MORPHOLOGY AND PATHOMORPHOLOGY

Pathomorphology of the Heart Conduction System: Comparative Study during Increase in Left or Right Ventricular Afterload

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Pathomorphology of the peripheral compartments of the heart conduction system under conditions of increased left or right ventricular afterload is characterized by interstitial edema, hemorrhages, and reversible and irreversible focal lesions. The percentage of damaged conduction cardiomyocytes increases in the wall of hemodynamically overloaded ventricle and in the ventricular septum. These changes are more pronounced in cases when the afterload increase is complicated by heart failure development. Acute dilatation of the heart and distention of the myocardium are events of great specific significance in the genesis of the conduction system disorders developing under conditions of increased right ventricular afterload in comparison with those developing under conditions of increase left ventricular afterload. These data attest the presence of a pathomorphological base for the appearance of arrhythmias during the acute phase of pressure overload of the heart, especially in cases when it is aggravated by heart failure.

Key Words: *pathomorphology; conduction system of the heart; afterload; left ventricle; right ventricle; ventricular septum*

Heart rhythm and conduction disorders are often observed in diseases associated with increased heart afterload, e.g. pulmonary embolism and arterial hypertension of different origin [5,9,10]. Pathomorphological changes in the myocardium developing in cardiac arrhythmias are poorly studied [4]. For example, structural bases of disorders in electrophysiology of the myocardium during the acute phase of pressure overload of the heart received little attention. We failed to find comparative data on the status of the cardiac conduction system during acute increase of the left or right ventricle (LV and RV, respectively) afterload. Clinical findings indicate that the severity of myocardial injury does contribute to the emergence of heart rhythm disorders, while arrhythmias, in turn, can provoke the development of heart failure and increase the probability of a lethal outcome [5,10]. Therefore, it is interesting to compare intramyocardial changes in cases when increased afterload is aggravated or not by heart failure.

We studied the pathomorphology of the heart conduction system under conditions of increased LV or RV overload and compared changes emerging when acute pressure overload was aggravated or not by the development of heart failure.

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MATERIALS AND METHODS

The study was carried out on guinea pigs (500-700 g) under conditions of an open chest with forced lung ventilation. Cardiovascular function was evaluated by recording ECG, pressure in the aorta, LV, and RV, and intraventricular pressure first derivative (dP/dt). The parameters were recorded and processed on a Mingograf-82 programmed complex based on a PC and a polycardiograph. The afterload was increased by ligation of the ascending aorta or pulmonary artery trunk leading to 100% elevation of systolic pressure in the heart ventricles in comparison with the initial level. The duration of vascular stenosis was 30 min.

The animals were divided into 5 groups. In group 1 (n=8, controls) all instrumental and surgical manipulations (forced ventilation of the lungs, opening of the thorax, catheterization of the ventricles) were carried out except stenosis modeling. In groups 2 and 3 stenosis of the aorta (n=15) or pulmonary artery (n=15) was not aggravated by the development of irreversible heart failure. In groups 4 and 5 stenosis of the aorta (n=3) or pulmonary artery (n=4) was aggravated by the development of irreversible heart failure with a lethal outcome within the first 30 min.

The heart was removed directly after experiment and dissected longitudinally into halves, one of which was fixed in 10% neutral formalin buffered after Lilly and embedded in paraffin. Longitudinal serial sections (5 μ) were stained with hematoxylin and eosin, with Schiff's reagent after MacManus with amylase control, and with ferric hematoxylin after Regaud. LV and RV walls and intraventricular septum (IVS) were examined under a microscope. The percentage of Regaud-positive conduction cardiomyocytes was evaluated in preparations stained by the method of Regaud. The percentage of the conduction system cells with PAS-positive amylase-resistant reaction of the sarcoplasm was evaluated in preparations incubated with amylase and stained by Schiff's reagent.

The results were statistically processed by standard methods of variation statistics. The arithmetic means of independent samples were compared by Student's t test. The results were presented as $M \pm m$.

RESULTS

The morphology of the intraventricular conduction system in controls corresponded to its status in health [1]. Conduction cardiomyocytes formed groups, mainly subendocardially, were rather large and looked clear in comparison with the adjacent cells of the contractile myocardium. Injuries detected by staining with ferric hematoxylin after Regaud were found in just a small part of conduction cardiomyocytes. The percentage of Regaud-positive cells was 8.8±1.6% in LV, 8.3±2.0% in RV, and 9.7±2.0% in IVS. Solitary conduction cardiomyocytes with nonspecific PAS-positive reaction of the sarcoplasm indicating irreversible injuries [3] were found in preparations incubated with amylase and stained with Schiff reagent.

