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MORPHOLOGICAL AND FUNCTIONAL CHANGES IN THE DESYMPATHIZED HEART OF RATS WITH ACUTE MYOCARDIAL ISCHEMIA

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Activation of the sympathicoadrenal system during occlusion of the coronary artery leads to a sharp rise in the blood catecholamine level [6] and to complex changes in metabolism in the heart muscle, which cause disturbances of the contractile function and rhythm of the heart [1, 6, 8]. It is not yet clear to what extent the catecholamines released by the sympathetic nerve endings of the heart contribute to determining the character of functional and structural disturbances in the myocardium in acute ischemia. The investigation described below was carried out to study this problem.

EXPERIMENTAL METHOD

Experiments were carried out on 79 chemically desympathized and 63 control male Wistar rats weighing 140-175 g. Guanethidine (Isobarin, from Pliva, Yugoslavia) was used to produce desympathization [5]. The method of imposing an increasing frequency of contraction on the heart [4] and creation of maximal loading by occlusion of the aorta for 10 sec were used as function tests. Parameters of the contractile function of the heart were recorded after 2, 5, and 10 sec. Systolic pressure in the left ventricle and its maximal rate of rise and fall (dP/dt), and the end-diastolic pressure (EDP) were measured. The intensity of contractile function (ICF) [3] and the contractility index (CI) [9] were calculated. Acute experiments were carried out under urethane anesthesia (160 mg/100 g) under open chest conditions with artificial ventilation. The pressure in the left ventricle was recorded by means of a catheter inserted through the apex of the heart and connected to the transducer of a Mingograph-34 electromanometer (Elema, Sweden). The ECG and the first derivative of pressure were recorded simultaneously by the DÉ-1 instrument. The results were analyzed by Student's t test. The hearts of the experimental and control rats were stained with hematoxylin and eosin, Scharlach R, Sudan black, and Nile blue sulfate to detect neutral fat and acid lipids, by Selye's method for fuchsinophilic granules, and by Shabadash's method for glycogen. Acute myocardial ischemia was induced by high ligation of the anterior descending branch of the left coronary artery.

EXPERIMENTAL RESULTS

Disturbances of the cardiac rhythm appeared during the first minutes after occlusion of the coronary artery. They were more severe in the control animals and took the form of the appearance of polytopic ventricular extrasystoles (single and grouped); ventricular fibrillation developed frequently. The arrhythmias in the ex-

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TABLE 1. Parameters of Contractility of Left Ventricular Myocardium of Control (I) and Desympathized (II) Rats 24 h after Ligation of Coronary Artery (M ± m)

Parameter	Group of animals	Experimental conditions					
		before ligation	first day after ligation	difference, % of initial value	before stimulation	frequency of stimulation per minute	
						450	480
SP, mm Hg	I	111±4,2	80±4,3*	—27,93	80±4,3*	54±5,49	50±4,61
	II	83±3,5	74±2,11*	—10,84	74±2,11*	64±1,02	58±1,02
EDP, mm Hg	I	8,2±0,4	6,6±0,62*	—19,51	6,6±0,62*	8,0±0,64	9,3±0,64
	II	6,2±0,7	5,6±0,77	—	5,6±0,77	7,3±0,33	8,0±1,25
ICF, mm Hg·min/mg	I	112,6±6,9	72,34±10,46*	—35,76	72,34±10,46*	53,7±5,74	51,1±4,94
	II	88,73±4,8	71,98±6,0*	—18,88	71,98±6,0	73,9±2,13	70,4±1,60
dP/dt_{max}, mm Hg·sec^{-1}	I	2667±159	1528±91,0*	—42,71	1528±91,0*	908±145	880±144
	II	2123±91	1070±144	—49,6	1070±144	917±133	900±97
dP/dt_{min}, mm Hg·sec^{-1}	I	1927±127	838±49,6*	—56,51	838±49,6*	533±56	540±57
	II	1433±89	750±19,2*	—47,66	750±19,2*	650±48	633±36
CI, sec^{-1}	I	44,75±1,48	31,36±1,32*	—29,92	31,36±1,32*	23,7±1,72	24,8±2,72
	II	38±1,02	19,69±2,81*	—48,18	19,69±2,81*	18,6±3,73	19,0±3,20
Heart rate, beats/min	I	331±11,29	352±17,4	—	352±17,4	—	—
	II	321±19,59	368±17,3	—	368±17,3	—	—

