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The Role of Arterial Elasticity in Determining the Degree of Chronic Heart Failure in Myocardial Infarction

Aim	To study the left ventricular (LV) contractile and pumping function during the recovery phase following ligation of the anterior descending coronary artery (CA).
Material and methods	Cardiodynamic parameters were studied in Wistar rats 2–4 weeks after experimental myocardial infarction (MI). MI was induced by ligation of the anterior descending CA under zoletil anesthesia. LV catheterization was performed with a standard FTH-1912B-8018 PV catheter inserted into the LV through the right carotid artery.
Results	After the induction of MI, the mortality rate of animals was 50%. Survived animals developed significant LV dilatation and a decrease in ejection fraction (EF) by an average of 31%. However, major indexes of the pumping function, including minute volume, heart work, and maximum ejection velocity, were within a normal range whereas the maximum filling velocity was almost doubled. Approximately 50% of hearts with dilated LV had normal EF, delayed relaxation, and increased LV diastolic pressure, which qualified this group as a diastolic dysfunction group. The systolic dysfunction group with EF less than 50% of normal had similar values of myocardial contractility and relaxation but differed from the diastolic dysfunction group in more than 50% reduced maximum LV ejection velocity and 1.7 times increased elasticity of the arterial wall. A close inverse correlation was found between these values (r= –0.91).
Conclusion	The study results showed that, with a similar myocardial contractile function, the cardiac pumping function is determined by the elasticity of the aortic wall. Therefore, restriction of reactive fibrosis during MI is an important task of modern cardiology.

Keywords	Myocardial infarction; Wistar rats; contractility; systolic and diastolic dysfunction; arterial wall elasticity
For citations	Lakomkin V. L., Abramov A. A., Prosvirnin A. V., Kapelko V. I. The Role of Arterial Elasticity in Determining the Degree of Chronic Heart Failure in Myocardial Infarction. Kardiologiia. 2023;63(12):54–59. [Russian: Лакомкин В.Л., Абрамов А.А., Просвирнин А.В., Капелько В.И. Роль упругости артериальной стенки в определении степени нарушения насосной функции сердца при инфаркте миокарда. Кардиология. 2023;63(12):54–59].

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Introduction

The survival of the body in myocardial infarction (MI) depends on both the size of the infarction and the adaptability of the circulatory system. The first 24 hours are the most critical period [1], when it is determined whether the circulatory system can compensate for the decrease in the cardiac contractile function. Ventricular dilation, hypertrophy of the intact areas, and fibrosis are the main factors of cardiac compensation.

Dilation of the heart is essential for sarcomeres to stretch more and develops when metalloproteinases, which break down the extracellular matrix, are activated. These enzymes cease to act within 2 weeks [2]. Replacement fibrosis is activated at the same time, which tightens the involved areas of the myocardium and thus maintains the elasticity of the left ventricle. This makes it difficult to fill and increases left ventricular (LV) diastolic pressure but increases its elasticity and contributes to the development of force during the contraction. Gradually developing hypertrophy of the intact myocardium helps to improve cardiac pump function. Epidemiological studies show that LV function improved spontaneously in most patients in about 1 month [3, 4].

The reasons for such improvement have not been adequately analyzed. The role of conventional echocardiography in MI to assess the state of the myocardium is diminishing due to changes in the preload and LV chamber shape and volume [5–7], which have considerable effect on LV volume and shape. It is necessary to know not only LV volume, but also LV pressure. LV catheterization is very limited for obvious reasons, but can be performed during coronary ligation in animals, which is a long-established model of MI. Data on intraventricular pressure, left ventricular ejection rate, and the contractile function of the myocardium can be obtained using catheterization [8]. This method was applied in this study in order to explore the compensatory mechanisms that ensure better recovery of the cardiac function.

ISSN 0022-9040. Kardiologiia. 2023;63(12). DOI: 10.18087/cardio.2023.12.n2494

Objective

Study left ventricular contractility and pump function during the recovery after ligation of the left anterior descending artery.

Material and Methods

The study was conducted using 5–6-month-old male Wistar rats weighing 357 ± 5 g. Animals were kept in the bioclinic of the cardiac center in cages (5 animals per cage) with free access to dry food and water. The light regime was controlled (12 hours of light and 12 hours of dark) with sufficient air change and at a temperature of 19–23 °C. All animal manipulations were performed following the International Guiding Principles for Biomedical Research Involving Animals, the requirements of the Ethics Committee of the Russian National Cardiology Research Center, and the provisions of the national standard GOST 53434–2009, and in accordance with Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes.

