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RESPONSE OF THE HEART TO FUNCTIONAL LOADS IN CHEMICALLY DESYMPATHIZED ANIMALS

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KEY WORDS: heart; catecholamines; desympathization.

Information on the regulatory and adaptive-trophic functions of the sympathetic nervous system has been obtained by recent investigations involving the use of immunochemical and chemical desympathization methods [3, 4, 11]. The question of the state of myocardial contractile function and the powers of adaptation of the heart of chemically desympathized animals under conditions of increased loads has so far received little study, despite its importance if the role of the sympathicoadrenal system in cardiopathology is taken into account.

In the investigation described below the reaction of the heart of chemically desympathized animals to functional loads was studied.

EXPERIMENTAL METHOD

Experiments were carried out on 22 chemically desympathized and 20 control male Wistar rats weighing 135-175 g. The substance Isobarin, from Pliva (Yugoslavia) [2, 12] was used to produce desympathization. The animals were aged 2 months. Functional loads consisted of imposing on the heart increasing frequencies of contraction [8], and a maximal resistance load was created by compressing the aorta for 10 sec. Parameters of the contractile function of the heart were recorded after 2, 5, and 10 sec. The systolic pressure (SP) was measured in the left ventricle, the maximal rate of its development and fall were determined, and the end-diastolic pressure (EDP) recorded. The intensity of contractile function (ICF) [6], the contractility index [16], and the relative duration of the diastolic pause (as a percentage of the total duration of the cycle) were calculated. Acute experiments were carried out under urethane anesthesia (160 mg/100 g) under open chest and artificial ventilation conditions. The pressure in the left ventricle was recorded by means of a catheter inserted through the apex of the heart and connected to the probe of a Mingograph-34 electromanometer (Elema, Sweden). The ECG was recorded simultaneously with the first derivative of pressure by means of a DE-1 differentiator. The results were subjected to statistical analysis by Student's method.

EXPERIMENTAL RESULTS

The initial indices of contractile function of the heart — the force of contraction of the muscle of the left ventricle, the rate of development and fall of pressure, and ICF of the myocardium — were lower in chemically desympathized rats than in control animals with the same cardiac frequency (Table 1). Imposing an increasing frequency of contractions on the heart gave rise to pulsus alternans in a high proportion (41.7%) of desympathized animals at a frequency of stimulation (320-330 beats/min) at which this phenomenon was not observed in the control animals. The control animals developed pulsus alternans in some cases at frequencies exceeding 480 beats/min. An increase in the cardiac frequency to 420-450 beats/min caused an increase in ICF by 13-16% in the control rats. In desympathized animals, under these

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same conditions, no appreciable rise in ICF was observed, but SP was reduced by 11-15% and was lower by 38-41% than in the control ($P < 0.01$). Indices of the rate of contraction and relaxation of the heart muscle also were lower than in the control animals. With a further increase in the frequency of contractions to 480-510/min the differences between reactions of the heart in the control and desympathized animals became even more marked (Table 1). It is well known that a sharp increase in cardiac frequency is a factor which increases the load on the calcium pump, as a result of the activity of which the rate and force of contraction and the rate and degree of relaxation of the heart muscle are changed. The more marked slowing of relaxation and increase in diastolic pressure may be indirect evidence of a decrease in the power of the calcium pump and of the sodium–calcium exchange mechanism [7, 8, 10] in the heart muscle of the desympathized animal and may be one cause of depression of its contractile function when a high frequency of contractions is imposed.

During resistance loading by compression of the ascending part of the arch of the aorta, absolute values of SP, ICF, and the rate of development and of fall of the pressure in the left ventricle in response to the first compression were higher in the control rats than in the desympathized animals. However, the degree of change in SP and ICF under these circumstances was greater in the desympathized animals. For instance, after 5 sec of the first compression SP in the desympathized animals was 92% higher than initially and ICF was 61.2% higher. In the control rats these parameters were increased by 59.6 and 45.1%, respectively. The increase in SP in the control animals was accompanied by an increase in the rate of myocardial contraction by 37.9%, compared with by only 6.7% in the desympathized rats. A marked decrease in the rate of relaxation of the heart muscle in the desympathized animals was noted. At the 10th second of the 1th compression it was 72.6% lower than initially in the desympathized rats, but only 32.9% lower in the control. The increase in EDP was particularly considerable during the 2nd and 3rd compressions. At the 5th second of the 2nd and 3rd compressions it was increased in the desympathized rats by 238 and 259% compared with the initial level, and was 15 and 27% higher, respectively, than in the control animals. The range of increase in SP and ICF during repeated compressions was much wider in the desympathized rats. At the 5th second of the 3rd compression SP and ICF were increased by 105 and 100%, respectively, compared with 44.7 and 11.5% in the control.

