IMMUNOLOGICAL MODIFICATION OF CHRONOTROPIC AND INOTROPIC CORONARY EFFECTS OF ADRENOMIMETICS

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Changes in responses of the coronary vessels and myocardium to regulatory (mainly adrenergic) influences may play an essential role in the development of pathological states of the heart [3, 4, 9], including, probably, those due to the influence of immune factors [1].

The aim of this investigation was to study the effects of certain immune agents, namely anticardiac cytotoxic serum (ACS) [2, 6] and immune complexes (IC) [7], on coronary and myocardial effects of adrenomimetics.

EXPERIMENTAL METHODS

Experiments were carried out on 17 dogs weighing 17-22 kg with an intact chest, anesthetized with chloralose (0.08 g/kg) and urethane (0.3 g/kg). The pressure at the entrance of the descending or circumflex branch of the left coronary artery, which was perfused with blood from the aorta by means of a constant delivery pump through a catheter with obturator [10] introduced into the coronary vessel through the right common carotid artery, was recorded. The mean aortic pressure (MAP) and the pressure in the left ventricle (LVP) also were recorded through catheters. The first derivative of LVP and the index of myocardial contractility P'_{max}/P_d [13], where P'_{max} denotes the maximum of the first derivative of LVP, and P_d denotes LVP developed at the time of P'_{max}, were recorded continuously by means of an "Index" computer [8]. To record pressure and the derivatives, electromanometers of the EMT-35 type and a Mingograf-34 automatic writer (from Elema-Schönander, Sweden) were used. Adrenalin and isoprenaline (IP) were injected into the coronary artery in doses of 3 and 5 μg before and after intracoronary injection of ACS (0.7 ml/kg) with a titer in the complement fixation test of 1:800, and obtained by immunizing rabbits with a homogenate of dog heart [6]. To investigate the effects of IC, a mixture of 0.3 ml of horse serum (antigen) and 1.5 ml of rabbit immune serum with a titer in the precipitation test of $1:2^{11}$, was injected into the coronary artery [7]. The significance of changes in the parameters studied was determined by the method of direct differences.

RESULTS

The response of the coronary vessels to adrenergic stimulation of the heart, estimated from the change in resistance of the perfused vascular bed, changed qualitatively after injection of ACS: In the initial state the adrenomimetics caused a decrease in vascular resistance, but after ACS this was replaced by an increase (Fig. 1a). On average, in response to injection of 5 μg adrenalin before ACS the perfusion pressure fell by 10.6 ± 2.2 mm Hg, but after ACS it rose by 12.8 ± 1.6 mm Hg (n = 17). Corresponding values for IP were 16.8 ± 3.2 and 8.4 ± 1.6 mm Hg (n = 11). The weaker coronary-dilating (before ACS) and the stronger coronary-constricting (after ACS) effects of adrenalin can evidently be explained by its direct α-receptor action and by its weaker affinity, compared with IP, for β-adrenoreceptors [11, 12]. Reversal of the response of the coronary vessels to adrenomimetics was observed as early as 2 min after injection of ACS (the earlier recording of the effects of the adrenomimetics was impeded by rapid changes in the resistance of the coronary vessels due to the action of the ACS itself [6]) and it persisted until the end of the experiment for 1 h, despite a gradual

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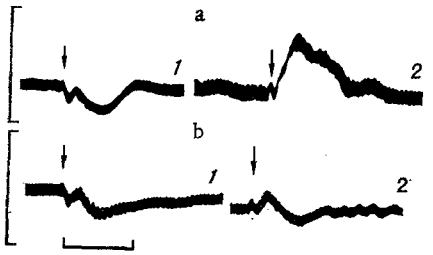

Fig. 1. Changes in perfusion in circumflex branch of left coronary artery, perfused with a constant volume of blood, in response to intracoronary injection of 5 μg adrenalin (a) before (1) and after (2) injection of ACS, and to injection of 3 μg adrenalin (b) before (1) and after (2) injection of IC. Calibration: 110-130 mm Hg, 1 min. Arrow indicates time of injection of adrenalin.