The state of pump and contractility functions of the heart was studied in 2 and 4 weeks after coronary ligation, that is during the period of stabilization. Rats were divided into 3 groups: control (Group 1; n = 8); infarct, 2 weeks (Group 2; n = 15); infarct, 4 weeks (Group 3; n = 15). Left anterior descending artery was ligated according to the standard procedure after anesthetizing with Zoletil (5 mg/kg). LV was catheterized with a standard PV catheter (FTH-1912B-8018) and an ADV500 system. LabChart ADInstruments 8.1.2, which allows calculating more than 20 parameters of contractility during a cardiac cycle, was used. Blood pressure was not measured, but its value was judged by the LV pressure at the peak rate of pressure rise; this moment almost coincides with the aortic valve opening. Myocardial contractility index was calculated by the standard method by dividing the peak rate of pressure rise by the amount of LV pressure at the time of the peak rate. At the end of the experiment, the hearts were extracted, weighed, and the LV weight was measured. The size of the infarct was determined by planimetric method using triphenyltetrazolium chloride and blue staining.

The findings were statistically processed using Microsoft Excel 2013. The data are expressed as mean and standard error of mean (M ± SEM). Statistical processing was performed using a two-tailed Student's test at the significance level $p < 0.05$.

Results

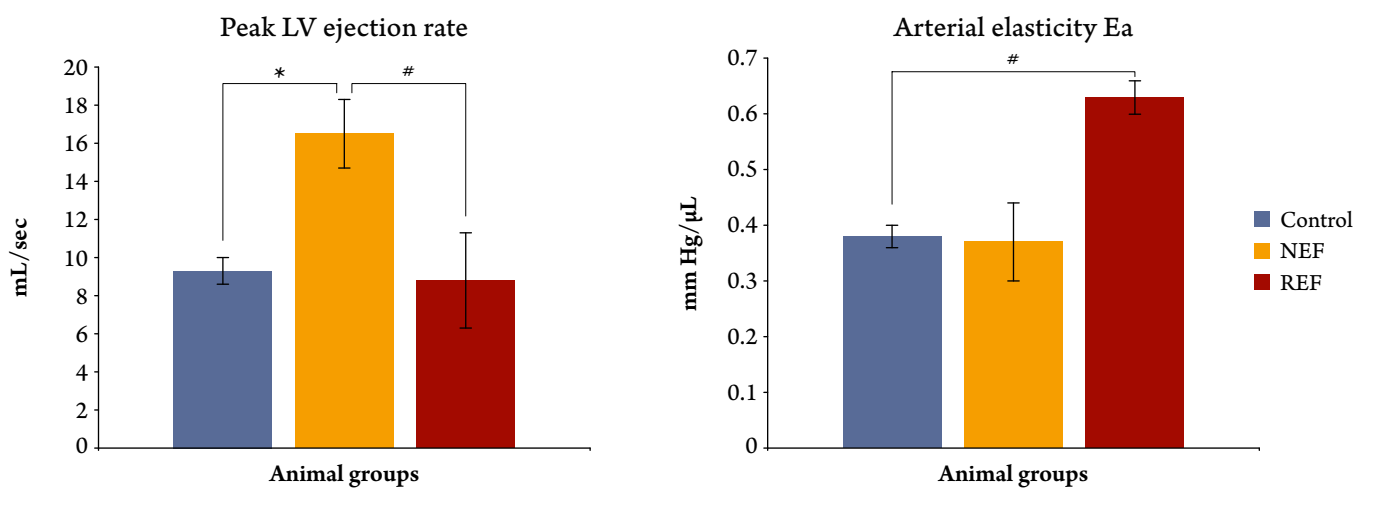
Dimensions of the heart and the size of myocardial infarction

The size of MI was 45 ± 3% of the section area in 2 weeks. Postoperative mortality in rats was 50%. In surviving animals, the weight of the ventricles increased almost 2-fold – from 0.53 ± 0.02 g in the control group to 1.02 ± 0.12 g in 2 weeks and to 1.03 ± 0.07 g in 4 weeks ($p < 0.001$).

