

Research Article

Clinical Effectiveness of Cardiocytoprotective Therapy in Patients with Acute Coronar Syndrome (ACS) – Myocardial Infarction (MI), Who Were Performed Balloon Angioplasty and Coronary Artery Stenting

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Abstract

The aim of the study was to increase the efficiency of restorative treatment of patients with Acute Coronary Syndrome (Miocardial Infarction) by incorporating the protocol therapy for the course of parenteral use of L-arginine and L-carnitine (Tivorel).

It has been determined that patients with ACS (MI) after percutaneous coronary intervention often develop reperfusion syndrome with manifestations of left ventricular insufficiency and rhythm disturbances. Substantial clinical and functional improvement was noted under the influence of standard medical treatment in patients of control group. At the same time postinfarction remodeling with systolic and diastolic function of the heart, with the development of heart failure syndrome and endothelial dysfunction of blood vessels, and also remained resistant to extrasystole therapy, progressed.

Patients in the experimental group under the influence of complex medical treatment with the inclusion of L-arginine and L-carnitine marked a significant decrease in the frequency of violations of rhythm and conduction for the second day of observation, as well as a decrease in the manifestations of post-infarction remodeling of LV, which ultimately manifested a significant improvement in myocardial contractility (EF increased by 13%) and decreased diastolic dysfunction. Improvement of the inotropic function of the heart and a significant reduction in the frequency and severity of reperfusion arrhythmias was achieved precisely due to cardiometabolic effects of L-carnitine. In addition, in patients undergoing additional treatment with L-arginine and L-carnitine after 10 days of treatment, the activity of ET-1 was significantly lowered and the concentration of nitrogen oxide metabolites in the blood plasma increased and reach the level of healthy subjects ($p > 0.05$). So, they recovered the endothelial function of the vessels.

Keywords

acute coronary syndrome; percutaneous coronary intervention; reperfusion syndrome; L-arginine; L-carnitine

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Problem statement and analysis of the latest research

Despite of certain achievements of modern cardiology, mortality from diseases of the circulatory

system in our country, it is in first rank in the structure of the mortality causes (67%) and makes 140.6 per 100 thousand able-bodied population. Moreover, there is an increase in the incidence of myocardial infarction among persons of working age

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(48.9 per 100 thousand), and coronary heart disease (CHD) continues to rank first place in the structure of the causes of primary disability (22.8%) [4]. The above facts determine the priority development and improvement of treatment methods for patients with acute coronar syndrome (myocardial infarction) [2, 7, 8].

The immediate cause of the development of ACS (MI) is the rupture of the atheromatous plaque and the formation of a blood clot in the coronary artery, which causes progressive stenosis. At the same time, the key role of such pathogenetic factors as dislipidemia, systemic low intensity inflammation, peroxid stress and endothelial function disorders, which underlie the violation of energetic metabolism and ischemic damage of cardiomyocytes, are discussed in the recent time. The indicated pathogenetic mechanism of development of ACS (MI) provides the possibility of medication influence on these pathological processes of metabolic and cytoprotective therapy.

The most promising and physiological metabolic preparations were L-carnitine and L-arginine. Many studies have shown that L-arginine has antihypoxic, membrane-stabilizing, antioxidant and detoxification activity, manifests itself as an active regulator of intermediate metabolism and energy supply processes [6, 14], but its main physiological role is the regulation of the functional state of vessels and the provision of appropriate the level of microcirculation of organs and tissues of the body [11, 13]. L-carnitine plays an important role in energy exchange in the myocardium by transferring free fatty acids from the cytosol into the mitochondria, providing the bioavailability of the high-energy substrate for the oxidative metabolism in the cardiomyocyte [9, 16], that makes positive effects on the metabolism and function of the left ventricle [10, 12, 17, 18].

The above facts became the basis for the study of clinical effectiveness and the possibility of correction of metabolic disorders in patients with ACS (MI).

The objective of the study: to increase the efficiency of rehabilitation of patients with ACS (MI) by incorporating into the protocol schedule of the course of parenteral use of L-arginine and

L-carnitine (Tivorel).

