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# Dynamics of connective tissue metabolism and NO-Synthesizing function during patients' treatment with carnitine containing drugs after myocardial infarction

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The article presents data on the effect of carnitine containing drug cardonat on endothelial dysfunction and pathological stroma restructuring of myocardium in patients after myocardial infarction within 6 months of medical rehabilitation.

Combination of cardonat with standard therapy promotes correction of collagen metabolism abnormalities, namely reducing the synthesis of abnormal collagen.

Also, this drug combination improves endothelial function: it increases the synthesis of nitric oxide, reduces the level of active nitrogen radicals. This generally provides a favourable clinical course of postinfarction period and reduces the pathological left ventricle remodelling.

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*Keyword:* Myocardial infarction, endothelial dysfunction, collagen metabolism, Cardonat.

### 1. Introduction

**Problem stating and analysis of recent researches:** Improving the effectiveness of treatment patients with different clinical forms of coronary heart disease (CHD) remains one of the most essential tasks of modern cardiology [3].

Despite the apparent success associated with the introduction of angioplasty and wider use of high-performance drugs which improve the prognosis of patients (statins, inhibitors of the renin-angiotensin-aldosterone system, antiplatelet agents), an integral component of the coronary artery disease treatment still remains antianginal and cytoprotective therapy [5, 6]. As, in the pathogenesis of postinfarction cardiac remodelling, the functioning of not only sympathetic-adrenal and renin-angiotensin-aldosterone system is important, but also of the

cascade of metabolic changes in cardiomyocytes [2, 9]. In recent decades, the so-called "metabolic" direction develops rapidly, which is aimed at theoretical and applied analysis of metabolic processes at different levels [1, 4]. Nowadays, the problem solution of the hypoxic myocardial metabolism recovery is aimed at optimizing use of oxygen in cardiomyocytes introducing drugs effecting intracellular metabolism and having cytoprotective properties [7, 8]. A new approach in this area is the study of these drugs, their effect on the problem of connective tissue synthesis resulting from active postinfarction collagen synthesis and endothelial dysfunction.

### The Aim of Research

To study the effect of cardioprotective, carnitine containing drug cardonat on endothelial function,

on its NO-synthesizing activity in particular, and processes of myocardium fibrosis in patients after myocardial infarction in the recovery period.

## 2. Materials and Methods

The research included 39 patients at the age of  $54,2 \pm 1,3$  years old with Q wave MI. The patients were divided into 2 groups: the 1st group (19 people) - patients who had had a standard therapy with aspirin, clopidogrel, nitrates (if indicated), statins, and enalapril and metoprolol at individually selected doses, the 2nd group (20 people) - patients who received cardonat (2 capsules 3 times per day) additionally to the standard therapy. Patients were examined at the beginning of therapy within 1, 3 and 6 months of medical rehabilitation.

The functional state of the endothelium was assessed by determining plasma concentrations of arginine, total nitric oxide (NO) and nitrite and nitrosothiol as mediated elements of NO-metabolism. The level of arginine was determined in the spectrum of amino acids by means of liquid chromatograph. To determine the total NO, there was used an assay kit of company "R & D Systems". A quantitative method for determining the concentration of nitrite was based on 2-stage diazotized Griess reaction and nitrosothiol level was determined by the Griess method by means of liquid chromatography. The metabolism of connective tissue matrix was studied on the basis of the free and bound oxyproline content of glycosaminoglycans in blood serum, which are antibodies to atypical collagen (IgM and IgG). Content of free and bound oxyproline in blood serum was determined by colorimetric method. For detection of glycosaminoglycans we used biochemical method of anion metabolic chromatography on DEAE-cellulose. Quantitative immunoenzymatic defining of IgM and IgG was performed by means of assay kit of "Vector-Best" joint stock company. The remodelling process and left ventricular systolic function were assessed on the basis of left ventricle volume parameters and its ejection fraction, which were studied by means of echocardiograph. All statistical data analysis was performed by means of Excel software package.

## 3. Results and discussion

While studying data of metabolism dynamics in the connective tissue, it was determined that levels of both free and bound oxyproline in blood serum tended to increase during the first month after MI, and then remained relatively stable. Such dynamics was present in both groups of patients, regardless of treatment. As for the level of glycosaminoglycans in blood serum, their concentration did not change in patients of the 1st group, while their significant reduction was observed in patients of the 2nd group. A significant treatment effect on the dynamics of antibodies to atypical collagens was determined. Although during treatment with cardonat introduction, there was not marked any significant difference in the dynamics of IgM among the patients of both groups, a significant decrease in IgG concentration was obvious beginning with the third month of medical rehabilitation.

