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Compensatory Changes of the Diastole under Conditions of Inflow Restriction to the Heart

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This work was designed to study changes in the mechanical properties of rat myocardium during short-term (2-3 sec) compression of the lower vena cava. A catheter was inserted into the left ventricle, allowing simultaneous measurement of left-ventricular volume and pressure. The decrease in the left-ventricular end-diastolic volume caused by inflow restriction was accompanied by less pronounced decrease in the left-ventricular stroke volume and maximum rate of left-ventricular pressure development. This was coincided with accelerated relaxation and deeper fall of the minimum left-ventricular diastolic pressure. The lower was left-ventricular end-systolic volume, the greater was the degree of these changes. It is assumed that the "restoring force" that naturally appears under conditions of low filling of the left ventricle is determined by elastic N2B part of the titin molecule that is compressed during strong shortening of myofibrils and accelerates their return to the previous length during relaxation. As a result of better filling of the left ventricle, the heart can maintain left-ventricular stroke volume at the appropriate level.

Key Words: *heart; contraction; relaxation; diastolic pressure; ventricular volume*

The pump function of the heart is realized under conditions of strict correspondence between inflow and outflow. The latter is determined by the degree of diastolic stretching of myocardial fibers that depends on both the blood inflow and the myocardial distensibility. Under conditions of reduced blood inflow to the heart caused by blood loss, sharp BP fall, or controlled hypobaria of the lower body, various compensatory mechanisms of the circulatory system are activated to maintain the required stroke volume. The question of whether myocardial properties changed under these conditions remained poorly understood; there was the only report on acceleration of left ventricular (LV) relaxation [9].

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Here we studied mechanical properties of the myocardium during short-term compression of the lower vena cava in rats with the simultaneous continuous recording of LV pressure and volume, which allows evaluating the compensatory capabilities of the myocardium during the period preceding activation of systemic compensatory mechanisms.

MATERIALS AND METHODS

Male Wistar rats (age 5-6 months, body weight 320-414 g) were used in the experiments. The animals were kept in cages (5 rats per cage) at 19-23°C and 12/12 h light/dark regimen with free access to water and pelleted food (vivarium of the National Medical Research Center of Cardiology). All manipulations were carried out in accordance with the International Recommendations for Biomedical Research with La-

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boratory Animals and the requirements of the Ethics Committee of the National Medical Research Center of Cardiology, and GOST R53434-2009.

Invasive study of the cardiac contractile function was performed in rats anesthetized with Zoletil 100 (5 mg/kg) using an FTH-1912B-8018 standard pressure-volume catheter introduced into LV through the right carotid artery and ADV500 transducer (Transonic). Signals were measured by a fragment of records with multiple (10-40 times) recording of parameters, the mean values of the parameters characterizing the cardiac function were calculated automatically using LabChart 8.1 software (ADInstruments) [1]. For short-term occlusion of the lower vena cava, a 2.5-cm incision was made from the end of the xiphoid process along the white line and a ligature was passed under the vein between the liver and the diaphragm, its ends came out and were freely available. Ligation of the lower vena cava resulted in a series of cardiac cycles with a gradual decline of LV inflow. The results are presented as *M*±*SEM*.

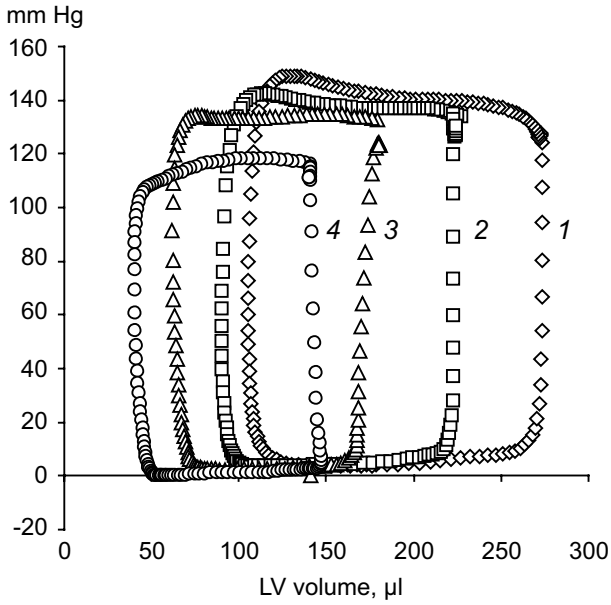

Fig. 1. Volume-pressure loops in rat LV. *1*) Initial state, *2*, *3*, *4*) consecutive cycles with short-term restriction of blood flow to the heart.