1. Materials and Methods

A total of 45 patients with acute coronary syndrome with ST segment elevation were investigated, who had undergone urgent balloon angioplasty and stenting of a heart attack-dependent coronary artery, and were treated at the cardiology department of the Ternopil University Hospital in 2018. The study selected patients aged 43 to 75 years, on average (59.57 ± 8.07) years. Among the studied contingent, men dominated (82.2%). The diagnosis was verified according to ESC recommendations [15] in the presence of a typical angina attack, the dynamics of specific changes in the electrocardiogram curve (ST segment rejection) and signs of necroresorptive syndrome.

The experimental group consisted of 30 patients, who received standard protocol treatment of ACS (MI) and additionally were prescribed 4.2 g L-arginine and 2.0 g L-carnitine (Tivorel) in the 100 ml solution for infusion once daily for 5 days intravenously. The control group included 15 patients with ACS (MI) who also had urgent balloon angioplasty and stenting of the heart attack-dependent coronary artery, but this group received only standard protocol treatment.

In addition to general clinical, instrumental and laboratory methods (general blood test, MB Creatinephosphokinase fraction (CFC-MB), Troponin T, oxygen saturation of arterial blood (SpO₂), ECG in 12 standard leads, etc.), performed an echocardiography in the B-mode with the Aloka SSD - 2000” (USA) with the definition of linear and volume indicators of the left ventricle, as well as the global (by the ejection fraction (EF) and local contractile activity of the myocardium by the Simpson method. The diastolic function of the left ventricle was evaluated with the time of isovoluminous relaxation left ventricle (IVRT), sometimes delayed rate of early left ventricular filling (DT), maximal rate of its early filling (E), and maximum left ventricular filling velocity in the period of the atrial systole (A) [1].

The functional state of the vascular endothelium was determined by the concentration of endothelin-

1 (ET-1) in the blood plasma and the content of stable NO metabolites [5]. The determination of endothelin-1 (ET-1) in serum was carried out using the Amersham Pharmacia Biotech Immuno-enzyme Kit and the affinity chromatography columns of the same firm as instructed. The method for determining the ultimate stable metabolites of NO in the blood is based on the restoration of nitrates (NOs) to nitrites (NO₂) with the determination of the latter by reaction with the Gris reagent. Calculation of the amount of nitrites is carried out according to the calibration schedule. There were received 3 results: the content of nitrate ions (Kmol/L, the content of nitrite ions (Kmol/L) and the total content of nitrite and nitrate ions (Kmol/L).

The statistical processing of the obtained results was performed using the statistical program package "Statistica 10.0" and the "Microsoft Exel-2013" program. Non-parametric statistical methods were used to assess the data - Mann-Whitney U-test for comparison of indicators in two groups ($p < 0.05$).

2. Results and Discussion

Among the examined, ACS (MI) in men, was met in 4.6 times more often than in women, which is comparable to the literature data. In most cases, ACS has developed on the background of arterial hypertension in 27 (60.0%) persons. Dislipidemia or hypercholesterolemia (total cholesterol ≥ 4.5 mmol/L, Low density lipoprotein (LDL) cholesterol ≥ 1.8 mmol/L, Th ≥ 2.0 mmol/L) occurred in 38 (84.4%) patients. In 31 (68.4%) patients combination of these two risk factors for IHD was traced. Among other unfavorable factors, the body weight was noted in 14 (31.1%) patients, type 2 diabetes mellitus (12.7%), and smoking in 28 patients (62.2%). Among women dominant persons of the elder age (7 patients) and all 9 women were in menopause.

The clinical picture of ACS (MI) in most of the examined patients was manifested by classical angina pectoris, characteristic changes in the electrocardiographic curve and necro-resorptive syndrome. Some patients (11.1%) were diagnosed with an atypical clinical onset of myocardial infarction.

Violations of heart rhythm and conduction were diagnosed in 93 (65%) of examined patients, most often ventricular or supraventricular extrasystoles (in 78.5%), paroxysms of atrial fibrillation (in 11.8%), ventricular tachycardia (in 5.4%), ventricular tachycardia blockade of different degree and localization (in 45.1%).

