to potentiate the antianginal and antiarrhythmic effect in patients with coronary artery disease with heart rhythm disturbances.

Keywords: ischemic heart disease, cardiac arrhythmias, metabolic therapy, cytoprotection, antianginal therapy.

Relevance. Coronary heart disease (CHD) is currently one of the main causes of disability and mortality in economically developed countries. The wide prevalence of this disease among the population of older age groups takes this problem beyond the medical, turning into a general biological one and being one of the priorities in cardiology. According to the literature data, it is known that the problem of sudden

coronary death (SCD) is closely related to cardiac arrhythmias. Epidemiological studies have shown that the incidence of SCD in various countries is more than 1 case per 1000 population per year. Among arrhythmias, the most common is ventricular arrhythmia - 83% of cases, bradyarrhythmia - 17%, respectively [1].

Analysis of the features of the course of coronary artery disease against the background of cardiac arrhythmias is of interest not only for research purposes, but also for physicians of various specialties. This is the study of not only the clinical manifestations of coronary artery disease, but also the choice of the most informative instrumental research methods that allow not only to verify the diagnosis, but also to evaluate the effectiveness of drug therapy. Basic therapy for coronary artery disease is designed to optimize the ratio between the needs of the heart muscle in oxygen, on the one hand, and its delivery to the myocardium, on the other. It is known that the main mechanism of action of modern drugs used for the treatment of coronary artery disease is the hemodynamic unloading of the myocardium by reducing the frequency of heart rate (HR), as well as pre- and afterload. Accordingly, these funds have only an indirect effect on the oxygen supply of the myocardium. In this regard, an alternative approach to the treatment of patients with coronary artery disease is required: to focus not only on the coronary arteries, but also on the cardiomyocyte as the main target of ischemia [1,2,6].

The strategy of protecting cardiomyocytes from ischemic damage, regardless of the causal mechanism, is the most important condition for the production of energy necessary for its normal functioning. At the molecular level, IHD is characterized by a change in the course of metabolic processes. Currently, it is known that myocardial ischemia in metabolic disorders has a number of features associated with a high concentration of free fatty acids in the blood, an accelerated process of their oxidation, and impaired glucose utilization. In this regard, there is a need for metabolic therapy aimed at improving the efficiency of oxygen utilization by the myocardium under conditions of ischemia [7,8].

In recent years, in the treatment of patients with CVD, more and more attention has been paid to the use of drugs with a metabolic effect. Means of metabolic action

exhibit a wide range of pharmacological activity with little systemic toxicity. The basis for the implementation of their therapeutic efficacy is the modulation of metabolic reactions, which is manifested by an increase in the body's natural adaptive processes [3, 4, 5, 7]. Despite a large number of publications, the problem of the effectiveness of the use of drugs of various pharmacological groups in the treatment of coronary artery disease, in particular in the treatment of patients with arrhythmias, remains unresolved. One of the possible ways to solve this problem is the early and long-term use of cytoprotective drugs that not only improve metabolic processes in the myocardium, but also correct myocardial perfusion disorders, which in some cases are markers of early damage.

Objective: to study the effectiveness of glutathione in IHD patients with cardiac arrhythmias.

Materials and methods of research

The object of our study were 100 patients of both sexes aged 55 to 73 years (mean age 60.6±1.24 years). Patients were with stable exertional angina II–III FC. The diagnosis of coronary artery disease was established according to the criteria of the Canadian Association of Cardiology (1976) with the definition of four functional classes of angina pectoris and justified taking into account the nature of the pain syndrome, exercise tolerance and data from instrumental research methods.