Hemodynamics

Changes in the size and function of the heart were almost the same in 2 and 4 weeks, thus, they were grouped together. A significant increase in the LV dimensions – its dilatation – was a common feature of these experiments. In general, left ventricular ejection fraction (LVEF) was reduced by 31% in the MI group, but the main indicators of the pump function – cardiac output (CO), stroke work, maximum ejection rate – were normal, and the maximal LV filling rate was increased almost 2-fold (Table 1). This data is indicative of the compensated pump function, due to which these animals survived. However, the indicators varied within the group in a fairly wide range. For example, CO varied from 57 mL/min to 159 mL/min. Such a wide range reflects a different degree of myocardial

Central illustration. The Role of Arterial Elasticity in Determining the Degree of Chronic Heart Failure in Myocardial Infarction



NEF, normal ejection fraction; REF, reduced ejection fraction; *, # $p < 0.005$.

Table 1. Cardiac hemodynamics in 2-4 weeks after MI

Parameter	Control	MI
Number of experiments	8	15
Cardiac output, mL/min	99 ± 7	96 ± 10
Heart rate, bpm	329 ± 7	318 ± 10
LV end-diastolic volume, mL	0.41 ± 0.03	0.62 ± 0.03**
LV end-systolic volume, mL	0.13 ± 0.02	0.29 ± 0.04*
LVEF, %	71 ± 3	49 ± 5*
Peak ejection rate, mL/sec	9.3 ± 0.7	12.9 ± 1.8
Stroke work, mm Hg x mL	34.4 ± 2.4	34.6 ± 4.5
Maximum LV pressure, mm Hg	120 ± 3	128 ± 6
Peak LV filling velocity, mL/sec	8.7 ± 0.7	16.0 ± 1.9*
Ea, mm Hg/μL	0.38 ± 0.02	0.46 ± 0.05
P@dP/dt max / P, s^{-1}	86±2	92±4

* p < 0.01, ** p < 0.001 versus the control. P – the left ventricular pressure at the aortic valve opening.

involvement and/or a different degree of the activation of compensatory mechanisms.

In approximately 50% of the experiments, LVEF was comparable with the control, which made it possible to divide the general group into diastolic and systolic dysfunction subgroups (Table 2). The systolic dysfunction (SD) subgroup differed from the control by reduced CO and stroke work. However, rats with SD continued to have normal LV systolic pressure and LV ejection rate comparable with the control due to LV dilatation and hypertrophy. The subgroup of rats with diastolic dysfunction (DD) was characterized by normal CO and stroke work but had an almost two-fold advantage over the control group in LV ejection and filling rate.

Left ventricular contractility

Table 3 shows that changes in myocardial contractility and relaxation, and LV diastolic pressure were uniform in both groups. There was almost no intergroup difference although these changes were slightly larger in the DD subgroup. Significantly increased LV ejection rate in the DD subgroup, which was 2 times as high as in the SD subgroup, was the main difference between them (see Table 2). At the same time, there was almost no difference in the peak rate of pressure rise (see Table 3), and the decrease in ejection in the SD subgroup was due to increased resistance, as evidenced by an almost 2-fold increase in the arterial wall elasticity (see Table 2). These indicators were closely inversely correlated (r = –0.91).

Discussion

Our findings, and the data obtained by other authors [9], showed that, despite the standard coronary ligation, the MI size was very variable from 26% to 60%. Cardiac remodeling develops – the end-diastolic and end-systolic LV volume increases 1.5-fold and 3.5-fold, respectively, and the indicators of myocardial contractility and relaxation

Table 2. Cardiac hemodynamics in systolic and diastolic dysfunction in 2–4 weeks after MI

Parameter	Control	SD	DD
Number of experiments	8	7	8
Cardiac output, mL/min	99 ± 7	71 ± 7*	112 ± 12#
Heart rate, bpm	329 ± 7	320 ± 14	317 ± 16
LV end-diastolic volume, mL	0.41 ± 0.03	0.66 ± 0.05**	0.58 ± 0.02***
LV end-systolic volume, mL	0.13 ± 0.02	0.40 ± 0.05**	0.20 ± 0.02*,#
LVEF, %	71 ± 3	30 ± 3***	66 ± 4###
LV peak ejection rate, mL/sec	9.3 ± 0.7	8.8 ± 1.8	16.5 ± 2.5*,#
Stroke work, mm Hg·mL	34.4 ± 2.4	21.7 ± 3.2*	42.9 ± 5.6#
Maximum LV pressure, mm Hg	120 ± 3	116 ± 6	137 ± 8
Peak LV filling velocity, mL/sec	8.7 ± 0.7	12.2 ± 2.2	19.4 ± 2.6**
Ea, mm Hg/μL	0.38 ± 0.02	0.63 ± 0.07*	0.37 ± 0.03#
LV dP/dt max / P, s^{-1}	86 ± 2	88 ± 4	96 ± 5

* p < 0.05; ** p < 0,01; *** p < 0.001 versus the control; # p < 0.05; p < 0.01;
p < 0.001 versus systolic dysfunction. P - left ventricular pressure at the aortic valve opening.