During resistance loading, when the heart is working mainly under isometric conditions, the desympathized heart could thus develop a high force of contraction, which during repeated compressions could reach or even exceed the level developed by the normal heart. Meanwhile, the rate of development of pressure and the rate of its fall were slowed in the desympathized heart.

Comparison of the results obtained with the two different functional loads shows that indices of contractile function — the maximal force of contraction of the heart and ICF — were considerably higher during resistance loading than during high frequency loading. These differences were particularly marked in desympathized animals, in which ICF during compression of the aorta was 233 mm Hg•min/mg, compared with 98 mm Hg•min/mg during frequency loading, i.e., it was more than twice as high.

The mechanisms responsible for the increased contractile function of the heart during resistance loading and during high frequency loading are known to be different. In resistance loading the increase in function takes place mainly through mobilization of the Frank–Starling mechanism, which is combined with the effect evoked by abrupt excitation of the sympathicoadrenal system [9]. The lower values of ICF in desympathized animals during the first compression were evidently due to disturbance of the liberation of noradrenalin in connection with degeneration of sympathetic nerve endings in the myocardium [1, 2]. The increase in ICF of the desympathized heart during repeated compressions of the aorta may be the result of the action of catecholamines entering the heart with the blood stream, and of the increased reactivity of the heart muscle to adrenalin [5, 15].

The mechanism maintaining cardiac function during high frequency loading is mainly associated with a change in the ionic balance in the extracellular and intracellular medium and with the effect of catecholamines which, on the one hand, increase the inflow of Ca^{++} into the cell and the rate of its uptake by the sarcoplasmic reticulum [14], and on the other hand, through the adenylate cyclase system of the cell, activate a complex series of reactions which maintain contraction of the heart muscle [11]. The decrease in ICF and in the force and rate of contraction and relaxation of the muscle of the desympathized heart when a high frequency of contractions is imposed upon it is evidence of disturbance of the normal functioning of this mechanism.

TABLE 1. Effect of Imposition of Increased Frequency of Contractions on Contractile Function of Left Ventricular Myocardium in Control and Chemically Desympathized Animals (M ± m)

Index of contractile function of heart	Experimental conditions	Before stimulation	Frequency of stimulation, per minute			
			420	450	480	510
Systolic pressure, mm Hg	Control	134±2,2	132±8,7	133±6,3	119±7,6	114±11,7
	Desympathization	92±4,6‡	82±3,6‡	78±4,3‡	69±5,3‡	63±6,0‡
	Difference, %	−31,3	−37,9	−41,4	−42,0	−44,7
End diastolic pressure, mm Hg	Control	10±0,7	11,5±0,8	11,6±0,6	11,6±1,1	11,7±0,5
	Desympathization	7,8±0,6*	8,6±0,6‡	9,0±0,3**	10,0±0,5*	10,2±0,7*
	Difference, %	−22,0	−25,0	−22,4	−13,8	−13,4
Intensity of contractile function, mm Hg · min/mg	Control	126±10,3	142±9,8	146±8,4	133±5,1	132±11,7
	Desympathization	95±9,8*	98±6,4†	98±7,3†	94±8,4*	91±7,5*
	Difference, %	−24,6	−31,0	−33,0	−29,3	−31,1
Maximal rate of development of pressure, mm Hg/sec	Control	7747±505	4917±403	4816±613	4200±602	4280±860
	Desympathization	6380±236*	3912±322	3845±456	3322±383	3171±364
	Difference, %	−17,6	−20,4	−20,1	−21,0	−26,0
Contractility index, sec^{-1}	Control	99,8±3,5	76,6±6,6	81,5±8,2	81,7±7,3	83,9±7,6
	Desympathization	84,6±4,4†	77,2±3,2	78,9±4,3	83,0±3,9	89,3±5,7
	Difference, %	−15,2	−0,78	−3,2	+1,59	+6,4
Maximal rate of fall of pressure, mm Hg/sec	Control	3757±224	3114±224	3071±322	3133±403	3120±576
	Desympathization	2877±191‡	2450±277	2450±238	2472±241	2083±322
	Difference, %	−23,4	−21,3	−20,0	−21,1	−33,2
Relative duration of diagnostic pause, %	Control	36,5±1,6	22,1±2,2	19,8±2,2	16,4±1,7	16,8±2,2
	Desympathization	36,0±1,4	27,9±1,4	24,3±1,5	20,8±1,8	20,0±1,2
	Difference, %	−1,4	+26,2	+22,7	+26,8	+19