All patients were tested for morphological and functional cardiac examination and contrast coronary angiography with subsequent angioplasty and stenting of the infarct-dependent coronary artery (on average, after 6.28 ± 1.43 hours after the onset of an angina attack). According to the results of the urgent coronary angiography (UCA), the final diagnosis was established for each patient. It can be stated that the number and anatomical severity of coronary artery disease did not differ significantly between patients of these groups (Fig. 1).

Analyzing the structure and frequency of development of complications in the examined groups of patients, it was found that development of acute aneurysm of the anterior wall of the left ventricle (33.3% vs. 0.0%, $p = 0.017$) and thromboendocarditis in the apex of the left ventricle (26.7% versus 0.0 %, $p = 0.037$) were significantly more frequent in patients undergoing protocol medication and cardio-rehabilitation treatment. At the same time, the patients in the experimental group, who were additionally prescribed a course of therapy with L-arginine and L-carnitine in the complex medical treatment, did not show any complications at all. Moreover, in the examined patients of both groups, which timely (within 2 to 12 hours after the onset of an anginal attack) had urgent angioplasty and stenting of the heart attack-dependent coronary artery, such complications as early post-infarction angina, cardiogenic shock, pulmonary edema, mechanical (rupture free wall of the left ventricle, interventricular septum, separation of papillary muscles) have not been recorded at all. At the same time, it should be noted that in patients with ACS, in the postoperative period (after percutaneous coronary intervention) reperfusion syndrome with different duration and severity of left ventricular insufficiency and violations of rhythm and conduction was most often developed (Fig. 2). As can be seen from the

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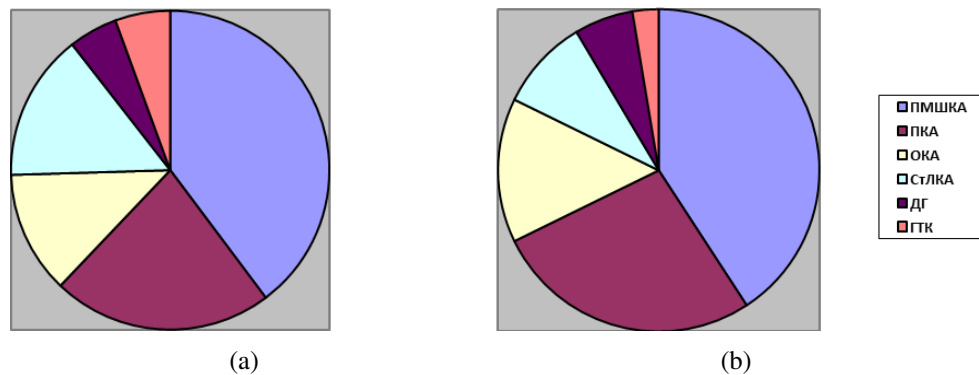


Figure 1. The structure of the distribution of the frequency of coronary artery damage in patients with ACS (MI) of experimental (a) and control (b) groups.

data presented, in the initial state immediately after the performed PK in patients with ACS (MI) both groups recorded the same frequency and types of violations of rhythm and conductivity ($p > 0.05$).

Under the influence of standard medical and restorative treatment, a significant decrease in the frequency of rhythm and conduction disorders in patients in the control group was observed for the second day of observation. Resistance to such treatment remained supraventricular and ventricular extrasystoles and blockades of the legs of the Gissa bundle. Moreover, these arrhythmias remained at the end of the second week of treatment, which justified the use of additional antiarrhythmic therapy.

Patients with ACS (MI) of the experimental group under the influence of complex medical treatment with the inclusion of L-arginine and L-carnitine also noted a significant decrease in the frequency of violations of rhythm and conduction already the second day of observation, but patients in this group had significantly higher sinus tachycardia and supraventricular extrasystoles. This result can be explained by an additional decrease in systolic and diastolic blood pressure due to the improvement of microcirculation under the influence of L-arginine. However, it should be noted that at the end of the course of the proposed comprehensive treatment (8-10 days), the frequency of violations of rhythm and conduction in patients in the experimental group was significantly lower compared with the comparison group ($p < 0.05$).