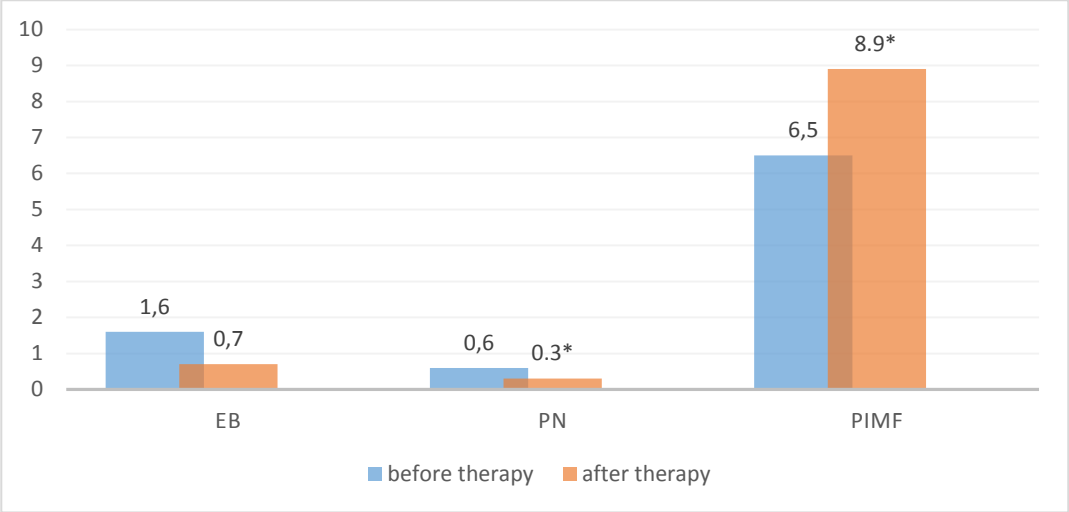
Research methods: instrumental - electrocardiography in 12 standard leads (ECG), 24-hour Holter ECG monitoring (HMECG), transthoracic echocardiography (EchoCG), tests with physical stress - VEM test, laboratory parameters - total cholesterol (TC), low density lipoproteins (LDL), high density lipoproteins (HDL), triglycerides (TG). Basic therapy for patients included: angiotensin-converting enzyme inhibitors (ACE inhibitors) - enalapril at a dose of 10 mg / day, lisinopril at a dose of 20 mg / day or losartan at a dose of 100 mg or valsartan at a dose of 40-80 mg, calcium channel blockers (CCBs) - - amlodipine at a dose of 5 mg / day and diuretics - hydrochlorothiazide 12.5 mg / day, beta-blockers - bisoprolol at a dose of 2.5-5 mg / day or nebivalol at a dose of 5 mg, acetylsalicylic acid (ASA) at a dose 75

mg / day, statins (atorvastatin) and short-acting nitrates for the relief of angina attacks (sublingually).

According to the study protocol, 70 patients (main group) received glutathione (Gluthione, Velpharm) 600.0 mg intravenously 2 times a day for 10 days in addition to the prescribed basic therapy. A re-examination was carried out after 30 days. The control group included 30 patients who received only basic therapy.

Research results

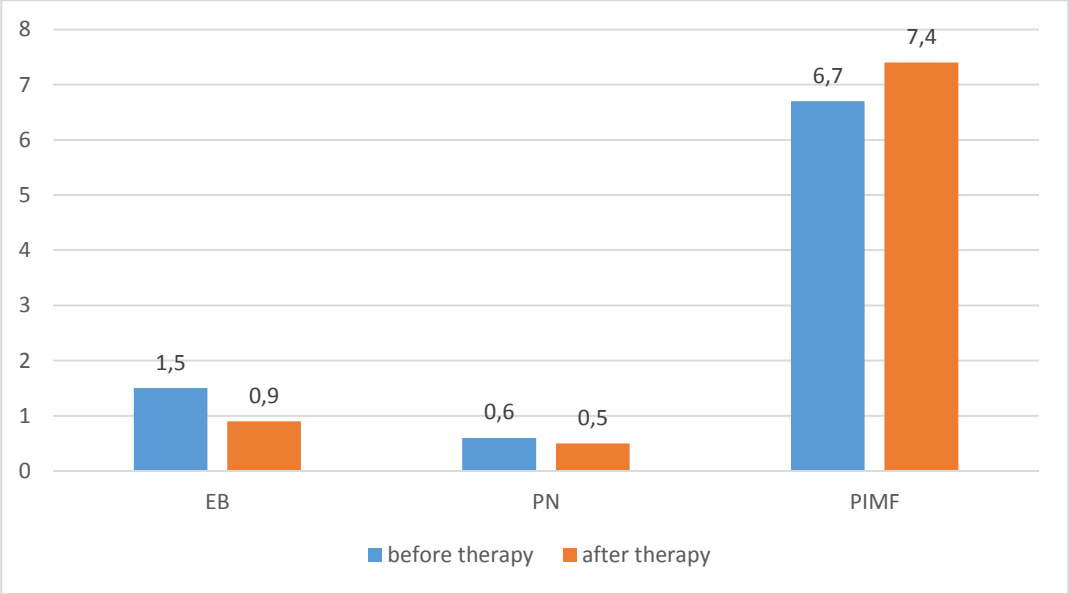
Under the influence of therapy, a decrease in the frequency, intensity and duration of attacks of pain or discomfort in the region of the heart during physical exertion was noted: the average duration of the pain episode before treatment was (2.5 ± 0.3) min, after treatment (1.2 ± 0.6) ($p<0.05$) min in the main group, in the control group - 2.4±0.2; 1.9±0.5 min, respectively (Fig. 1).