The levels of damaged conduction cardiomyocytes in LV and IVS increased in stenosis of the aorta (Fig. 1, *a*; 2, *a*). If stenosis of the aorta was not complicated by heart failure, the level of Regaud-positive cells in the conduction system was 43.1±4.5% in LV and 31.0±4.0% in IVS. The relative content of cells with PAS-positive amylase-resistant sarcoplasm reaction in those cases was 33.4±6.9% in LV and 8.0±2.5% in IVS. In stenosis of the aorta complicated by heart failure the percentage of Regaud-positive cells in the conduction system reached 76.1±3.9% in LV and 81.1±7.9% in IVS. The relative content of cells with nonspecific PAS-positive staining of the sarcoplasm in those cases was 30.6±15.9% in LV and 15.3±6.4% in IVS. Microscopic examination of the preparations stained with hematoxylin and eosin showed interstitial edema, more pronounced in aortic stenosis with heart failure, in zones of the conduction cardiomyocyte location.

Pulmonary artery stenosis resulted in an increase in the levels of damaged conduction cardiomyocytes in RV wall and IVS (Fig. 1, *b*; 2, *b*). When pulmonary artery stenosis was not complicated by heart failure, the relative content of Regaud-positive conduction system cells was 24.4±4.8% in RV and 24.1±4.0% in IVS. The percentage of cells with PAS-positive amylase-resistant reaction of the sarcoplasm was 25.3±3.5% in RV and 27.8±4.1% in IVS. In pulmonary artery stenosis complicated by heart failure, the percentage of Regaud-positive conduction system cells was 62.4±7.3 in RV and 58.6±8.4% in IVS. The relative content of cells with nonspecific PAS-positive staining of the sarcoplasm in those cases was 21.2±6.2% in RV and 23.6±11.7% in IVS. Microscopic examination of sections stained with hematoxylin and eosin showed pronounced interstitial edema in zones of conduction cardiomyocyte location; vast hemorrhages were seen in some preparations. These changes were more pronounced in pulmonary artery stenosis complicated by heart failure.

Hence, a significant part of conduction system cells in IVS and in the ventricular wall working under conditions of high pressure is damaged in stenosis of the aorta and pulmonary artery. The level of damaged conduction cardiomyocytes in intact (*vs.* exposed to high pressure) ventricle does not increase in comparison with the control, the majority of cells looking intact. These data indicate that injuries in the conduction system cells are not caused by systemic neurohumoral

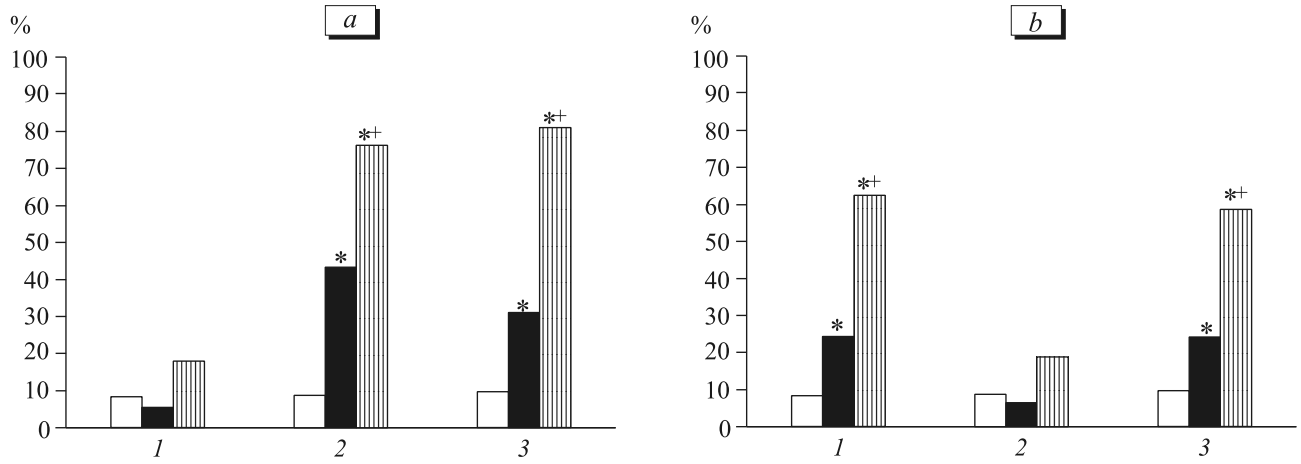

Fig. 1. Percentage of Regaud-positive conduction cardiomyocytes in stenosis of the aorta (*a*) and pulmonary artery (*b*). Here and in Fig. 2: *1*) RV; *2*) LV; *3*) IVS. Light bars: control; dark bars: increased afterload without heart failure development; vertically hatched bars: increased afterload with heart failure development. $p<0.01$ compared to: *control, +increased afterload without heart failure.