The results of the Echo-Cardiographic study (Table 1) show that in the initial state of patients with ACS (MI) of the experimental and control groups they do not differ statistically, but differ significantly from those of healthy people (referent values). At the same time, it should be noted that systolic and diastolic LV dysfunction was diagnosed in patients with ACS (MI), as evidenced by an increase in the incidence of LDV lv, LSV lv, A, IVRT, DT and decreased FE, E, E/A. The short-term left ventricular function due to the development of ACS (MI) decreased by an average of 22%.

Under the influence of standard therapy for up to 10 days in patients with ACS (MI), indices of LDV lv, IVRT, DT, A significantly increased, respectively, and such indices of intracardiac hemodynamics as E, E/A, FE were decreased. Thus, on the 10th day of the MI in patients with control group, in the background of medical and restorative treatment according to the standard scheme, there was a remodeling of the heart with a gradual increase in the volume of its cells and decreased contractility. At the same time, patients developed diastolic dysfunction mainly due to the relaxation type. After a one-month course of standard treatment in patients with this group, there was a continuation of post-infarction remodeling of the lungs, which was manifested by a significant increase in LDS lv, IVRT, DT and a decrease in E, E/A. FE somewhat increased to 28 days of ongoing therapy (by 1.5-4.3%) compared to an index of 1-10 days of standard treatment

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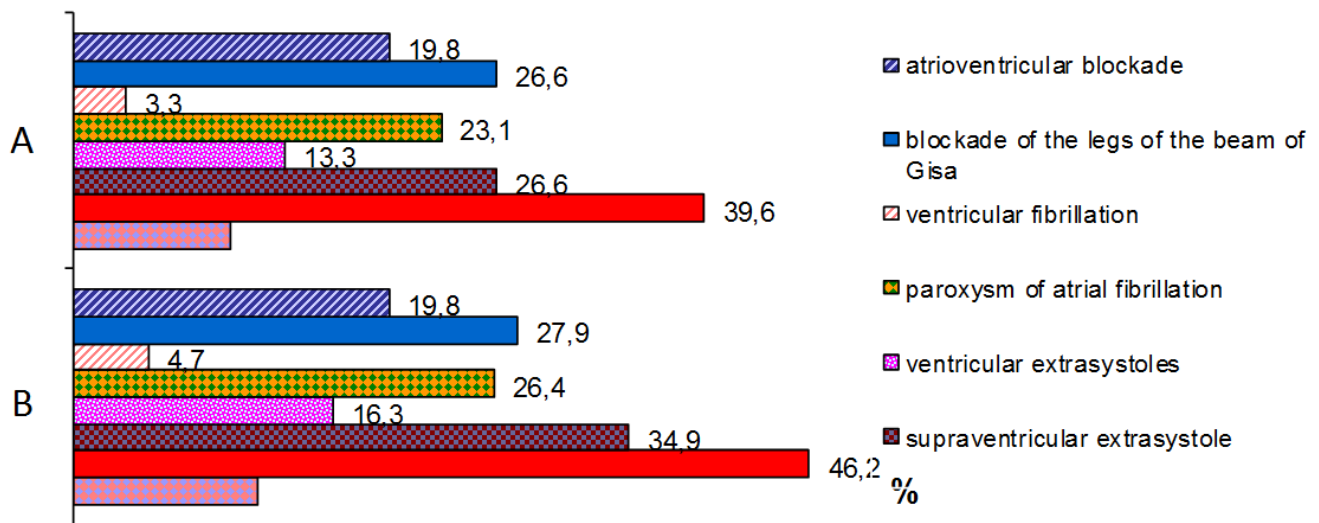


Figure 2. Frequency of development of violations of rhythm and conduction in patients with ACS (MI) in experimental (A) and control (B) groups.

Table 1. Dynamics of hemodynamic parameters under the influence of complex therapy with the inclusion of L-arginine and L-carnitine in patients with ACS (MI) (M±m).

