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The role of cardioprotection in the prevention of complications progression in the treatment of patients with acute myocardial infarction

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Abstract
The aim of this work was to increase the effectiveness of treatment of patients with ACS by including L-carnitine and L-arginine in the complex therapy. The study included 103 patients with acute coronary syndrome (ACS) with ST segment elevation, of which 37 patients who underwent urgent coronary angiography followed by balloon angioplasty and heart attack-dependent coronary artery stenting, as well as an additional cytoprotective therapy, constituted the first studied group. 34 patients who used cytoprotective treatment without coronary arteries stenting made up the 2nd studied group. The control group consisted of 32 patients who received only standard protocol treatment for ACS (MI). The functional state of endothelium was determined by the concentration of endothelin-1 (ET-1) in blood plasma and the content of stable NO metabolites; the parameters of the general blood test were examined and the level of the MV fraction of creatine phosphokinase (MV-CPK). In patients with acute MI, expressed disturbances of the morphological and functional parameters of the heart are observed, namely, the progression of its post-infarction remodeling, followed by a disturbance of the systolic and diastolic functions of the heart and the progression of heart failure syndrome and endothelial vascular dysfunction. Structural and functional disorders of the heart parameters are accompanied by a more frequent progression of the complicated course of MI; on the first day after percutaneous coronary intervention, reperfusion syndrome with manifestations of acute left ventricular failure and rhythm disturbances (tachycardia, high grade extrasystole, fibrillation, was most often diagnosed with standard drug therapy)) and conductivity (left bundle branch block, AV blockade II-III degree). The additional inclusion of a mixture of L-arginine and L-carnitine in standard drug therapy significantly reduces the incidence and severity of MI complications such as reperfusion arrhythmias and acute left ventricular failure.

Keywords: Acute myocardial infarction, treatment, endothelial dysfunction

Introduction
In Europe, ischemic heart disease (CHD) causes 1.8 million deaths annually, which is 20% in the structure of deaths. Acute myocardial infarction (MI) is the most common cause of disability and death of patients [1]. In the EU countries, the prevalence of acute coronary syndrome (ACS) with ST segment elevation reaches up to 144.0 per 100 thousand population/year and there is a tendency to an increase in the incidence of MI among the able-bodied population [2]. In our country, official statistics indicate that per 100 thousand people 135.7 cases of acute and recurrent MI are recorded, including 56.0 cases among the able-bodied population [5].

It should be noted that in economically developed countries there is a gradual decrease in the incidence of acute and distant mortality from ACS with elevation of the ST segment [2, 3, 4]. At the same time, despite the achievements of modern cardiology in the widespread introduction of new drug and cardiac surgical methods of treating ACS, mortality remains significant according to European registers. Nosocomial mortality from acute MI ranges from 4 to 12% [2, 3], and annual mortality is about 10% [4]. The above facts prove the urgent need for further improvement of the methods of treatment and rehabilitation of patients with MI.

Given that the immediate cause of the most frequent 1st subtype of MI is rupture of an atherosclerotic plaque followed by progressive coronary artery thrombosis [6], it is advisable to clarify the significance and role of pathogenetic factors such as peroxide stress, low-intensity systemic inflammation and the occurrence of endothelial dysfunction, which are the basis of damage not only to atherosclerotic plaques, but also to impaired energy metabolism and ischemic damage to cardiomyocytes. The indicated pathogenetic mechanism opens up the possibility for the drug effect of cytoprotective therapy on these pathological processes.

The most promising and physiological metabolic drugs may be L-carnitine and L-arginine.