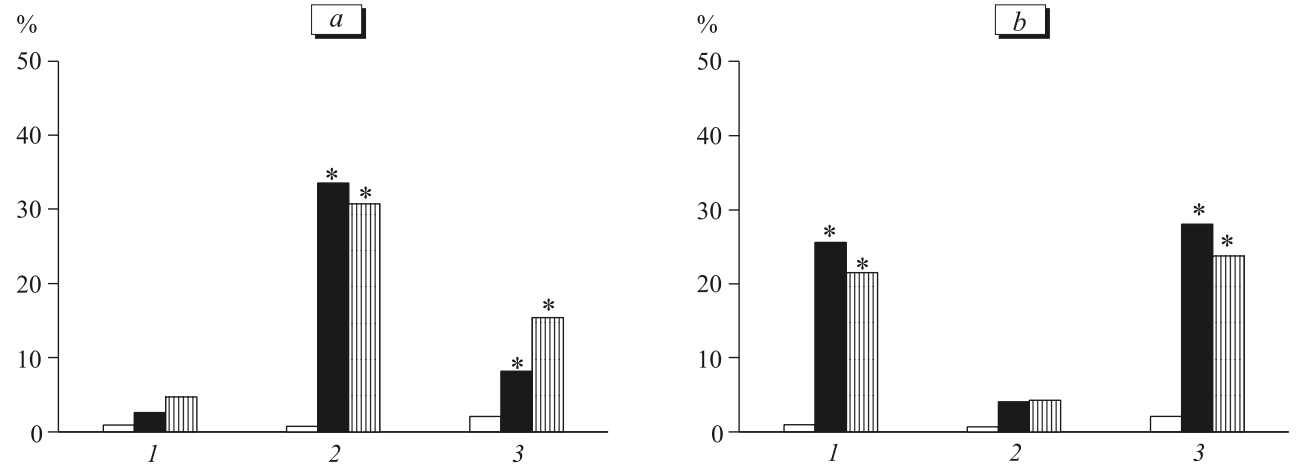

Fig. 2. Percentage of conduction cardiomyocytes with PAS-positive amylase-resistant reaction of the sarcoplasm in stenosis of the aorta (*a*) and pulmonary artery (*b*).

factors, but by changes in the heart work, primarily hyperfunction of the myocardium and disorders of the metabolic processes in it, and also by dilatation of ventricular cavity and stretching of the ventricular walls working under conditions of sharply increased afterload. The degree of acute dilatation of the heart is determined by specific structural characteristics of its walls. That is why the increase of hemodynamic loading leads to a more pronounced dilatation of RV and to moderate dilatation of LV [2,5]. Our data suggest that stretching of the myocardium is a significant specific factor in the genesis of the conduction system disorders under conditions of RV *vs.* LV afterload. Not only the RV, but also the right atrium and caval veins are dilated in acute pulmonary heart [5,9]. Hence, we cannot rule out the probability of injuries to the conduction routes and automation centers located in these formations in hemodynamic situations associated with an increase of the RV afterload.

Comparative analysis of the conduction system pathomorphology under conditions of high afterload of LV or RV indicate that the changes in IVS were similar by their nature and intensity to changes in the wall of the ventricle working under conditions of high pressure loading. Previous morphofunctional analysis of myocardial circulation in experimental stenosis of the aorta and pulmonary artery detected similar increase in the density of functioning capillaries in hemodynamically overloaded ventricle and IVS [8], which was presumably caused by their increased contractile activity. The data in general indicate an important role of IVS in the work of both ventricles and are in line with modern concepts according to which IVS is a functional part of not only LV, but also RV [2].

Our previous studies have shown that pressure overload of one ventricle leads to an increase in the number of damaged contraction cardiomyocytes (in

contrast to conduction ones) in the walls of both cardiac ventricles [7]. This means that structural disorders in contraction cardiomyocytes can be caused by changes in the heart work and by systemic alterative factors, among which the sympathoadrenal system is assumed to play an important one. Activation of the sympathoadrenal system in experimental stenosis of the aorta or pulmonary artery has been demonstrated in our previous studies [6]. It is known that the contraction cardiomyocytes are more sensitive to catecholamine damage than conduction cardiomyocytes. This seems to explain the increase in the number of injuries in contraction cardiomyocytes and lesser changes in the conduction system structure in the wall of the intact cardiac ventricle in comparison with the ventricle exposed to pressure overload.

On the whole, the results indicate that the pathomorphology of the conduction system of the heart under conditions of increased LV or RV afterload is characterized by interstitial edema, hemorrhages, and reversible and irreversible focal lesions. These changes can disorder the conditions of stimulation formation and conduction in the heart, leading to the appearance of arrhythmias. These changes were maximum in cases when increased afterload was complicated by the development of heart failure. These data indicate the presence of a pathomorphological base for arrhythmia development during the acute phase of pressure overload of the heart, particularly if it is complicated by heart failure.

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