Indication and their referent values		1 st day	10 th day	28 th day	p1	p2	p3
LDV lv, ml (156.4±1.4)	1	151.5±1.2	146.3±1.4	144.4±1.4	<0.05	<0.05	<0.05
	2	152.1±1.4	158.8±1.6	159.2±1.6	<0.05	<0.05	<0.05
LSV lv, ml (81.3±3.8)	1	88.6±2.7	86.5±3.2	81.3±2.8	>0.05	>0.05	<0.05
	2	89.3±2.3	89.4±2.5	93.9±2.3	>0.05	>0.05	>0.05
FE, % (59.8±0.3)	1	46.9±0.4	51.2±0.2	53.8±0.23	<0.05	>0.05	<0.05
	2	47.9 ±0.4	46.5±0.3	48.6±0.6	>0.05	>0.05	>0.05
IVRT,ms (88.5±2.1)	1	82.6±1.3	76.3±1.3	68.1±2.1	<0.05	<0.05	<0.05
	2	83.7±2.1	78.4±1.5	74.3±2.1	>0.05	>0.05	<0.05
DT, ms (196.4±4.7)	1	169.9±5.3	185.4±5.2	234.4±4.8	<0.05	<0.05	<0.05
	2	179.5±4.4	186.6±4.6	194.6±4.5	>0.05	>0.05	>0.05
E, sm/s (45.67±1.7)	1	61.5±1.8	63.2±1.8	65.61±1.6	>0.05	>0.05	<0.05
	2	62.2±1.3	53.2±1.3	48.7±1.4	<0.05	>0.05	<0.05
A, sm/s (36.8±1.1)	1	44.3±1.3	37.2±1.2	32.8±1.1	<0.05	<0.05	<0.05
	2	42.7±1.1	48.5±1.2	54.8±1.1	<0.05	<0.05	<0.05
E/A (1.23±0.04)	1	1.36±0.04	1.43±0.04	1.03±0.04	>0.05	<0.05	<0.05
	2	1.44±0.05	1.35±0.06	1.19±0.05	>0.05	>0.05	<0.05

Notes:

- 1, 2 - accordingly indicators in patients with MI (n=30) and control group (n=15);
- p1, p2, p3 – the rates are significantly different in patients with MI in the 1st and 10th day of the treatment, on the 10th and 28th day and in patients on the 1st and 28th day;
- The underlying values are significantly different from those in the control group (p<0.05).

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($p < 0.05$). However, this indicator after the completion of treatment was significantly lower than in healthy subjects. The obtained data indicate insufficient hemodynamic efficacy of standard therapy in this group of patients.

In patients with ACS (MI) of the experimental group, who received treatment with L-arginine and L-carnitine before the standard therapy, a significant increase in DT and FS and a decrease in LDV lv and E/A, changes in the rest hemodynamic indices were insignificant compared to the baseline data, but there was a tendency towards a decrease in post-arterial cardiac remodeling. At the same time, the development of diastolic dysfunction according to the relaxation type was noted. Thus, on the 28th day of the applied therapy, the IVRT and FE values increased significantly and E, A, E/A decreased compared with the original value. Thus, the addition to standard medical and restorative treatment in these patients L-arginine and L-carnitine contributed to the reduction of the size of the left chambers of the heart, manifestations of post-infarction remodeling of the lungs, which eventually showed a significant increase in FE (an average of 13%), myocardial contractility and diminished diastolic dysfunction.

A promising task was also to clarify the peculiarities of changes in the parameters of endothelial function of the vessels in patients with acute myocardial infarction (MI). In the course of the study, it was found that in the initial state, the parameters of the functional state of the endothelium in patients with ACS (MI) of the two groups under study did not differ significantly among themselves, but were significantly affected in comparison with the reference ones. Thus, when entering the treatment, the level of endothelin-1 in blood plasma in patients with ACS (MI) was 2.1 times higher than the reference norm (respectively, 0.96 ± 0.04 and 0.46 ± 0.03 ng/ml) and its activity did not significantly change immediately after the urgent angioplasty of the coronary vessel and its stenting. At the same time, the patients in the control group undergoing protocol medication and rehabilitation, the level of endothelinum decreased significantly, but at the end of the inpatient stage of treatment did not reach the level of healthy subjects (0.66 ± 0.06 ; $p > 0.05$).