L-carnitine is one of the well-known broad-spectrum cardiometabolic drugs [7]. It is known that it plays an important role in energy metabolism in the myocardium due to the transport of unsaturated fatty acids from the cytosol into the mitochondria, facilitates the oxidation of long chain fatty acids and modulates the ratio of CoA to CoA-SH, participates in the binding of acyl residues in peroxisomes and mitochondria [8, 9]. That is, L-carnitine provides the bioavailability of a high-energy substrate for oxidative metabolism in a cardiomyocyte, positively affects the metabolism of amino acids, assimilates an array of free radical compounds. In addition, several meta-analyzes revealed that during hypoxia, the content of L-carnitine in cardiomyocytes decreases sharply, and taking the drug ensures that it is restored to a sufficient level, which positively affects the energy metabolism and contractile function of the myocardium [10, 11, 12], and also stabilizes cell membranes [8, 9]. After determining the leading role of nitric oxide in the pathogenesis of IHD, studies began on the effectiveness of the clinical use of L-arginine, which has an antihypoxic, antioxidant, cytoprotective properties and shows itself as an active regulator of energy supply processes [13]. However, its main role is to regulate the functional state of blood vessels and ensure the appropriate level of microcirculation [15]. In addition, many studies have shown that the use of L-arginine after the coronary artery stenting reduced the number of restenoses [13, 14]. The above scientific concepts became the rationale for the study of the clinical efficacy of combined use of L-carnitine and L-arginine in the treatment of patients with myocardial infarction.

Objective: to increase the effectiveness of treatment of patients with ACS by including L-carnitine and L-arginine in the complex therapy.

Materials and Methods: The study included 103 patients with acute coronary syndrome (ACS) with ST segment elevation, of which 37 patients who underwent urgent coronary angiography followed by balloon angioplasty and heart attack-dependent coronary artery stenting, as well as an additional cytoprotective therapy, constituted the first studied group. 34 patients who used cytoprotective treatment without coronary arteries stenting made up the 2nd studied group. The control group consisted of 32 patients who received only standard protocol treatment for ACS (MI). Cytoprotective therapy included the administration of 4.2 g of L-arginine and 2.0 g of L-carnitine in the solution form for infusion of 100 ml once a day for 5 days. Among the studied population, men of working age (83.5%) prevailed, which averaged (57.54±8.02) years. The diagnosis of ACS (MI) was verified according to the recommendations of ESC [2] in the presence of a typical anginal attack, the dynamics of specific changes in the curve of the electrocardiogram (reciprocal shift of the ST segment), and signs of resorption-necrotic syndrome.

Confirmation of the diagnosis was carried out using laboratory and instrumental methods of examination. The parameters of the general blood test were examined and the level of the MV fraction of creatine phosphokinase (MV-CPK) was determined using an automatic biochemical analyzer from Roche (Switzerland) - Cobas integra 400 plus. The MV-CPK content index of more than 25.0u/l indicated a high probability of damage to the heart muscle. Quantitative determination of troponin T was carried out by Elecsys 2010 electrochemiluminescent biochemical analyzer from Roche Hitachi (Switzerland). The troponin test score of a more reference value of 14.0ng/l was evaluated as positive.

The functional state of endothelium was determined by the concentration of endothelin-1 (ET-1) in blood plasma and the content of stable NO metabolites [16]. The study of the level of endothelin-1 (ET-1) in the blood serum was carried out using an enzyme-linked immunosorbent assay and affinity chromatography columns from Amersham Pharmacia Biotech. In order to directly determine the concentration of ET-1 in the studied plasma, enumeration was carried out taking into account the degree of the sample concentration during chromatography. The method for determining the final stable NO metabolites in the blood is based on the reduction of nitrates (NO_3) to nitrites (NO_2) with the determination of the latter by reaction with the Gris reagent. The optical density is measured on a spectrophotometer Ф-46 (ФЭК) at a wavelength of 540 nm. Calculation of the amount of nitrite is carried out according to the calibration graph. 3 results were obtained: 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). Determination of the systematic measurement error was carried out by the method of drain serum.

The electrocardiogram (ECG) was recorded with a ЮТАС six-channel electrocardiograph in 12 standard and W. Nehb and AVL-W. Nehb leads. Echocardioscopy (ECS) was performed on a Philips HD11XE device, probe number S4-2 in Doppler mode. Statistical processing of the results was carried out using the statistical software package Statistica 10.0 and the Microsoft Excel-2013. For the data evaluation non-parametric statistical methods were used, such as U-test Mann-Whitney to compare indicators in two groups ($p<0.05$).

Research results and discussion.