*$P < 0.05$.

perimental animals were of the single ventricular extrasystole type. Analysis of the ECG showed no clear differences in the time course of the parameters in the experimental and control animals. Cardiac contractility 24 h after ligation of the coronary artery was depressed in both control and desympathized rats (Table 1). A difference was found in the maximal rate of rise of the systolic pressure and the value of CI, which were lower in desympathized animals than in the controls, by 29.97% ($P < 0.05$) and 37.21% ($P < 0.01$) respectively. It will be recalled that the contractile function of the desympathized heart was initially lower than that of the intact heart, and for that reason the equal values of the parameters of cardiac contractility reflect different degrees of depression of this function in the control and desympathized rats after occlusion of the coronary artery: the degree of lowering of the parameters of cardiac function of the control rats was greater (Table 1). The maximal force and rate of cardiac contraction of the control rats with increased aortic resistance was achieved during the first occlusion and continued during the next two occlusions. The range of increase of systolic pressure (SP) during the first occlusion was greater than before the operation but it did not exceed the value of this parameter in the control animals. During loading with an increasing frequency of contractions in the infarcted heart of the control rats up to 450 beats/min, SP fell by 32% and ICF by 25%. Under similar conditions SP and ICF in the heart of the desympathized animal fell by 13 and 8% respectively (Table 1).

Morphological examination of the muscle of the left ventricle 2, 6, and 24 h after occlusion of the artery revealed definite differences in the time course of the structural changes in the myocardium of the experimental and control hearts. The hemodynamic disturbances in the control rats after 2 h were widespread in character and consisted of dilatation of the blood vessels and their engorgement with blood, and the formation of areas of stasis and perivascular hemorrhages; the structure of the muscle fiber was unchanged. In desympathized rats hemodynamic disturbances were confined mainly to the zone of ischemia, muscle fibers had lost their cross-striation and were unevenly stained, with signs of fuchsinophilia; glycogen was absent not only in the zone of ischemia, just as in the control animals, but also in many muscle fibers outside its limits. No significant trend could be detected in the heart of the control animals after 6 h. In the experimental rats muscle fibers in the zone of ischemia were swollen and vacuolated, in some parts they were fragmented with fuchsinophilia and fatty degeneration, and a marked leukocyte response was observed. In boundary areas the muscle fibers were hyperchromic, without their cross striation, and showed fatty degeneration. After 24 h signs of infarct formation were present in the myocardium of the desympathized animal; neutral fat accumulated in the muscle fibres, in the vessel walls, and beneath the epicardium. A characteristic feature of the control rats at this time was the appearance of granules of acid lipids in the muscle fibers and in the vessel walls, which were absent in the myocardium of intact and desympathized animals (Fig. 1 and 2).

These findings are evidence that if the influence of the sympathetic nervous system of the heart is depressed by desympathization of the animal, the ischemic focus undergoes more rapid localization. It was also shown that in desympathized rats with the same type of myocardial lesion arrhythmias appeared in a smaller percentage of cases and they were less severe, evidence of exhaustion of the reserves of the mediator, noradrenalin, in the heart of the desympathized animal. Data on the diffuse infiltration of the heart muscle and walls of the vessels of the heart with neutral fat in the desympathized rats and the accumulation of acid lipids