In contrast, patients of the experimental group who additionally included a course of therapy with L-arginine and L-carnitine for the next 10 days of inpatient treatment, the activity of ET-1 decreased by 33.3% ($p < 0.05$), and after one month of treatment, its activity in blood plasma was significantly lower by 43% and reached the level of healthy subjects (0.52 ± 0.05 ng/ml; $p > 0.05$). That is, the use of integrated drug therapy with the inclusion of L-arginine and L-carnitine against the background of an individualized cardio-rehabilitation program in patients with SCS contributed to a rapid decrease (within 10 days) and complete restoration (within 28 days) of endothelin-1 activity in plasma these patients.

Simultaneously with changes in the activity of endothelin-1 in patients with corticosteroids (MI) in the period of exacerbation of the disease there was a sharp decrease in the level of metabolites of nitric oxide ($\text{NO}\epsilon = 17.75 \pm 0.42$ mkmol/l at normal – 36.92 ± 0.37 mkmol/l), that could indicate a marked microcirculation disorder in these patients. So the concentration of nitrates and nitrites in the initial state in patients of both groups decreased by almost 2.0 times, and their total content in blood plasma dropped by 45.0%. It should be noted that the generally used protocol treatment did not ensure the complete restoration of the endothelial function of the vessels in this group of patients with ACS (MI), the total concentration of metabolites of nitric oxide in plasma was 19% lower than the reference index ($p < 0.05$). At the same time, the use of integrated drug therapy with the inclusion of L-arginine and L-carnitine in patients in the experimental group significantly affected the concentration of nitrites and nitrates in the blood plasma, their level significantly increased already in 10 days of treatment and at the end of the inpatient stage of the complex drug and restorative cardio-rehabilitation treatment has reached the reference norm.

Thus, the obtained results of the comprehensive study of the clinical and functional state of patients with ACS (MI) suggest that in most cases, ACS (MI) has developed on the background of a combination of such risk factors as arterial hypertension, dis- or

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hypercholesterolemia, excess body weight, diabetes mellitus Type 2 and smoking (in more than 60% of all subjects). The clinical picture of ACS (MI) in the most of examined patients was manifested by classical angina pectoris, characteristic changes in the electrocardiographic curve and necro-resorptive syndrome, and atypical clinical onset of myocardial infarction was diagnosed in 11.1% of patients. It should be noted that in patients with ACS, in the postoperative period (after percutaneous coronary intervention), reperfusion syndrome with varying durability and severity of left ventricular insufficiency and rhythm and conduction disorders were most often developed. Under the influence of standard medical and restorative treatment in patients in the control group, a significant decrease in the frequency of rhythm and conduction disturbances in the control group was observed for the second day of observation, but supraventricular and ventricular extrasystoles and obstruction of the legs of the GIS beam remained resistant to such treatment, which justified the use of additional antiarrhythmic therapy. At the same time, patients with ACS (MI) of the experimental group under the influence of complex medical treatment with the inclusion of L-arginine and L-carnitine on the background of an individualized cardio-rehabilitation program for the second day of observation marked a significant decrease in the frequency of violations of rhythm and conduction, but remained significantly higher the frequency of sinus tachycardia and supraventricular extrasystoles, which could be explained by the compensatory response to an additional decrease in systolic and diastolic blood pressure under the influence of the proposed this treatment.

Diagnosis in the initial state of patients with acute myocardial infarction (MI) of marked violations of the morpho-functional parameters of the heart, post-infarction remodeling with violation of systolic and diastolic function of the heart, with the development of the syndrome of heart failure and endothelial dysfunction of the vessels that were stored immediately after an urgent percutaneous intervention, became the basis for inclusion in the protocol of the therapy program of parenteral use of L-arginine and L-carnitine. It was found that in the

initial state of patients with acute myocardial infarction (MI) there was a remodeling of the heart with a gradual increase in the volume of its chambers and decreased contractile ability and the simultaneous development of diastolic dysfunction, mainly in the relaxation type, and the course of standard treatment did not stop post-infarction remodeling of LV, although the FE was somewhat increased, not reaching the level of healthy persons. That is, the findings suggest insufficient hemodynamic efficacy of standard therapy in this group of patients.