The clinical finding of ACS in the examined patients was manifested by classical anginal syndrome, characteristic changes in the electrocardiogram and a diagnostic increase in the markers of myocardial necrosis. Disturbance of the rhythm and conduction of the heart was diagnosed in 71.0% of the examined patients, including supraventricular or ventricular extrasystoles most often recorded (in 53.3%). Also, sinus tachycardia was recorded in 31.1% of patients, atrial fibrillation / flutter paroxysms were recorded in 3.8%, ventricular tachycardia was recorded in 1.9%, and blockades of various degrees and localization were recorded in 21.4%. It is also worth noting the insignificant difference in the frequency of rhythm and conduction disturbances in the selected groups of patients in the initial state (Table 1).

At the same time, it was found that among the patients of the first studied group who, after balloon angioplasty and stenting of a heart attack-dependent artery, were prescribed cytoprotective therapy in addition to standard protocol treatment, reperfusion syndrome was significantly less frequent compared with patients in the control group. In particular, these are sinus tachycardia (13.5% versus 46.9%, p=0.027), high grade ventricular extrasystole (5.4% versus 31.25%, p=0.008) and supraventricular extrasystole (10.8% versus 53.1%, p=0.046). It should be noted that such rhythm disturbances as atrial fibrillation (0.0% versus 2.9% and 9.4%, $p>0.05$), ventricular fibrillation (0.0% versus 0.0% and 6.25% $p>0.05$), paroxysmal ventricular tachycardia (0.0% versus 0.0% and 6.25%, $p>0.05$) in the structure of arrhythmias of patients of the first studied group was not found, in contrast to

patients of the other two groups, who did not have an intervention. However, there was no significant difference in the rates of occurrence of these life-threatening rhythm disturbances between the groups. In addition, we emphasize that when comparing the frequency of conduction disturbances, a significantly more frequent occurrence of left bundle branch block was recorded (25.0% versus 2.7%, p=0.009) and complete atrioventricular block (18.7% versus 0.0%, p=0.008) in patients of the control group who were not prescribed metabolic therapy with L-arginine and L-carnitine. We also note that in patients of the second studied group who received cytoprotective therapy, the incidence of arrhythmias and blockade in the acute MI period is significantly lower than similar parameters in patients without additional metabolic protection.

Table 1: The frequency of heart rhythm disturbances in patients of the studied groups before and after the proposed treatment programs.

Type of rhythm and conduction disturbances		Studied group 1 (n=37)	Studied group 2 (n=34)	Control group (n=32)
Sinus bradycardia	1	8,6%	8,8 %	9,4 %
	2	0,0%	4,9%	7,4%
Sinus tachycardia	1	49,5 %	48,6 %	48,6%
	2	13,5%*	35,3%	46,9%
Supraventricular extrasystole	1	60,2%	61,5%	61,5%
	2	10,8 % *	41,2 %	53,1 %
Ventricular extrasystole	1	42,5%	40,5%	40,5%
	2	5,4 % *	23,5 %	31,25 %
First-degree atrioventricular block	1	17,2%	16,5%	17,5%
	2	2,7 %	5,9 %	15,6 %
Second-degree atrioventricular block	1	15,0%	14,8%	15,5%
	2	2,7 %	8,8 %	12,5 %
Third-degree atrioventricular block	1	10,5%	10,0%	22,5%
	2	0,0 %*	5,9 %	18,7 %
Left bundle branch block	1	8,8%	22,5%	27,0%
	2	2,7 % *	14,7 %	25,0 %
Right bundle branch block	1	16,5%	15,5%	14,0%
	2	8,1 %	8,8 %	12,5 %
Supraventricular tachycardia	1	6,5%	9,6%	11,5%
	2	0,0 %	2,9 %	9,4 %
Ventricular tachycardia	1	5,0%	5,0%	7,5%
	2	0,0 %	0,0 %	6,25 %
Ventricular fibrillation	1	5,5%	4,5%	8,25%
	2	0,0 %	0,0 %	6,25 %

Notes:
1) * - $p<0.05$; compared to the control group.
2) 1,2 - indicators before and after treatment respectively. The underlined data differ from the data before treatment ($p<0.05$)

