EFFECT OF IMMUNE COMPLEXES, ACTING ON THE HEART, ON CARDIO- AND HEMODYNAMICS IN DOGS

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The study of the role of immune factors in the pathogenesis of heart lesions and accompanying circulatory disturbances is attracting increasing attention [1, 4, 9]. Among the immune factors with a harmful action on the heart, great importance is attached to immune complexes (IC), which can evoke acute immune inflammation, damage blood vessel walls [7, 10], and facilitate the development of atherosclerosis [2, 6]. Circulating IC are found quite frequently in patients with myocardial infarction [5, 11]. However, the character of their effect on cardiac function and the hemodynamics has been inadequately studied.

The aim of the present investigation was to study the effect of IC, obtained in vitro and injected into the coronary blood flow, on cardiac function and the hemodynamics in dogs.

EXPERIMENTAL METHOD

Experiments were carried out on 12 mongrel dogs weighing 17-25 kg, anesthetized with chloralose and urethane (0.07 and 0.3 g/kg respectively). IC were obtained in vitro by mixing 0.3-0.5 ml of horse serum (antigen) and 1.5-1.8 ml of immune rabbit serum containing 25-30 mg of γ-globulin in 1 ml, and with a titer of $1{:}2^{8}-1.2^{10}$ in Ouchterlony's precipitation test. These properties of antigen and antibodies gave the maximum of precipitate after reacting for 45-60 min. The mixture of horse serum and immune rabbit serum was injected into dogs before forming a precipitate (15 min after the beginning of the reaction), in a dose of 0.1 ml mixture/kg body weight. To obtain maximal action of IC on the heart and to limit their effect on other organs, the IC were injected into one branch of the left coronary artery (LCA) by means of a special catheter with obturator, while perfusing LCA with a constant blood volume. Thoracotomy was not used for the experiments and the animal breathed naturally. The systematic arterial pressure (SAP), central venous pressure (CVP), and pressure in the left and right ventricles (LVP and RVP respectively) were recorded during the experiments. The rate of change of pressure in the ventricles (dp/dt) also was recorded by electronic differentiation of the pressure curve. The cardiac output (CO) and volumes of the heart (end-diastolic and end-systolic – EDV and ESV respectively) were determined by the thermodilution method. To determine EDV and ESV, a thermistor with low time constant was fixed rigidly in the blood flow in the ascending part of the aorta to the catheter used for catheterization of the coronary vessels. Cardiac, systolic, and work indices (CI, SI, and WI), the ejection fraction (EF) of the left ventricle, the index of contractility (IC) and its index of relaxation (IR) were calculated from the data [3]. Change in tone of the vessels of the heart and hind limb were judged from changes in vascular resistance during autoperfusion of the vascular regions mentioned above with a constant blood volume (resistography). Responses of the capacitive vessels of the hind limb were judged from changes in the venous outflow of blood measured by the use of an extracorporeal reservoir [8].

The ECG was recorded in standard leads, amplified limb leads, and Wilson's chest leads. The total peripheral resistance (TPR) and total lung resistance (TLR) also were calculated.

EXPERIMENTAL RESULTS

Injection of IC into the coronary circulation of a dog was followed within a few minutes by the development of a marked shock reaction with SAP falling on average to 78 mm Hg (by 39%, Table 1). After 15 min a marked tendency was observed for SAP to recover, and after 45 min it has reached on average 92% of its initial level. The absence of any significant dilatation of the resistive limb vessels and the increase of TPR and TLR (on average by 27-57%) were evidence that the fall of SAP was due to disturbance of the pumping function of the heart.

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TABLE 1. Shock Reaction with Fall of SAP after Injection of IC

Parameter	Initial value	Time after injection of IC, min			
		5	15	30	60
SAP, mm Hg	127±7,9	77,9±9,2**	98,3±9,4*	100,7±8,3*	99,4±7,2*
CVP, mm water	32,3±3,8	18,5±4,2*	24,6±3,9**	25,3±3,6*	27,2±3,3
Perfusion pressure in coronary artery, mm Hg	98±11,4	101±8	97,2±10,8	98,2±9,1	92,5±9,2
CO, ml/ min	2019±185	1138±168**	1472±178*	1585±145**	1567±143**
TPR, dynes·sec·cm^{-5}	5113±504	6548±1138	5960±697	5574±611	5632±645
WI of left ventricle, kgm/m^2· min	4,496±427	1,688±395**	2,579±486**	3,004±398*	2,366±252**
SI, m/ l · m	12,4±1,1	8,6±0,9	9,9±1,2	11,7±0,99	9,6±0,98
TLR, dynes·sec·cm^{-5}	511±61	805±123**	719±127*	602±88**	600±86**

Legend. Here and in Table 2: *P < 0.05, **P < 0.01 compared with initial value.