Note: *($p<0.05$) significance of differences in relation to the initial data, EB pain episodes, PN-nitroglycerin intake, PMPP- threshold power of physical activity

Fig.1. Analysis of clinical and instrumental research methods (main group)

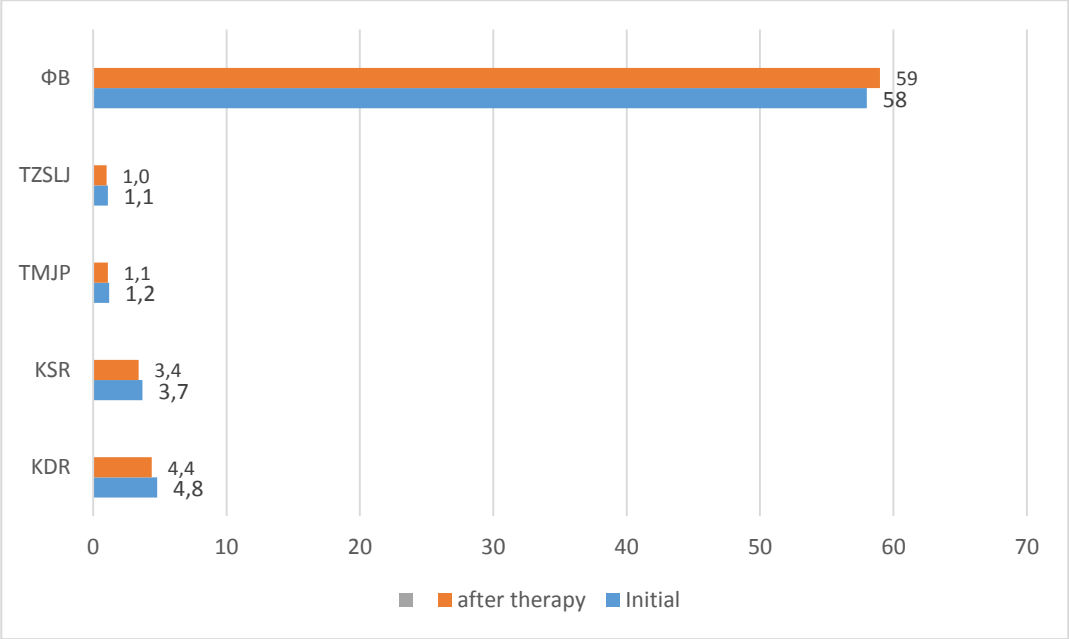
The number of pain episodes decreased from 1.6±0.3 to 0.7±0.2 per day. Along with this, the number of nitroglycerin tablets taken per day ranged from 0.6±0.2 to 0.3±0.12 ($p<0.05$). An indicative result is also an increase in the power of threshold physical activity from 6.5 ± 3.3 to 8.9 ± 4.2 W ($p<0.05$).



Note: EB pain episodes, PN-nitroglycerin intake, MPPT-threshold physical activity power

Fig.2. Analysis of clinical and instrumental research methods (control group)

