Sympathoadrenal System under Conditions of Increased Left and Right Ventricular Afterload

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 138, No. 11, pp. 597-600, November, 2004
Original article submitted July 12, 2004

Adrenergic plexuses in the myocardium and adrenal medulla were studied histochemically under conditions of increased left or right ventricular afterload. Under conditions of high afterload not accompanied by heart failure the density of sympathetic myocardial innervation remained unchanged in the loaded ventricle, but increased in the intact ventricle. Comparison of the state of the sympathoadrenal system under conditions of increased afterload complicated or uncomplicated by heart failure revealed common prognostically unfavorable changes: sharp decrease in the density of adrenergic nerve plexuses in the ventricular myocardium and activation of adrenal chromaffin cells.

Key Words: *sympathoadrenal system; afterload; left ventricle; right ventricle; heart failure*

Heart function under conditions of increased pressure load (afterload) is related to greater energy consumption compared to increased volume load (preload) [2], which determines less favorable course of cardiovascular disorders accompanied by increased afterload [12]. The sympathoadrenal system plays an important role in adaptation to overload and in the development of heart failure [3,4].

Here we studied adrenergic innervation of the myocardium and the state of adrenal medulla under conditions of increased afterload to the left (LV) and right ventricle (RV) and determined changes prognostically unfavorable for heart failure.

MATERIALS AND METHODS

The experiments were performed on 40 guinea pigs weighing 500-700 g. Open-chest surgery was performed under conditions of artificial ventilation. The animals were intraperitoneally narcotized with 25 mg ketamine and 60-80 mg/kg sodium thiopental.

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Functional activity of the cardiovascular system was studied by recording electrocardiogram (ECG), pressure in LV and RV, and its first derivative (*dP/dt*). The data were recorded and analyzed on a Mingograf-82 complex. The increase in afterload was produced by 30-min clamping the aorta or pulmonary artery, inducing 100% increase in ventricular systolic pressure from the baseline level.

The animals were divided into 5 groups. Group 1 included sham-operated guinea pigs without stenosis (n=10). The animals with stenosis of the aorta (n=12) and pulmonary artery not accompanied by heart failure (n=10) entered groups 2 and 3, respectively. Stenosis of the aorta (n=3) and pulmonary artery (n=5) was complicated by heart failure in guinea pigs of groups 4 and 5, respectively. The animals were euthanized by intraperitoneal injection of sodium thiopental in a lethal dose 45 min after catheterization.

For histochemical study samples from the middle third of LV and RV and left adrenal medulla were used. The samples were frozen on dry ice and cryostat sections (25 μ) were prepared at -15-20°C. For histochemical detection of catecholamines (CA) the sections were incubated in 2% glyoxylic acid (pH 6.9-

0007-4888/04/1385-0529

7.0) [8]. The relative area of adrenergic nerve plexuses in the myocardium was estimated planimetrically. CA luminescence of the adrenal medulla was studied under a LYuMAM-I3 microscope with a FMEL-1U4,2 attachment. The results were analyzed by Student's *t* test.

RESULTS

In control animals the relative area of adrenergic nerve plexuses in the myocardium of RV and LV was 1.4 and 1.0%, respectively (Fig. 1, *a*, *1*; *b*, *1*). Our results are consistent with published data on higher density of sympathetic innervation in the right chambers of the heart [9].

Under conditions of increased afterload not accompanied by heart failure (Fig. 1, *a*, *2*, *3*; *b*, *2*, *3*) the relative areas of adrenergic nerve plexuses in the myocardium of RV and LV were 2.6 and 1.0%, respectively, in animals with stenosis of the aorta, and 1.3 and 2.8%, respectively, in pulmonary artery stenosis.