In addition to a high risk of progressing arrhythmias, the course of ACS is associated with a high probability of various complications. Cardiac asthma (36.9%), acute left ventricular aneurysm (27.2%) and epistenocardic pericarditis (24.3%) prevailed in the structure of complications of the examined patients in both groups. Analyzing the structure of complications, it was revealed that the progression of acute aneurysm of the left ventricle walls was more often observed in patients who were not prescribed a mixture of L-arginine and L-carnitine (43.75% versus 18.9% and 20.6%, $p_1=0.05$ and $p_2=0.027$) than in patients of both studied groups. It was also recorded that patients of the control group significantly more often progressed acute left ventricular failure, in particular cardiogenic shock (15.6%, p=0.013) and pulmonary edema (18.75%, p=0.006), while in patients of the first studied group these complications did not occur at all. Note that life-threatening conditions such as rupture of the free wall of the left ventricle or interventricular septum or detachment of the papillary muscles did not complicate MI at the hospital stage of treatment among patients of both groups treated with cardiocytoprotectors (Fig. 1)

The course of MI is associated with the appearance of structural and functional changes in the myocardium, its remodeling, and the progression of clinical and instrumental signs of heart failure [3]. Analyzing the data of echocardiography revealed significant differences in the parameters of the ejection fraction of the left ventricle and the size of the heart chambers in patients of the examined groups (table. 2). At the same time, we note that in the studied groups receiving additional cytoprotective therapy with L-arginine and L-carnitine, a significant decrease in LV CRD and an increase in the ejection fraction of the left ventricle were diagnosed (16% and 15%, respectively). The use of standard drug therapy in patients of the control group was not accompanied by the restoration of structural and functional restructuring of the geometric shape of the heart, that is, pathological remodeling of the left ventricle progressed in these patients.