RESULTS

Reduced inflow to the heart was accompanied by a natural left shift of the volume-pressure curves and a decrease in LV stroke volume (Fig. 1). The decline in LV filling rate roughly corresponded to the decrease in LV end-diastolic volume (EDV), while the decrease in LV stroke volume was considerably less pronounced (Fig. 2, *a*) and coincided with the time course of maximum rate of LV pressure development (+dP/dt). On average, EDV reduction by 30% corresponded to the decrease in the maximum LV filling rate to 66±5%, while the maximum rate of LV pressure development (+dP/dt) and stroke volume decreased to 81±6 and 81±4%, respectively, which reflected close relationship between these parameters. Reduced blood inflow to the heart did not affect HR. We did not record BP in these experiments, but it apparently decreased (Fig. 1). Changes in BP were assessed by the level of LV pressure, at which the maximum rate of LV pressure development was reached, this value closely corresponded to the beginning of the ejection phase. When the EDV was reduced by 30%, this value decreased to 84±2%, *i.e.* its changes corresponded to the stroke volume dynamics.

During rapid decrease in the blood inflow to the heart, the relationship between LV pressure and volume in the onset of diastole drops more abruptly than

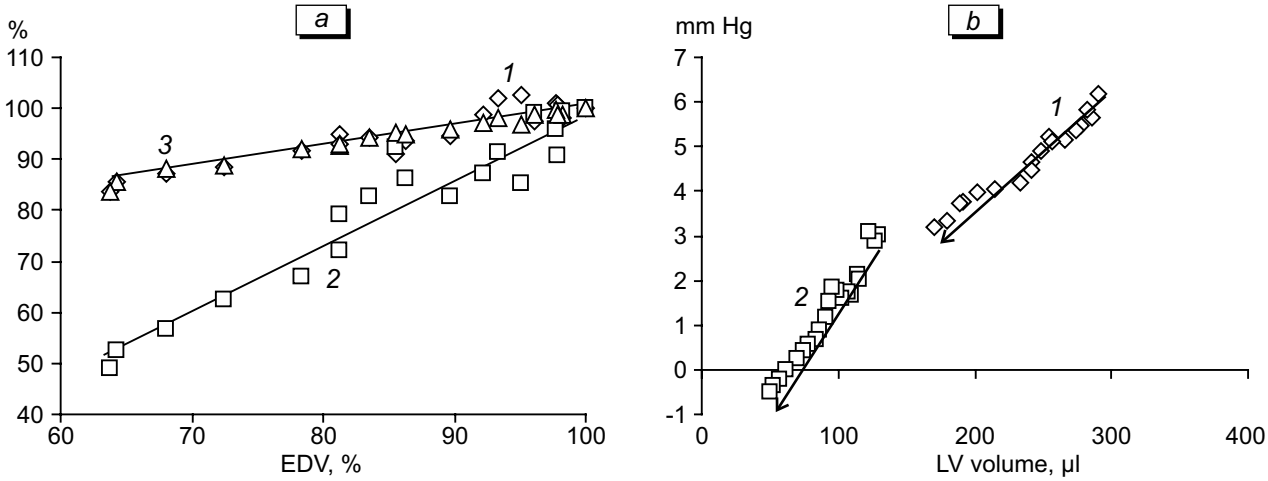

Fig. 2. The correlations between the decrease in EDV and stroke volume (1, rhombs), maximum rate of LV filling (2, squares), and maximum rate of LV pressure development (3, triangles) (*a*); the correlations between EDV and LV end-diastolic pressure (*1*) and between ESV and minimum diastolic pressure (2) (*b*) in each cardiac cycle at short-term restriction of blood flow to the heart.