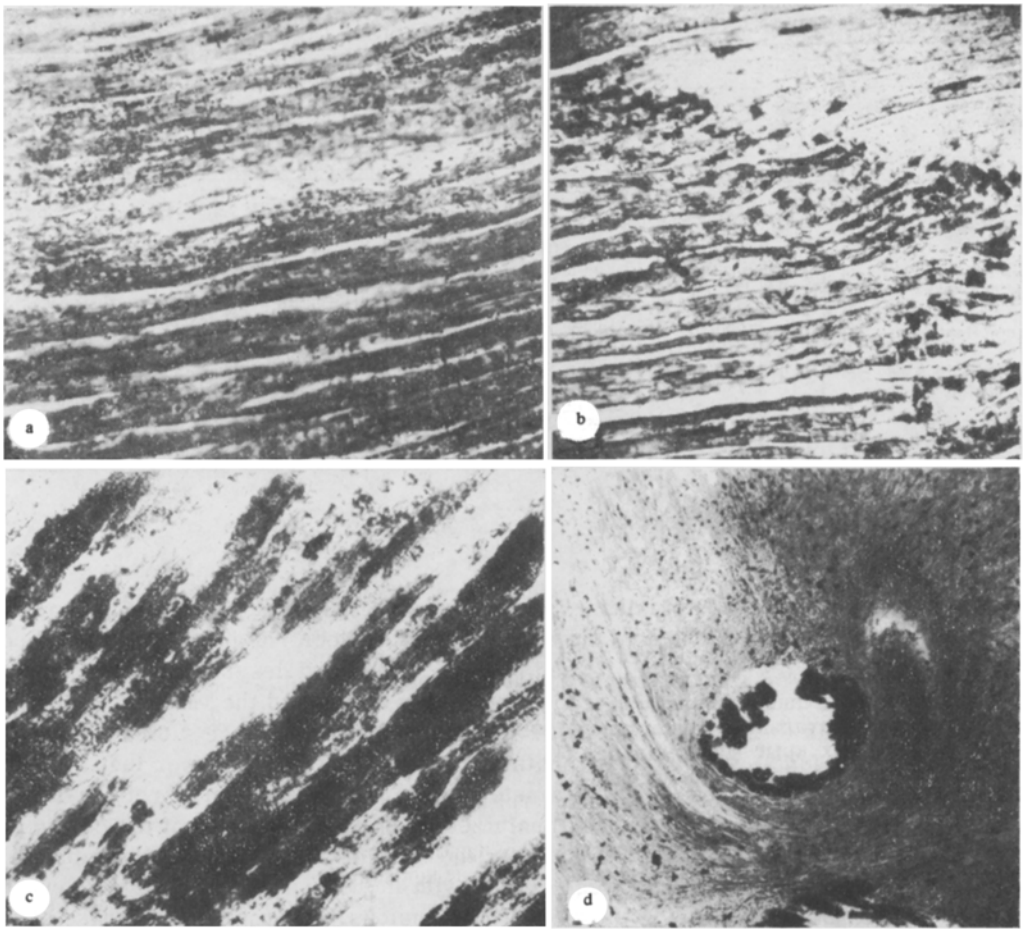

Fig. 1. Myocardium of left ventricle of control rat (period of ischemia 24 h): a) loosening of muscle fibers with loss of cross striation, small foci of infiltration by leukocytes in zone of ischemia (hematoxylin-eosin, 100×); b) fuchsinophilia of single fibers in zone of ischemia (stained by Selye's method, 70×); c) fatty degeneration of fragmented fibers in zone of ischemia (Sudan black, 300×); d) acid lipid granules in vessel wall and in muscle outside zone of ischemia (Nile blue, 70×).

in the heart of the control animals indicate a difference in the character of change in lipid metabolism in the desympathized and normally innervated heart in acute myocardial ischemia. Free fatty acids are known to play an important role in the energy metabolism of the myocardium, for which they are the principle source of energy. Meanwhile high concentrations of these compounds inhibit the contractile function of muscle fibers, especially in myocardial infarction [1, 7]. The accumulation of neutral fat in the heart of the desympathized animal points to a disturbance of lipolysis. The discovery of acid lipids in the myocardium of the control animals is evidence of intensification of lipolysis and depressed utilization of fatty acids [1, 7]. In both cases the developing fatty infiltration of the muscle fibers is an indication of a disturbance of energy formation in the myocardium and is one of the factors responsible for depression of the contractile function of the heart.