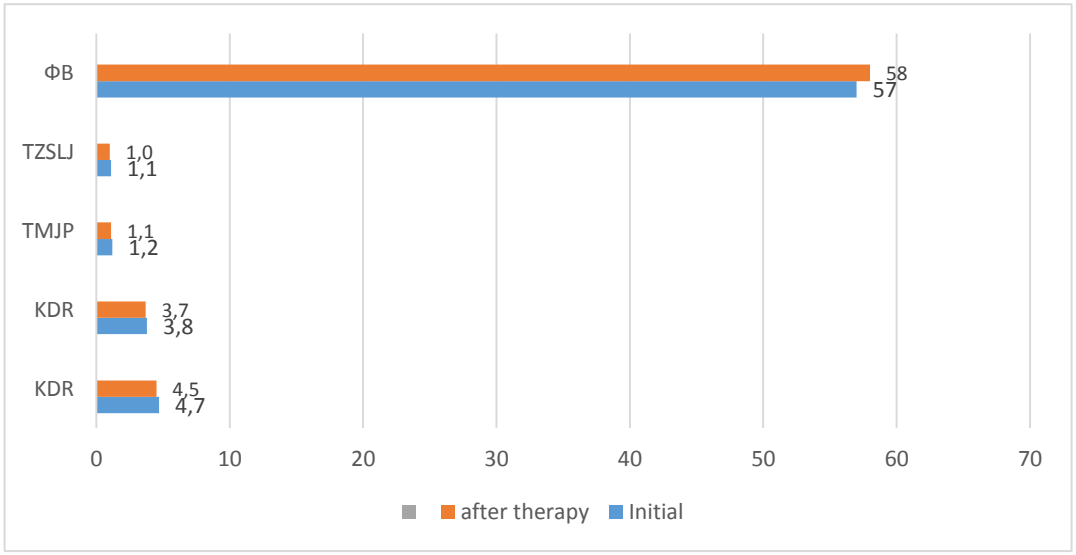
In the control group, as can be seen from Fig. 2, there is no positive dynamics in the studied indicators. An increase in exercise tolerance under the influence of gluthione in the examined individuals may be due to the effect of the drug on the metabolism of cardiomyocytes in conditions of their insufficient supply of oxygen. This is confirmed by a decreasing trend in the value of the double product, which reflects a decrease in myocardial oxygen consumption. Along with this, in patients on the background of gluthione, the level of total oxygen consumption by the body significantly decreases when performing dosed loads of various intensity. A more efficient metabolism of cardiomyocytes contributes to a less rapid consumption of their functional reserve during physical activity, which ultimately leads to an increase in the power of the threshold load in patients with coronary artery disease. We have received positive data on the improvement of myocardial contractility in the main group.



Rice. 3. Analysis of ECHOCG parameters in the examined individuals (main group)

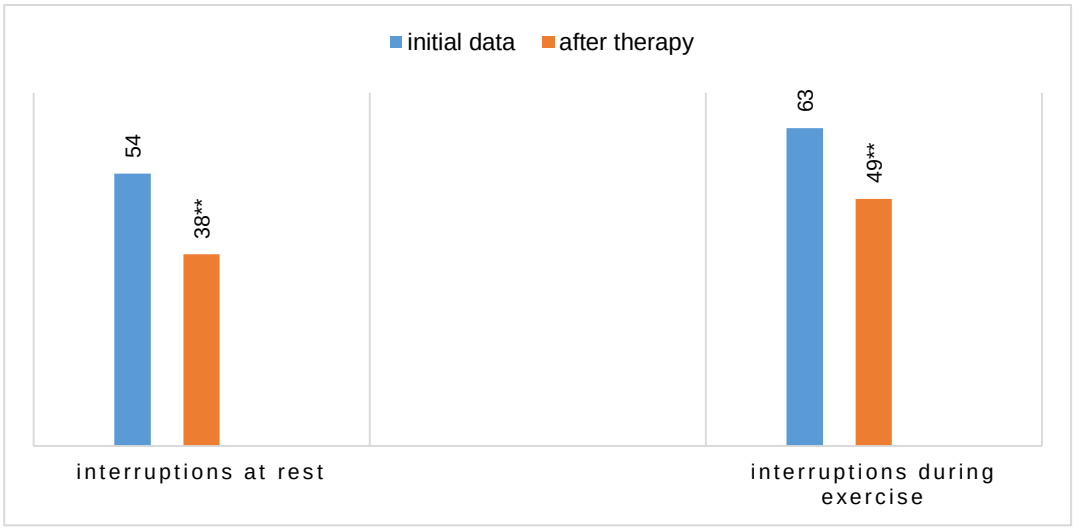
After treatment, among the main groups of indicators of myocardial systolic function, a decrease in end-diastolic size (EDD), end-systolic size (ESD) and an increase in ejection fraction (EF) were noted. The data obtained do not differ in statistical significance (Fig. 3). This situation is associated with a short period of examination of patients after treatment.