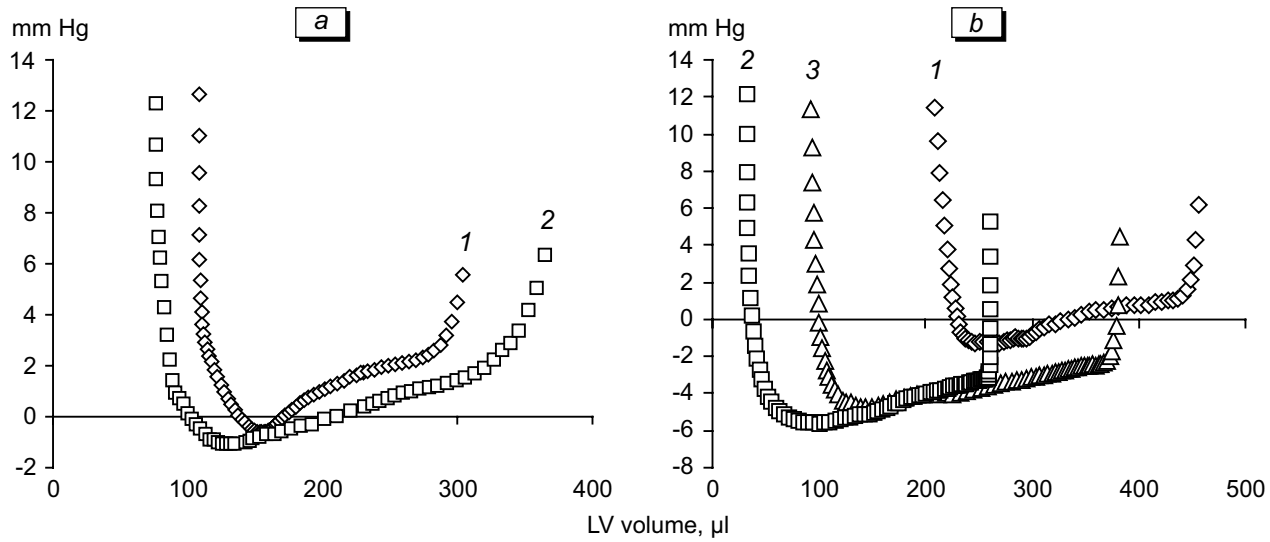

Fig. 3. LV volume—pressure curves in diastole at different initial ESV (*1*) and during subsequent flow restriction (*2*, *3*). *a*) ~100 µl (initial ESV), *b*) >200 µl.

in the end of the diastole (Fig. 2, *b*). Faster myocardial relaxation apparently contributed to this process, as was seen from linearly reduced constant of relaxation time. The correlation between the end-systolic volume (ESV) and this constant in most experiments was very high (r=0.98-0.99). Accelerated myocardial relaxation at low ESV during permanent inflow restriction was previously observed in dog heart [9], it contributes to a decrease in minimum diastolic pressure and facilitates LV filling during the early diastole. We found that this phenomenon was weakly expressed at low initial ESV (~100 µl, Fig. 3, *a*) and clearly expressed at higher baseline ESV (~200 µl, Fig. 3, *b*). It can be seen that the greater was the difference between the initial and final ESV, the deeper decreased minimum LV diastolic pressure.

It is known that the more the heart empties during systole, the more noticeable is the phenomenon of active blood pumping from the atrium to the ventricle. This phenomenon was discovered in 1930 by Lewis Katz in the isolated turtle heart, and he first identified the heart as a suction pump. Much later, this phenomenon was demonstrated in the dog heart by Brecher (1956). This phenomenon most naturally may be explained by the presence of the so-called "restoring force" that acts via titin (connectin), a myofibrillar protein that connects the ends of myosin filaments to sarcomere boundary (Z-line). It represents a spring, the elastic component of which is completely relaxed in sarcomeres that do not experience any tension (the so-called natural length =1.85 µm) [3]. The spring stretches at sarcomere lengthening, counteracting its overextension, and when it is shortened less than the unloaded, "passive" length, it compressed generating energy for the subsequent return to its natural length.

It was shown in experiments in skinned heart muscle, that at a lowest length of sarcomeres the rate of their elongation during relaxation was the highest [8]. Rat myocardium characterized by higher content of elastic N2B isoform demonstrates higher elongation rate than bovine myocardium with low N2B content. Treatment of myofibrils with trypsin that destroys titin eliminated the "restoring force" [6]. According to some calculations [4,6] for rat cardiomyocytes within the range of sarcomere length of 1.6-2.1 µm, titin is responsible for 90% of the passive force and at least 60% of the restoring force.

The role of titin and its main "heart" isoform N2B in the implementation of restoring force is especially important for the hearts of small animals, such as rats and mice [5]. High HR of these animals (400-600 bpm) strongly limits the duration of the diastolic phase, so a rapid return of actin and myosin filaments to their previous position is critical for the pumping function of these hearts. Reduced content of N2B isoform in doxorubicin-induced diastolic dysfunction was associated with delayed relaxation [2].

Thus, the stronger the LV contraction and the lower the ESV, the faster the relaxation occurs, the more deeply minimum LV diastolic pressure decreases, and thus, a LV filling improves. These data are consistent with the results of experiments in the dog heart, in which blood flow to LV was automatically restricted or completely stopped by closing the mitral opening [7]. The less was LV inflow, the deeper LV minimum diastolic pressure decreased, and it was the lowest when the inflow was completely blocked.

The observed changes represent one of the mechanisms of urgent self-regulation of the heart, which is activated at myofibrillar level. Additional arguments

in favor of this view are the data on titin ability to inhibit actomyosin interaction with strong contraction in conditions of low ventricular filling [5]. The participation of sympathetic activation in this process, which naturally occurs when LV inflow is reduced over a long time, is hardly possible, because the duration of compression was very short (2-3 sec).

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