Patients with ACS (MI) of the experimental group who received standard therapy with treatment with L-arginine and L-carnitine on the background of an individualized cardio-rehabilitation program, with a re-examination (10 days), a significant increase in FE, DT, and a decrease in LDV lv, the coefficient E/A, and this tendency to reduce post-infarction remodeling of the heart, which eventually manifested a significant increase in FE, myocardial contractility and decreased diastolic dysfunction. The obtained positive effect of the proposed treatment on the inotropic function of the heart and a significant decrease in the frequency and severity of reperfusion arrhythmias, in our opinion, was achieved precisely due to the cardiometabolic effect of L-carnitine, which, according to many researchers, plays an important role in the energy exchange in the myocardium due to the transfer of free fatty acids from the cytosol within the mitochondria and thus provides the bioavailability of the high-energy substrate for the oxidative metabolism in the cardiomyocyte [10, 12]. In addition, by facilitating the oxidation of long chain fatty acids and modulating the ratio of KoA to KOA-SH, the compound is involved in the binding of acyl residues in peroxisomes and mitochondria and positively affects the exchange of amino acids by assimilating the array of free radical compounds, which ensures the stabilization of organelles and cellular membranes and It prevents the accumulation in the cytoplasm of cardiomyocytes of fatty acid esters, which can lead to fatal ventricular arrhythmias [16, 17, 18].

In the course of the study, it was also found that in the initial state, the indexes of the functional state of the endothelium in patients with ACS (MI)

of both groups under study were significantly affected in comparison with the reference ($p < 0.05$) and were manifested by marked microcirculation disorders due to a significant increase in the activity of endothelin-1 and lower levels of nitric oxide production. At the same time, patients in the control group undergoing protocol medication and rehabilitation significantly decreased the endothelin level, while the concentration of nitric oxide metabolites in the blood plasma increased, but at the end of the inpatient stage, they did not reach the level of healthy subjects ($p < 0.05$).

In contrast, patients in the experimental group who additionally included a course of therapy with L-arginine and L-carnitine on the background of an individually-adapted cardio-rehabilitation program after 10 days of treatment, has the significantly decreased activity of the ET-1 and the concentration of nitrogen oxide metabolites in blood plasma, reaching the level of healthy persons ($p > 0.05$). That is, such complex treatment in patients with ACS (MI) contributed to the rapid and complete restoration of the studied parameters of endothelial function of the blood vessels. The result of the treatment can be explained by the use of L-arginine as the main substrate for the synthesis of nitric oxide. In many studies, it has been demonstrated that the use of L-arginine after stenting reduced the number of restenoses [3, 6, 14] due to its antihypoxic, antioxidant and membrane-stabilizing activity, but its main physiological role is the regulation of the functional state of vessels and the provision of an appropriate level of microcirculation of organs and tissues of the body [11, 13, 16].

In general, due to the complex application of combined drug therapy with the inclusion of L-arginine and L-carnitine (Tivorel) on the background of an individualized cardio-rehabilitation program, a significant improvement in the parameters of central cardioghemodynamics and restoration of endothelial function of the vessels was achieved, that was accompanied by a significant decrease in the incidence and severity of such complications of ACS as reperfusion arrhythmias and acute cardiac (left ventricular) insufficiency.

3. Conclusions

1. In patients with acute myocardial infarction (MI) in the initial state there are marked violations of morpho-functional parameters of the heart, the development of its post-infarction remodeling with violation of systolic and diastolic function of the heart and development of the syndrome of heart failure and endothelial dysfunction of blood vessels.
2. Morpho-functional disorders of the heart parameters led to the development of complicated flow of ACS (MI), in the first day after percutaneous coronary intervention on the background of standard medical and restorative therapy, the reperfusion syndrome with manifestations of acute left ventricular insufficiency and rhythm and conduction disorders were most often diagnosed.
3. The use of integrated drug therapy with the inclusion of L-arginine and L-carnitine (Tivorel) on the background of an individualized cardio-rehabilitation program resulted in a significant improvement of the parameters of central cardioghemodynamics and restoration of endothelial function of the vessels, accompanied by a significant decrease in the incidence and severity of such complications of ACS (MI) as reperfusion arrhythmias and acute left ventricular failure.

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