In the control group, the parameters studied by ECHOCG were also not significantly changed (Fig. 4). The use of gluthione had a beneficial effect on a number of ECG monitoring parameters characterizing myocardial ischemia. Compared with baseline data, the total number of episodes of ST segment depression decreased by 29.5% ($p<0.05$) in the main group, and 12%, respectively, in the control group.



Rice. 4. Analysis of ECHOCG parameters in the examined persons (control group)

With IHD, ventricular extrasystole (PV), the most common arrhythmia. Traditional antiarrhythmic drugs used for the treatment of PVC in patients with coronary artery disease only in 58.5% of cases can stop arrhythmia. At the same time, various side effects occur in the course of therapy in 5-30% of cases. Therefore, the normalization of metabolic processes in the myocardium is also essential. Our study involved patients with cardiac arrhythmia according to the type of extrasystolic arrhythmia 2 and 3 gradations according to Lown.



Note:

** p<0.01 significance of differences between groups

Fig.5. The frequency of occurrence of PVC after the therapy (n, main group)

During treatment with gluthione in patients of the main group, there was a subjective decrease in the severity of interruptions in the work of the heart by 50% ($p<0.01$) at rest and by 29% ($p<0.01$) during exercise (Fig. 5). In the control group, a significant decrease in the studied parameters is not traced (Fig. 6). During the daily monitoring of the ECG by Holter, there was also a significant decrease in the total number of PVCs. The number of patients who showed a decrease in the number of PVCs after the therapy by at least 50% was 39 (56%), in the control group 8 (27%).

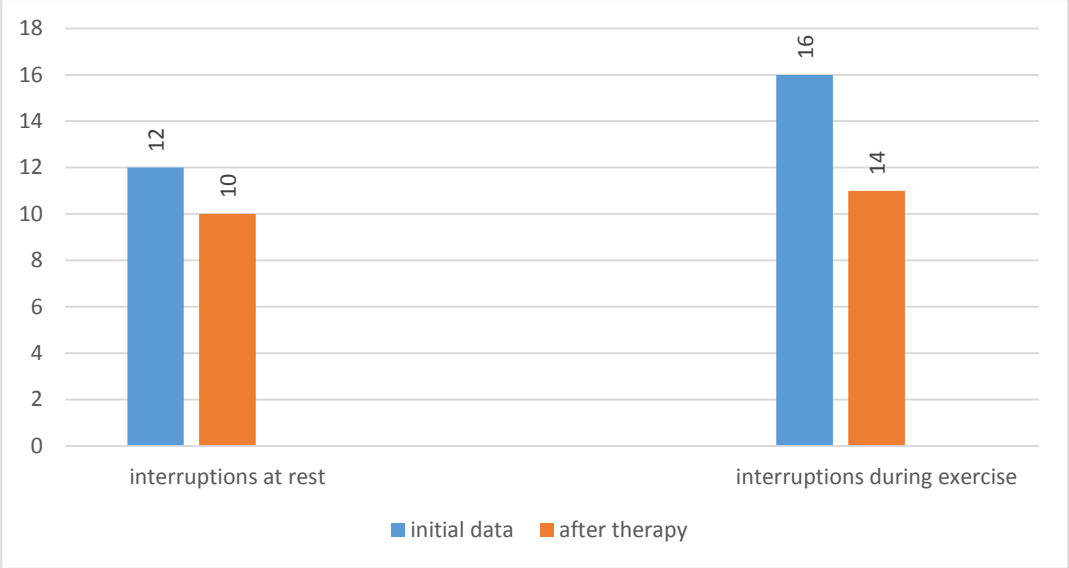


Fig.6. The frequency of occurrence of PVC after the treatment (n, control group)

Severe ventricular arrhythmias occur with more pronounced metabolic disorders in the ventricular myocardium, and the intake of gluthione leads to a significant improvement in metabolic processes in the heart in this group of patients. The direct relationship between the initial amount of PVCs and their decrease under the influence of treatment indicates that the drug gluthione has a potentiating effect on antiarrhythmic drugs.

During therapy with gluthione, there was a decrease in total cholesterol, LDL and TG with a simultaneous increase in HDL. However, the data obtained do not differ in statistical significance (Fig. 7, 8).