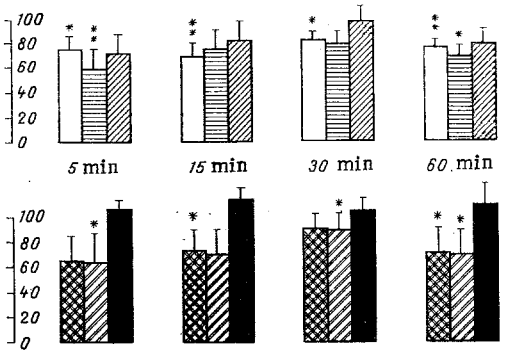

Fig. 1. Changes (in % of initial value) of pumping function of the heart after intracoronary injection of IC. Unshaded columns – LVP, horizontally shaded – CI, obliquely shaded – SI, cross-hatched – ECV, double cross-hatched – ESV, shaded black – ejection fraction of left ventricle. Here and in Fig. 2: * P < 0.05, **P < 0.01 compared with initial value.

In fact, during the first minutes of the response the cardiac ejection (CE) fell by 36-43% and remained below its initial level until the end of the period of observation. Changes in CE correlated closely with changes in SAP (r = 0.92). Besides CE, there was also a significant decrease in EDV and ESV of the left ventricle, down to 63% of the initial value on average 5 min after injection of IC (Fig. 1). However, the ejection fraction, unlike EDV and ESV, not only was not reduced but actually showed a tendency to increase, indicating no significant disturbance of myocardial contractility.

Injection of IC was followed by a decrease in the rate of change of intraventricular pressure, evidently due to a decrease in the preload and postload on the heart, which takes place in this hemodynamic situation. Meanwhile the index of contractility of the left ventricle changed, but not significantly, and for the right ventricular myocardium it showed a definite tendency to increase. This tendency was even more marked in the case of parameters characterizing myocardial relaxation. Contractility was thus not significantly disturbed in the acute period of the response to the action of IC on the myocardium (Table 2).

The ECG changes indicated absence of any significant disturbance of intraventricular conduction and the appearance of microfocal hypoxemic changes in the region of injection of IC. No significant signs of myocardial injury were found after injection of IC.

There is evidence that inhibition of the pumping function of the heart under the influence of IC is based, not on reduction of myocardial contractility, but on a substantial decrease in the venous return of blood to the heart. In particular, besides EDV and ESV, during the first minutes of the response there was a significant fall in CVP, and the end-diastolic pressure (EDP) fell in the left and right ventricles. Restriction of the venous return of blood was evidently due to marked storage of blood at the periphery of the vascular system

TABLE 2. Changes in Cardiodynamics and Myocardial Contractility after Intercoronary Injection of IC (M±m)

Parameter	Initial value	Time after injection of IC, min			
		5	15	30	60
Left ventricle					
LVP, mm Hg	147±11,4	108,2±9,9*	98,5±11,4*	117,2±7*	110,5±5**
dp/dt_{max}, mm Hg	4019±317	2743±374*	3016±319*	3246±286*	2998±162**
dp/dt_{min}, mm Hg	3541±291	2224±481*	2742±470	2756±456	2817±378
EDP, mm Hg	2,3±1	0,4±1*	1,1±0,5	1,5±0,5	0,6±0,6*
IC $(dp/dt_{max}/P)$, sec^{-1}	53,6±4,9	47,5±5,2	51,7±5,1	50,9±5,1	49,2±5
IR	11,8±2	11,8±1,1	12,1±1,5	12,7±2	13±1,6
Right ventricle					
RVP, mm Hg	24,7±1,5	19,2±2,2**	19,4±2,2	20,8±2	21,1±1,6
dp/dt_{max}, mm Hg	638,4±125	421,4±78	456±83	440,7±7,5	442,6±67
dp/dt_{min}, mm Hg	356±46	269±59	318±55	313±52	301±46
EDP, mm Hg	1,1±0,4	0±0,46	−0,02±0,7	−0,03±0,6*	0,08±0,4**
IC $(dp/dt_{max}/P)$, sec^{-1}	46,8±6,1	41,2±4	49,6±3,8	50,3±5,2	50,8±4
IR	7,7±0,7	8,4±0,9	8,7±0,7	8,7±0,7	8,5±0,8