*P < 0.05.
†P < 0.02.
‡P < 0.01.
** P < 0.001.

Note. All values of P given by comparison with indices for control animals. Frequency of contractions in control and desympathized animals before stimulation 363 ± 15.9 and 369 ± 6.7 beats/min, respectively.

The results of this investigation show that blocking influences of the sympathetic nervous system of an animal by chemical desympathization leads to a reduction in the adaptive capacity of the heart under conditions calling for mobilization of the interval—force mechanism, which is activated by catecholamines, but does not reduce adaptive capacity when the heart is functioning under isometric conditions.

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EFFECT OF HYDROCORTISONE ON THE DEVELOPMENT OF EXPERIMENTAL ATHEROSCLEROSIS IN RABBITS

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In the study of the pathogenesis of atherosclerosis attention is increasingly being paid to the role of immunologic factors in the onset and development of the disease [1, 4, 8]. An autoimmune theory of the pathogenesis of atherosclerosis has recently been formulated [5].

An important place in these investigations is occupied by analysis of immunologic mechanisms in the development of experimental atherosclerosis in rabbits, for the role of specific sensitization in the formation of atherosclerotic lesions in the arteries can be studied in detail [1, 3, 9].

Additional information in this direction can be provided by experiments with hydrocortisone which, with its wide spectrum of action, also has a marked immunodepressive effect [7]. This property of the glucocorticoids in experimental atherosclerosis was the object of the present investigation.

EXPERIMENTAL METHOD

Experiments were carried out on 51 rabbits. The results of a study of the immunocompetent system in 22 healthy rabbits also were used. Experimental atherosclerosis was induced by Anichkov's method (dose of cholesterol 0.2 g/kg body weight). To depress the immune response in the rabbits' lymphoid organs hydrocortisone was injected intramuscularly in a dose of 3.75 mg five times a week for 4 weeks (total dose 75 mg per course) and for 12 weeks (225 mg per course).

During the experiment the serum levels of atherogenic lipoproteins (combined fraction of β- and pre-β-lipoproteins) and cholesterol were determined. The atherosclerotic index in the aorta was calculated by Avtandilov's method after staining the blood vessels with Sudan III *in toto*.

The quantitative morphological study of the immunocompetent system was conducted on preparations from the mesenteric and para-aortic lymph nodes after staining by Brachet's method in the manner described by Pigarevskii et al. [6]. Cells that are the most characteristic indicators of the immune response, namely small lymphocytes, lymphoblasts, plasmablasts, and immature and mature plasma cells, were subjected to quantitative analysis in the T- and B-zones of the lymph nodes. The level of circulating antibodies against collagen and elastin was determined by Chudomel's reaction using guinea pig complement and, as antigens, collagen and elastin isolated by the method of Ivanovskii et al. [2].

EXPERIMENTAL RESULTS

Analysis of the blood serum showed that the level of the combined fraction of β- and pre-β-lipoproteins and of cholesterol in the blood of the rabbits receiving hydrocortisone in addition to an atherogenic diet was indistinguishable from the corresponding values in animals receiving the atherogenic diet alone, and by the end of the experiment it was 15-20 times higher than initially.

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