It can be concluded that the difference observed in the functional and structural changes in the myocardium of normal and desympathized animals can be attributed to the state of the sympathetic nervous system of the heart and, in particular, to the abolition of weakening of the pathogenic effect of increased concentrations of noradrenalin mediator on the myocardium in the desympathized rats, such as is observed under these conditions in control animals on account of the marked excitation of the sympathicoadrenal system. This conclusion is confirmed also by the fact that adrenal function is preserved in the desympathized animals [2].

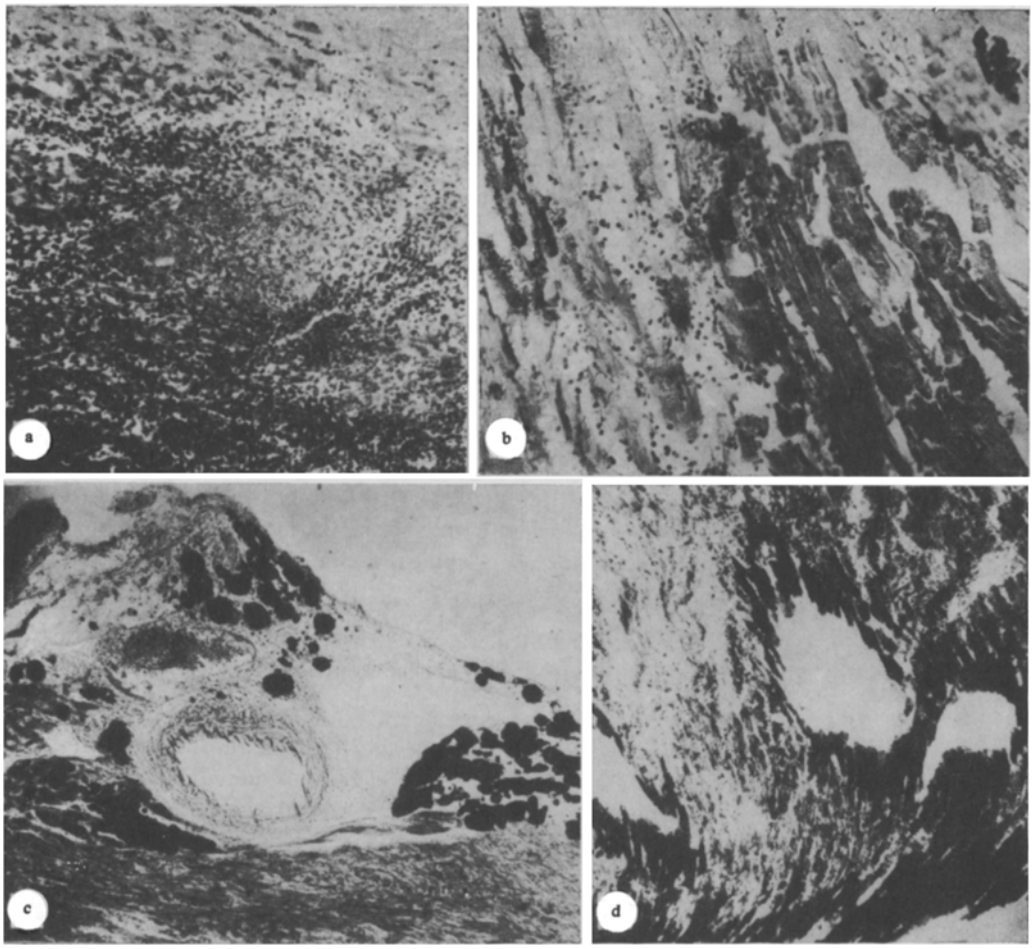

Fig. 2. Myocardium of left ventricle of desympathized rat (period of ischemia 24 h). a) Leukocytic infiltration of necrotic muscle fibers (hematoxylin–eosin, 100×); b) region of necrotic fibers stained by PAS reaction (diastase + PAS reaction, 100×); c) increase in amount of neutral fat (Sudan black, 70×); d) fatty infiltration of muscle and vessel outside zone of ischemia (Sudan black, 70×).

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