These data show that the density of adrenergic innervation increased in the intact ventricle of the heart: in RV of guinea pigs with stenosis of the aorta and in LV in animals with pulmonary artery stenosis. Changes in CA content in nerve plexuses of the intact ventricle reflected the reaction of the sympathetic neuroeffector system. Cardiac adrenergic neurons were activated under conditions of increased afterload without contractile dysfunction of the myocardium. Our previous studies showed that functional activity of neurons in the stellate ganglion increases during massive pulmonary embolism and high RV afterload not complicated by heart failure [5]. It can be hypothesized that systemic factors and increased afferent traffic from the myocardium activate the neuroeffector system. Reflex activation of neurons in sympathetic ganglia was previously reported [1,10]. Activity of cardiac sympathetic nerves increases under conditions of reflex stimulation from atrial and ventricular mechanoreceptors [10]. The velocity and frequency of afferent pulses from ventricular receptors are directly proportional to the maximum ventricular pressure [11]. Similar changes in the sympathetic nervous system were observed in various hemodynamic situations (*e.g.*, stenosis of the aorta or pulmonary artery and embolic occlusion of the pulmonary vessel) char-

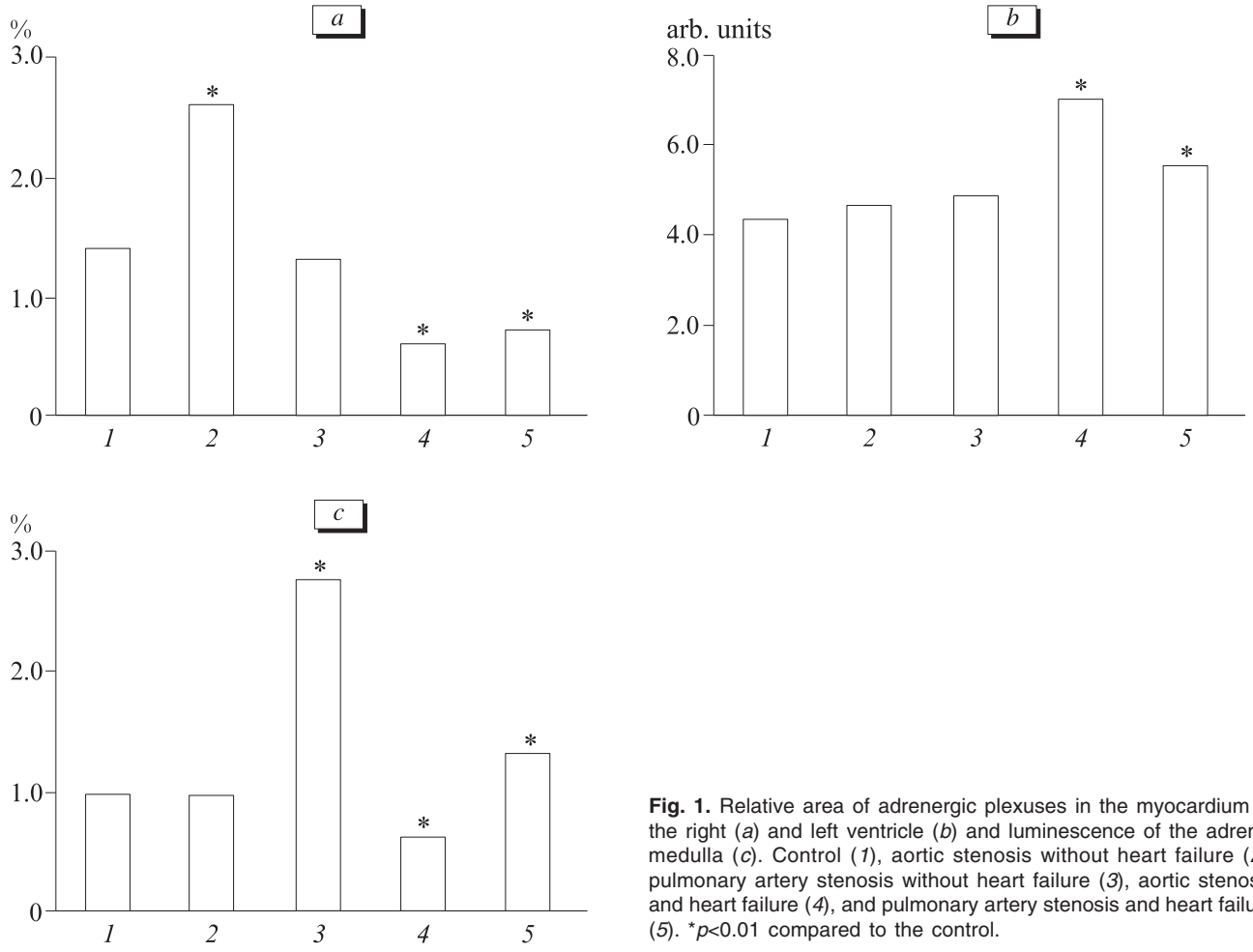

Fig. 1. Relative area of adrenergic plexuses in the myocardium of the right (*a*) and left ventricle (*b*) and luminescence of the adrenal medulla (*c*). Control (*1*), aortic stenosis without heart failure (*2*), pulmonary artery stenosis without heart failure (*3*), aortic stenosis and heart failure (*4*), and pulmonary artery stenosis and heart failure (*5*). **p*<0.01 compared to the control.

acterized by the increase in afterload to the cardiac ventricle [5,6]. These data suggest that enhanced afferent traffic from ventricular mechanoreceptors under conditions of increased afterload contributes to activation of cardiac sympathetic nerves.

Activation of the sympathetic neuroeffector system does not increase CA content in nerve plexuses of the ventricular myocardium under conditions of high afterload (LV, aortic stenosis; RV, pulmonary artery stenosis). This is probably related to the release of CA from nerve endings during functional activation of the loaded ventricle. Experiments on dogs with uncomplicated massive pulmonary embolism produced similar results [5,6].

The results of our work and previous studies [5,6] indicate that increased LV and RV afterload produce similar changes in sympathetic innervation of the heart in different animals. These data show that the density of adrenergic myocardial nerve endings remains unchanged in the loaded ventricle, but increases in the intact ventricle under conditions of high afterload not accompanied by heart failure.