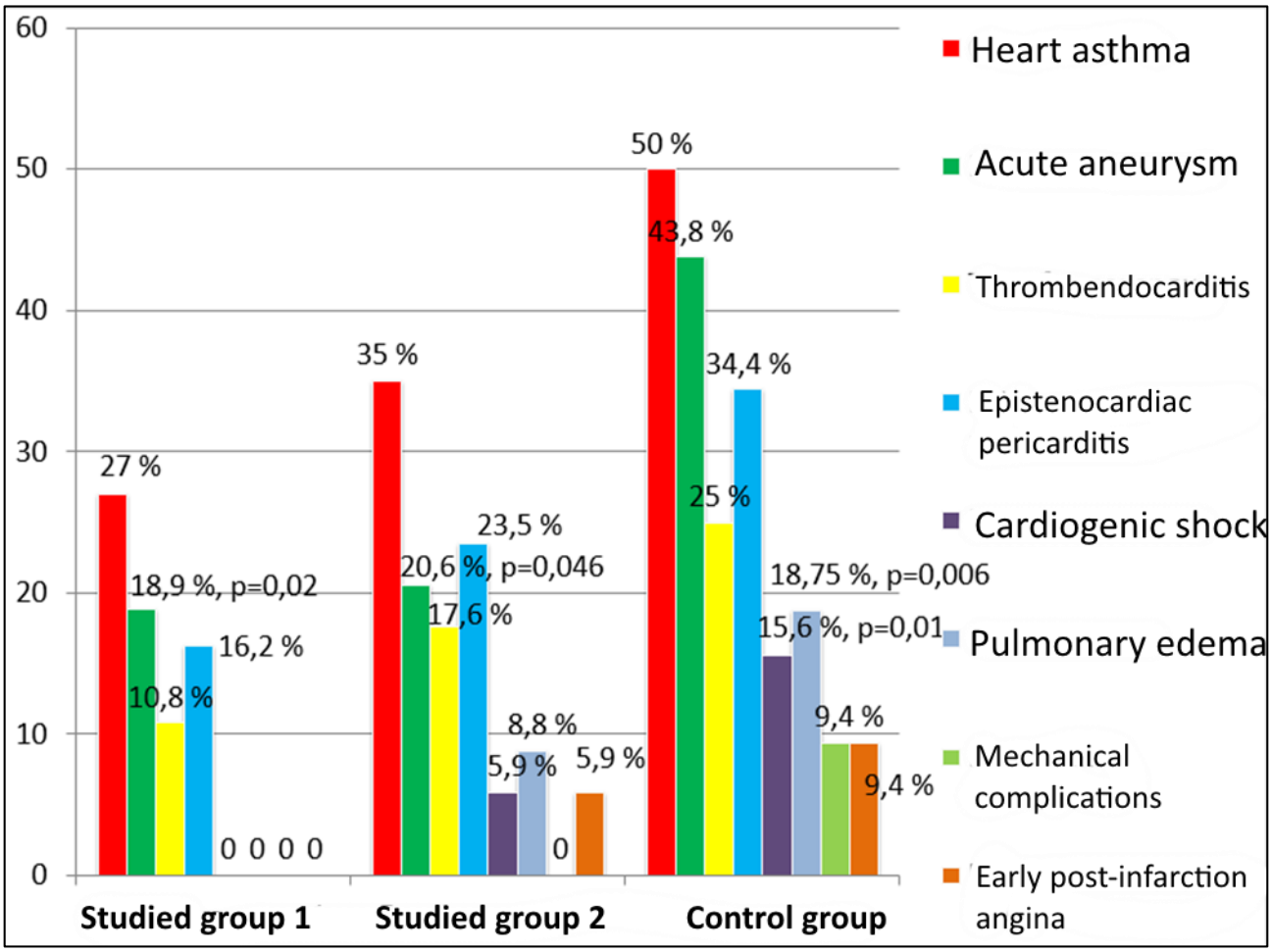

Fig 1: The frequency of progression of MI complications in the examined groups of patients (studied group 1, n = 37; studied group 2, n = 34; control group, n = 32)

Table 2: Dynamics of echocardiogram parameters in groups of patients with MI under the influence of the applied treatment programs. (M ± m)

Indicator		Studied group 1 (n=37)	Studied group 2 (n=34)	Control group (n=32)
Aorta, cm	1	3,43±0,05	3,42±0,08	3,42±0,14
	2	3,43±0,14	3,42±0,11	3,42±0,15
Left atrium, cm	1	3,66±0,07	3,58±0,12	3,59±0,12
	2	3,66±0,07	3,58±0,12	3,59±0,12
End-diastolic size of the left ventricle, cm	1	5,85+0,45	5,6+0,35	5,85+0,45
	2	4,90±0,50*	4,9±0,7*	5,78±0,62
Interventricular septum, cm	1	1,08±0,06	1,16±0,08	1,17±0,06
	2	1,08±0,06	1,16±0,08	1,17±0,06
Posterior left ventricle wall, cm	1	1,11±0,07	1,13±0,13	1,17±0,08
	2	1,11±0,07	1,13±0,13	1,17±0,08
EF, %	1	40,36+1,25	40,85+1,45	40,05+1,15
	2	46,5±2,33*	44,22±3,27*	42,48±1,54
Right ventricle, cm	1	2,10±0,2	2,23±0,3	2,24±0,20
	2	2,10±0,2	2,23±0,3	2,24±0,20

Notes:
1,2 - parameters indicators before and after treatment, respectively.
* - significant difference compared with the control group (p<0.05)
The underlined indicators significantly differ from the data before treatment.

A promising task was also to investigate the therapeutic efficacy of the proposed complex treatment for endothelial vascular dysfunction. In the course of the study, it was found that in the initial state, the indicators of the functional state of the endothelium in all patients with ACS (MI) did not significantly differ from each other, but were significantly impaired compared to the reference ones.

At the same time, in patients of the control and second studied groups who underwent protocol drug and metabolic rehabilitation treatment, the level of endothelin decreased significantly, but at the end of the inpatient phase of treatment it was less than the level of healthy individuals (P<0.05). At that time, in patients of the first studied group who, after intervention on coronary vessels, a complex course of therapy additionally included the course of therapy with L-arginine and L-carnitine in the next 10 days of the stationary stage of treatment, ET-1 activity decreased by 33.1% (P<0.05). That is, the use of complex drug therapy with the inclusion of L-

arginine and L-carnitine in patients with ACS (MI) contributed to a rapid decrease in the activity of endothelin-1 in the blood plasma of such patients.