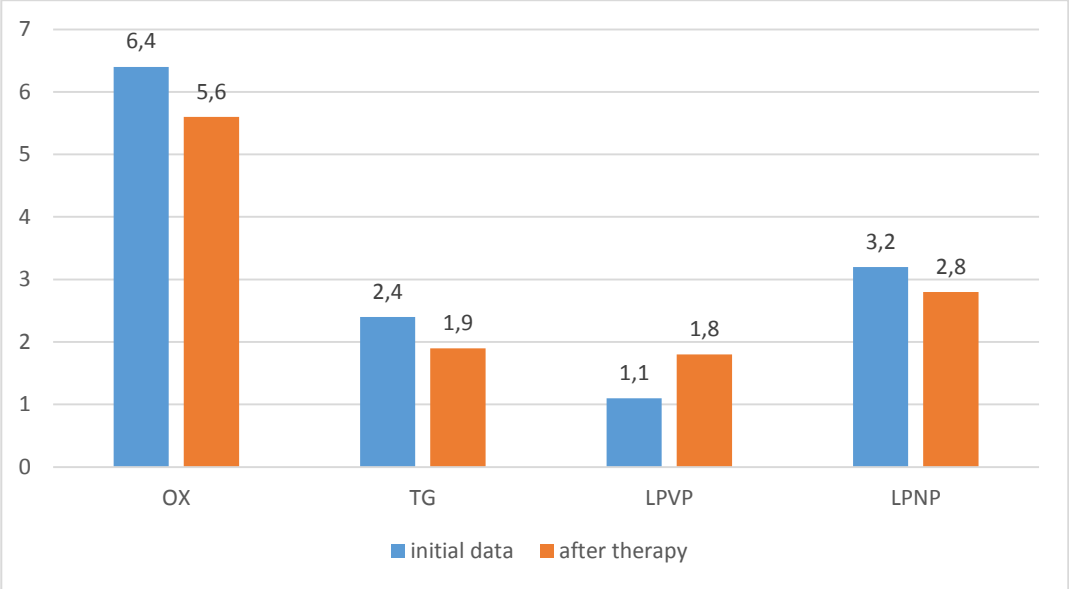


Fig.7. Indicators of lipid metabolism in the examined individuals after therapy (main group, mmol/l)

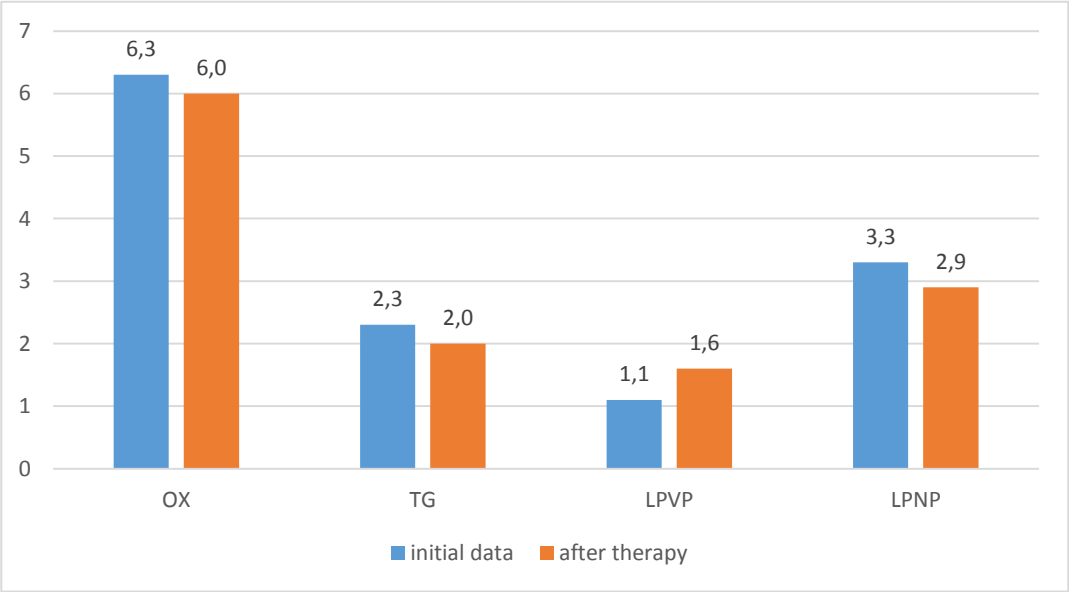


Fig.8. Indicators of lipid metabolism in the examined individuals after therapy (control group, mmol/l)

With the introduction of the drug gluthione, there have been no cases of a significant decrease or increase in both blood pressure and heart rate.