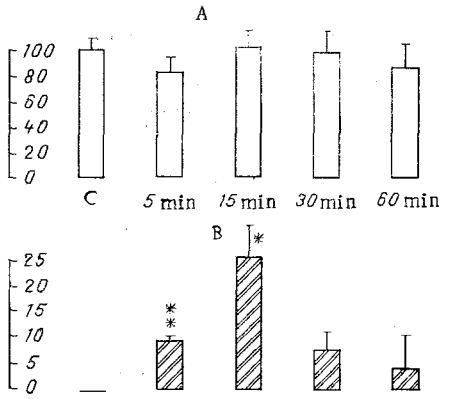

Fig. 2. Changes in resistance and capacity of hind limb vessels after intracoronary injection of IC. A) Perfusion in femoral artery (in % of initial value); B) quantity of blood stored in venous part of vascular system (in ml/kg). C) control.

(Fig. 2). The volume of blood stored in the skin and muscles of the animals reached 25 ± 5.6 ml/kg body weight, and this was clearly mainly due to dilatation of the capacitive compartment of the vascular system.

Intracoronary injection of IC was thus accompanied by the development of a hypotensive response with marked inhibition of the pumping function of the heart and a decrease in the work of the heart. Inhibition of the pumping function of the heart and the decrease in CE are evidently based on a substantial decrease in the venous return of blood to the heart on account of its storage at the periphery of the vascular system. The action of IC on the heart in the acute period does not lead to any marked myocardial damage or to a decrease in its contractility.

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ANALYSIS OF DISTURBANCE OF MUSCLE CONTRACTILITY BASED ON ESTIMATION OF THE DEGREE OF POTENTIATION OF ITS EVOKED MECHANICAL RESPONSE

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In a previous study of muscle contractility in patients with disturbance of neuromuscular transmission the writers showed that, during chronic denervation of the muscle an increase in amplitude of the evoked mechanical response (EMR) of the muscle, an increase in the temporal parameters of the contractile act, and a decrease in the ability of the muscle to exhibit staircase and post-tetanic potentiation (PTP) are observed [1]. It was also shown that the maximal amplitude of EMR observed during PTP is a stable value for each muscle, and that the increase in PTP depends on the difference between the maximal amplitude of EMR and that detectable at the given moment.

The aim of the present investigation was to analyze the ability of a muscle to undergo PTP, depending on the initial amplitude of EMR of the muscle and its ability to increase the amplitude of EMR in response to paired stimulation.

EXPERIMENTAL METHOD

Observations were made on 24 healthy subjects, 10 patients with a lesion affecting mainly the spinal motoneurons and axons of peripheral motor nerves, 30 patients with chronic disturbance of neuromuscular transmission associated with myasthenia and 8 patients with a metabolic disturbance due to hypothyroidism. The tests were carried out on an MG-400 electromyograph (Medicor, Hungary), with dc amplification channel. Supramaximal stimulation of the ulnar nerve was carried out in the region of the wrist by square pulses of current from 0.05 to 0.1 msec in duration. Single, paired, and tetanic (50 pulses/sec for 5 sec) stimulation was used. The force of isometric contraction of the adductor pollicis muscle was recorded using a strain gauge mechanograph with linear parameters of sensitivity from 10 g to 2 kg and from 1 to 20 kg. Electrical and mechanical responses were photographed from the oscilloscope screen. The following parameters of EMR of the muscle were studied: the amplitude of EMR in response to a single stimulus, defined in the literature as P_t; the duration of the contractile act (DCA) – the total time of contraction and semirelaxation of the muscle; the amplitude of EMR and DCA in response to the second stimulus, when using paired stimuli (P_2 and DCA_2); the maximal amplitude of tetanic contraction (P_0); the value of PTP – the ratio of the amplitude of EMR, measured in the muscle 10 sec after tetanus, and the initial amplitude of EMR; the ratios P_t/P_0, P_2/P_t, and DCA_2/DCA also were studied.

EXPERIMENTAL RESULTS

When healthy subjects were tested a considerable fluctuation of amplitude of EMR (from 4.9 to 14.7 N) and of the ability of the muscle to undergo PTP (from 120 to 200%) were observed. The value of PTP was

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