Table 3: Dynamics of indicators of vascular endothelial function in patients with ACS (MI) under the influence of the proposed treatment programs (M ± m)

Indicators		1 day	10 day	p_1	p_2
Endotelin-1, ng/ml	1	0,46±0,03	0,47±0,04	>0,05	>0,05
	2	0,96±0,04	0,64±0,06	<0,05	>0,05
	3	0,97±0,05	0,75±0,04	<0,05	<0,05
	4	0,97±0,06	0,78±0,06	<0,05	<0,05
NO_2, μmol/l	1	11,46±0,34	11,56±0,43	>0,05	>0,05
	2	4,89±0,42	7,85±0,39	<0,05	<0,05
	3	5,66±0,43	6,71±0,32	<0,05	<0,05
	4	5,88±0,44	6,74±0,32	<0,05	<0,05
NOз, μmol/l	1	25,46±0,53	25,58±0,63	>0,05	>0,05
	2	12,86±0,46	18,89±0,51	<0,05	<0,05
	3	13,27±0,43	18,70±0,42	<0,05	<0,05
	4	14,41±0,42	18,72±0,43	<0,05	<0,05
NOε, μmol/l	1	36,92±0,37	37,14±0,47	>0,05	>0,05
	2	17,75±0,42	25,74±0,52	<0,05	>0,05
	3	19,37±0,42	24,45±0,52	<0,05	<0,05
	4	20,39±0,43	25,46±0,53	<0,05	<0,05
Notes:	1. 1,2,3,4 - indicators in healthy people (n = 26), in the first studied group of patients with ACS (MI) (n = 37) and in the second studied group (n = 34), control group (n = 32), respectively. 2. P1, P2 - the significance of the difference between the parameters in the 1st and 10th day of treatment and 10th day of treatment and a group of healthy people, respectively. The underlined indicators significantly differ from the corresponding indicators of a group of healthy people.				

Along with changes in the activity of endothelin-1 in patients with ACS (MI) during the period of exacerbation of the disease, a decrease in the level of nitric oxide metabolites occurred, which may indicate a expressed disturbance of microcirculation in these patients. So, the concentration of nitrates and nitrites in the initial state in patients with ACS (MI) decreased almost 2.0 times, and their total plasma content fell by 45.0% compared with values in healthy people. At the same time, we note that conventional protocol treatment did not fully restore the vascular endothelial function in the control group of patients with ACS (MI), their total concentration of nitric oxide metabolites in the blood plasma was 19% lower than the reference indicator (P<0.05). At the same time, the use of complex drug therapy with the inclusion of L-arginine and L-carnitine in patients of the first studied group significantly affected the concentration of nitrites and nitrates in the blood plasma, their level significantly increased already up to 10 days of treatment.

Discussion

Summarizing the results of the study, clinical homogeneity and comparability of the studied and control groups in the initial state and an insignificant difference in the frequency of progression of rhythm and conduction disturbances in them should be noted. At the same time, the structure of complications changed significantly depending on the treatment program used. So, in patients of the studied group 1, who underwent angioplasty and heart attack-dependent coronary artery stenting with the simultaneous use of cytoprotective therapy with L-arginine and L-carnitine, a significant decrease in the frequency of sinus tachycardia and supraventricular and ventricular extrasystole was noted. In our opinion, it was due to the elimination of this trigger that patients of this group achieved the complete elimination of life-threatening arrhythmias such as atrial fibrillation, ventricular fibrillation, and paroxysmal ventricular tachycardia. At the same time, we note that additional cytoprotective therapy in patients with ACS (MI), who underwent standard drug treatment without revascularization of the coronary artery, also led to a significant decrease in the incidence of clinically significant cardiac arrhythmias and conduction. In addition, in patients of the control group who received standard treatment without additional cytoprotective agents, the occurrence of the left bundle branch block and a complete atrioventricular block was recorded significantly more often.