Glutathione (gluthione) is a linear tripeptide with a sulfhydryl group, which includes L-glutamine, L-cysteine and glycine. It plays an important role in protecting the cells of the body, being a strong antioxidant. In the human body, a lack of glutathione leads to many diseases. Experiments in vivo and in vitro have shown that a lack of glutathione can lead to mitochondrial damage and cell death caused by an

increase in toxic oxygen species, leading to an increase in free radicals. Glutathione is able to prevent cell damage by binding to toxic substances and/or their metabolites.

Thus, the data obtained indicate that gluthione opens up additional therapeutic possibilities for the pharmacotherapy of coronary artery disease. Due to the original mechanism of action aimed at optimizing the energy metabolism of the myocardium, this drug should be used in combination therapy to potentiate the antianginal and antiarrhythmic effect in patients with coronary artery disease with heart rhythm disturbances.

References:

1. Aronov D.M., Lupanov V.P. Diagnosis and treatment of chronic ischemic heart disease. The quality of life. Medicine. 2003; No. 2:16-24.

2. Gatsura V.V. Pharmacological correction of energy metabolism in ischemic myocardium.- M.: Medicine, 1993.- 254 p.

3. Korkushko O.V., Shatilo V.B., Ishchuk V.A. et al. Metabolic therapy as a promising direction in the treatment of patients with coronary heart disease. - 2008. - No. 2. - P. 5–15.

4. Moibenko A.A. Endogenous mechanisms of cardioprotection as a basis for pathogenetic therapy of heart diseases / A.A. Moibenko, V.E. Dosenko, A.N. Parkhomenko - K .: Nauk. Dumka, 2008. - 520 p.

5. Moroz V.M., Lipnitsky T.M., Kozlovsky V.A., Bandurka N.N. Search for new methods of treatment of cardiac arrhythmias: experimental study of membrane densitoners // Russian Journal of Cardiology.- 2003.- N 1.- P.72-76.

6. Acquired obesity and poor physical fitness impair expression of genes of mitochondrial oxidative phosphorylation in monozygotic twins discordant for obesity / L. Mustelin, K. H. Pietilainen, A. Rissanen, A. R. Sovijarvi et al. // Am J Physiol Endocrinol Metab. – 2008. – Vol. 295. – P. E148–E154.

7. Liu S, Li C, Li T, Xiong J, Zhao X. Effects of early hypertension control after ischaemic stroke on the outcome: a meta-analysis. Cerebrovasc Dis. 2015;40(5-6):270-8. doi: 10.1159/000441097.

8. Katsanos AH, Filippatou A, Manios E, Deftereos S, Parissis J, Frogoudaki A et al. Blood pressure reduction and secondary stroke prevention: a systematic review and metaregression analysis of randomized clinical trials. Hypertension. 2016. pii: HYPERTENSION AHA.116.08485.

9. Xue H, Lu Z, Tang WL, Pang LW, Wang GM, Wong GW et al. First-line drugs inhibiting the renin angiotensin system versus other first-line antihypertensive drug classes for hypertension. Cochrane database of systematic reviews. 2015;1: CD008170.

10. Wang WT, You LK, Chiang CE, Sung SH, Chuang SY, Cheng HM et al. Comparative effectiveness of blood pressure-lowering drugs in patients who have already suffered from stroke: traditional and bayesian network meta-analysis of randomized trials. Medicine (Baltimore). 2016;95(15):3302.

11. Jeffers BW, Robbins J, Bhambri R. Efficacy of calcium channel blockers versus other classes of antihypertensive medication in the treatment of hypertensive patients with previous stroke and/or coronary artery disease: a systematic review and meta-analysis. Am J Therap. 2015;17(3):193-199. doi: 10.1111/ jch.12462

12. Davies NM, Kehoe PG, Ben-Shlomo Y, Martin RM. Associations of anti-hypertensive treatments with Alzheimer's disease, vascular dementia and other dementias. J Alzheimers Dis. 2011;26(4):699-708.