In cases when increased afterload was complicated by heart failure (Fig. 1, *a*, *4*, *5*; *b*, *4*, *5*) the relative area of adrenergic nerve plexuses in RV and LV was 0.6% in animals with stenosis of the aorta and 0.7 and 1.3%, respectively, in animals with pulmonary artery stenosis. Our results are consistent with published data that CA content in adrenergic neurons and myocardial terminals decreases during heart failure and sudden death [9]. Desympathization of the myocardium results from predominance of CA release over their synthesis and neuronal uptake. Abnormalities in biosynthetic processes can be associated with destruction of sympathetic neurons [9]. Our assumption is confirmed by published data that massive pulmonary embolism complicated by heart failure produces severe destructive changes in most adrenergic neurons. These changes are accompanied by a sharp decrease in CA content in the stellate ganglion and nerve plexuses of the ventricular myocardium [5]. Damage to neurons is probably related to hyperfunction and systemic alteration (*e.g.*, arterial hypoxia and circulatory disturbances in the stellate ganglion). A considerable number of neurons with pathomorphological signs of ischemic damage were revealed in sympathetic ganglia under conditions of increased RV afterload accompanying massive pulmonary embolism [5].

The intensity of CA luminescence in the adrenal medulla remained unchanged in animals with uncomplicated course of increased afterload to LV and RV (Fig. 1, *c*, *2*, *3*), but became high in animals with heart failure (Fig. 1, *c*, *4*, *5*). Our results are consistent with published data that CA content in adrenal chromaffin cells increases during massive pulmonary embolism complicated by heart failure [6]. A comparative study of the adrenal medulla and myocardial sympathetic innervation under conditions of increased afterload confirms the absence of a relationship between the hormonal and transmitter response in the sympathoadrenal system [7].

Evaluation of the state of the sympathoadrenal system in animals with increased afterload complicated or uncomplicated by heart failure revealed prognostically unfavorable changes: sharp decrease in the density of adrenergic nerve plexuses in ventricles and activation of adrenal chromaffin cells. These changes in the desympathesized myocardium increase the relative role of hormones in the structure of sympathoadrenal influences on the heart. The cardiovascular response to increased load differs in animals of the same species, sex, and age, which contributes to the long-term maintenance of hemodynamic characteristics or development of heart failure. The course of acute pressure overload depends on individual physiological mechanisms for sympathoadrenal influences, including reactivity of the sympathetic nervous system and adrenal medulla, metabolism and state of structures responsible for the synthesis, release, and inactivation of CA, and rate of damage to adrenergic neurons and chromaffin cells. These processes probably determine the sympathoadrenal response, which plays a role in the adaptation to pressure overload or development of heart failure.

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