The positive result of the proposed cytoprotective treatment on 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 energy metabolism in the myocardium due to the transfer of free fatty acids with cytosol inside the mitochondria and thereby ensures the bioavailability of the high-energy substrate for oxidative metabolism in cardiomyocytes [10, 11]. In addition, by facilitating the oxidation of long chain fatty acids and modulating the ratio of CoA to CoA-SH, the compound participates in the binding of acyl residues in peroxisomes and mitochondria and positively affects the metabolism of amino acids, assimilating an array of free radical compounds, stabilizes organelles and cell membranes, and prevents accumulation in the cytoplasm cardiomyocyte fatty acid esters, which can lead to the occurrence of fatal ventricular arrhythmias [12, 14].

Having found in the initial state in patients with ACS (MI) expressed disturbances of the morphological and functional parameters of the heart, the progression of post-infarction remodeling with impaired systolic function of the heart and their possible pathogenetic relationship with the progression of endothelial vascular dysfunction.

We set the task to investigate the effectiveness of rehabilitation treatment of patients with ACS (MI) by including a course of parenteral use of L-arginine and L-carnitine in the protocol treatment program. It was found that

in the initial state in patients with ACS (MI) systolic dysfunction of the left ventricle (LV) is diagnosed, as evidenced by a decrease in the ejection fraction of the heart (EF). Moreover, in patients of the control group against the background of drug and restorative treatment according to the standard scheme, there was a remodeling of the heart with a gradual increase in the volume of its chambers, in particular the left ventricle and a decrease in its contractility. That is, the data obtained indicate insufficient hemodynamic effectiveness of standard therapy in this group of patients. Whereas in patients with ACS (MI) of the first studied group, to whom treatment with L-arginine and L-carnitine was added to standard therapy after an intervention, examination (on day 5) showed a tendency to decrease post-infarction remodeling of the heart and the progression of acute left ventricular aneurysm. Thus, the addition of L-arginine and L-carnitine to the standard treatment in these patients contributed to a decrease in the manifestation of postinfarction LV remodeling, which ultimately manifested itself in a significant increase in EF, myocardial contractility, and a decrease in systolic dysfunction and the incidence of acute left ventricular failure (pulmonary edema and cardiogenic shock).

The use of complex drug therapy with the inclusion of L-arginine and L-carnitine in patients with ACS (MI) contributed to the rapid and complete restoration of the studied parameters of vascular endothelial function in these patients. This treatment result can be explained by the use of L-arginine, as the main substrate for the synthesis of nitric oxide. Thus, in many studies it was shown that the use of L-arginine after stenting reduced the number of restenoses [13, 14] due to its antihypoxic, antioxidant and membrane-stabilizing activity, but its main physiological role is the regulation of the functional state of blood vessels and ensuring an appropriate level of organ microcirculation and body tissues [13, 15].

In general, due to the complex use of combined drug therapy with the inclusion of L-arginine and L-carnitine, a significant improvement in the parameters of central cardiac hemodynamic and restoration of vascular endothelial function was achieved, which was accompanied by a significant decrease in the frequency of progression and severity of such complications of ACS (MI) as reperfusion arrhythmias and acute cardiac (left ventricular) failure.

Conclusions

1. In patients with acute MI, expressed disturbances of the morphological and functional parameters of the heart are observed, namely, the progression of its post-infarction remodeling, followed by a disturbance of the systolic and diastolic functions of the heart and the progression of heart failure syndrome and endothelial vascular dysfunction.
2. Structural and functional disorders of the heart parameters are accompanied by a more frequent progression of the complicated course of MI; on the first day after percutaneous coronary intervention, reperfusion syndrome with manifestations of acute left ventricular failure and rhythm disturbances (tachycardia, high grade extrasystole, fibrillation, was most often diagnosed with standard drug therapy)) and conductivity (left bundle branch block, AV blockade II-III degree).
3. The additional inclusion of a mixture of L-arginine and L-carnitine in standard drug therapy significantly reduces the incidence and severity of MI complications such as reperfusion arrhythmias and acute left ventricular failure.

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