Evaluation of endothelium functioning, NO-synthesis in particular, revealed that cardonat introduction promoted a significant increase of arginine beginning with the sixth month of medical rehabilitation (table). A similar regularity was observed in the dynamics of the total NO, the level of which increased significantly with cardonat introduction after six months of treatment. However, unlike the standard treatment in such case, cardonat introduction promoted a significant increase of the nitrite concentration after one month of therapy, and the reduction of nitrosothiol beginning with the third month of medical rehabilitation, which proves, on the one hand, the optimization of NO-synthesis, and on the other hand, a significant inhibition of reactive nitrogen radicals formation, which are known to damage cardiomyocytes significantly. Nitrosothiol content, which is formed during the metabolism of active nitrogen radicals, was significantly different in the blood of patients treated with cardonat during 6 months in comparison to those patients who had had a standard therapy.

From the mentioned above, we noted that the elevated level of free oxyproline in patients' blood serum after MI proves activation of collagen synthesis during postinfarction period.

Elevated concentrations of IgM may be considered as an early marker of activated “hard” collagen synthesis, and IgG proves more outlying changes of collagen synthesis. Thus, activation of collagen synthesis, on the one hand, aims at formation of a connective tissue matrix of the heart and at a complete scarring in the area of myocardial necrosis (post-MI), on the other hand, it leads to atypical collagen synthesis in patients after MI. The latter results not only in increased “stiffness” of the left ventricle, but also in its pathological remodelling. Patients’ medical rehabilitation with the use of standard therapy supplemented with the medications simulating the processes of collagen synthesis (e.g.

angiotensin-converting enzyme inhibitors), makes positive effect on these pathogenetic chains. Due to its wide range of medicinal properties cardonat encourages effective cardioprotective therapy both for reducing cardiomyocytes hypoxia and for processes of collagen synthesis. The gradual increase of arginine concentration in recovery period provides direct synthesis of NO and improves processes of endothelium- dependent of vessels relaxation. Reduced level of nitrosol in patients after MI who were treated with cardonat, also indicates reducing of peroxynitrite further damaging effect on cardiomyocytes, and thus improving systolic function and reducing left ventricular cavity dilatation.

**Table 1:** Indices of NO-synthesizing function in patients with MI during treatment with standard therapy and cardonat (M ± m).

Index units. of measurement	Term of the medical rehabilitation after MI			
	Before treatment	1 month.	3 months.	6 months.
Standard therapy (n=19)				
α-arginine, micromole/l	0,20±0,02	0,24±0,02	0,29±0,03*	0,28±0,02**
Δ		20,0	45,0	40,0
Total NO, micromole/l	31,65±1,32	33,05±1,14	36,97±1,12**	37,13±0,94***
Δ		4,4	16,8	17,3
Nitrites, micromole/l	11,21±0,19	11,48±0,21	11,86±0,23	11,74±0,27
Δ		2,4	5,8	4,7
nitrosothiol, micromole/l	4,63±0,16	4,45±0,12	4,23±0,10	4,29±0,14
Δ		-3,9	-8,6	-7,3
Standard therapy + cardonat (n=20)				
α- arginine, micromole/l	0,24±0,01	0,27±0,02	0,31±0,03*	0,35±0,02****
Δ		12,5	29,2	45,8
Total NO, micromole/l	33,10±1,40	37,28±1,13*	37,17±1,15*	38,96±0,89***
Δ		12,6	12,3	17,7
Nitrites, micromole/l	11,16±0,17	11,94±0,20**	12,09±0,22***	12,37±0,18****
Δ		7,0	8,3	10,8
nitrosothiol, micromole/l	4,41±0,11	4,25±0,14	4,03±0,10*	3,53±0,08****
Δ		-3,6	-8,6	-20,0
Notes: 1. The reliability of changes to the parameters at the beginning of treatment: * - P<0.05, ** - p<0.02, *** - p<0.01; **** - p<0.001.				
2. Δ - increase or decrease (-) of indeses in the treatment in percents to index at the beginnig of treatment.				

Analysis of hemodynamic based on echocardiography showed that the most significant recovery of left ventricular contractility (increase in ejection fraction and reduction in end-diastolic ventricular volume) was observed in patients who were treated with cardonat.

#### 4. Conclusions

- During the medical rehabilitation of Patients after MI, collagen synthesis function gradually becomes active simultaneously with the formation of antibodies to atypical collagen, reserves of arginine gradually increase, the processes of active nitrogen radicals formation are inhibited.
- The regulation of the collagen synthesis and breakdown processes, decrease of atypical collagen formation, improvement of NO metabolism with introducing cardonat to standard therapy, allows to optimize the medical rehabilitation of patients after MI.
- Significantly improving the connective tissue matrix metabolism and nitric oxide metabolism during prolonged medical rehabilitation of patients after MI, cardonat encourages the inhibition of pathological left ventricle remodelling, reducing postinfarction dilation and improving systolic function.

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