ISSN 0022-9040. Kardiologiia. 2023;63(12). DOI: 10.18087/cardio.2023.12.n2494

Table 3. Left ventricular contractility in systolic and diastolic dysfunction in 2–4 weeks after MI

Parameter	Control	SD	DD
Number of experiments	8	7	8
Maximum rate of LV pressure rise, mm Hg/sec	9970 ± 379	6000 ± 324***	7900 ± 935
Contractility index, s^{-1}	117 ± 5	70 ± 5***	81 ± 7**
Maximum rate of LV pressure decrease, mm Hg/sec	8200 ± 542	3590 ± 293***	5070 ± 724**
Relaxation time constant (tau), msec	7.8 ± 0.4	13.2 ± 0.5***	12.7 ± 1.0**
Minimum LV pressure, mm Hg	0.4 ± 0.4	7.0 ± 1.1***	10.0 ± 4.0*
LV end-diastolic pressure, mm Hg	4.5 ± 0.5	10.7 ± 1.6*	16.5 ± 4.6*

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ versus the control.

decrease [10]. Our findings (see Table 1) are comparable to these data.

The results of our work showed that, despite the significant dilatation of LV, LVEF and CO were preserved in some of the experiments, and the other group had low LVEF and reduced CO. It is noteworthy that the parameters of myocardial contractility almost did not differ in these groups (see Table 3), therefore, the difference in pump function was due to extracardiac factors. An almost 2-fold increase in the arterial wall elasticity was most likely such factor in the SD group. Higher peripheral resistance requires an increase in systole, limits the stroke volume, increases the end-systolic volume, which hampers LV filling.

When considering the causes of the increased arterial wall stiffness in the SD group, attention should first be paid to the factor of fibrosis. Myocardial damage results an inflammatory reaction, which causes changes in the composition of collagen in the extracellular matrix of the myocardium. Reparative fibrosis is necessary to strengthen the weakened LV wall, which reduces the LV wall tension and the degree of myocardial hypertrophy [11]. However, reactive excessive fibrosis can spread not only to the damaged area, but also to adjacent tissues, including the aorta, thus disrupting the cardiac function [2]. Type I collagen prevails in the normal myocardium (80–90%), while type III collagen, which provides tissue elasticity, is only 5–11% [2]. Reduced elastin to collagen ratio [12] affects the relationship between arterial wall elasticity and changes in collagen fraction [7]. Activation and proliferation of endogenous populations of fibroblast are the main source of collagen synthesis, secretion, and precipitation in response to various stimuli [13], and the transition of the smooth muscle cell phenotype from a contractile to a synthetic state can contribute to the progression of the disease [14].

The use of various factors limiting the degree of reactive fibrosis can reduce the collagen content and the LV wall tension [14]. The aortic wall elasticity is a factor that increases systolic and pulse blood pressure [15], and the pulse wave velocity is as a non-invasive indicator of aortic elasticity. The aortic wall elasticity is an independent risk factor for mortality of circulatory system diseases [16].

It is important medical task to able to stop the pathological LV and aorta remodeling [17, 18]. Vasodilators are not very effective on large elastic arteries, but they can significantly reduce the amplitude of wave reflection and the augmentation index by diminishing the elasticity of muscle arteries. Angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, diuretics are commonly used to reduce vascular stiffness [15].

Conclusion

Our findings showed that, if peripheral resistance is not elevated, left ventricular ejection fraction can remain normal even despite considerable left ventricular dilatation. Reduced ejection rate into the aorta, stroke volume, and cardiac output were observed in the hearts of rats with increased aortic wall elasticity. Limiting reactive fibrosis in myocardial infarction is an important task for modern cardiology in this regard.

Funding

The study was a part of the State Assignment of the Ministry of Health of Russia, reg. # 121031300048-3.

No conflict of interest is reported.

The article was received on 20/05/2023

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