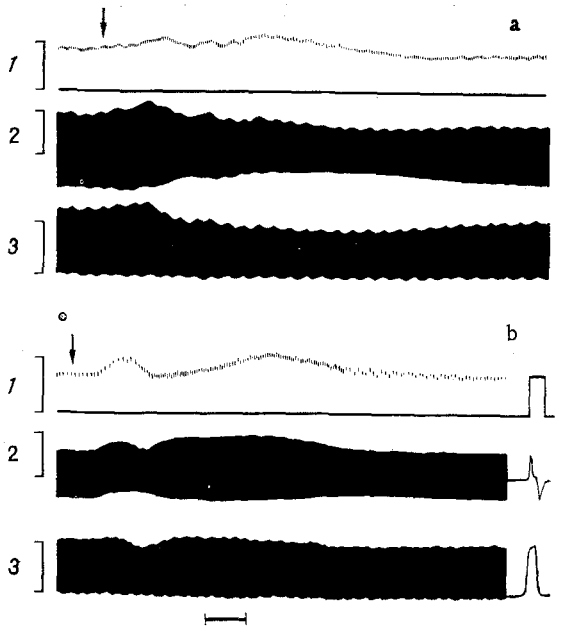

Fig. 2. Changes in index of myocardial contractility P'_{max}/P_d (1), first derivative of LVP (2), and LVP itself (3) in response to intracoronary injection of 5 μg adrenalin before (a) and after (b) injection of ACS. Calibration (from top to bottom): 1) 50 sec^{-1}; 2) 4000 mm Hg/sec; 3) 100 mm Hg. Time marker 10 sec. Arrow indicates time of injection of adrenalin.

increase in vascular resistance (the perfusion pressure rose from 118 ± 4 to 128 ± 8, 135 ± 9, 144 ± 9, and 154 ± 10 mm Hg at 10, 20, 30, and 60 min respectively after injection of ACS). The dilator reserve of the coronary vessels showed little change under these circumstances, judging from the response to papaverine (2 mg, into the coronary artery). Under the influence of IC the response of the coronary vessels to adrenalin (3 μg, n = 7) became biphasic (Fig. 1b): The pressor phase (+8.3 ± 1.0 mm Hg) was followed by a depressor phase (−6.2 ± 1.1 mm Hg), whereas before injection of IC the response was entirely depressor (−8.8 ± 1.1 mm Hg).

TABLE 1. Effect of ACS on Relative Changes (in %) in Index of Myocardial Contractility P'_{max}/P_d, P'_{max}, HR, and MAP (M ± m) Induced by Adrenomimetics

Parameter	Phase of inotropic action of adrenomimetics	Adrenalin				IP			
		before injection of ACS	after injection of ACS	P	n	before injection of ACS	after injection of ACS	P	n
P'_{max}/P_d	I	36±6	45±7	>0,1	15	27±5	39±6	>0,05	10
	II	53±8	43±7	>0,1	15	28±9	51±9	>0,05	10
P'_{max}	I	75±10	85±8	>0,1	17	45±8	60±14	>0,05	11
	II	82±17	99±9	>0,1	17	27±5	68±11	<0,01	11
HR	II	−3±5	60±10	<0,001	17	−2±10	42±12	<0,001	11
MAP	—	−28±9	4±6	<0,001	17	−63±11	−20±11	<0,01	11

Note. No significant changes in HR were observed during phase I of the inotropic action of adrenalin and isoprenaline, whether before or after injection of ACS. Response of MAP was determined as its maximal deviation.

ACS caused significant changes in the character of the hemodyanamic response to adrenergic stimulation of the heart and virtually abolished the cardiogenic depressor reflex to intracoronary injection of adrenomimetics [5]: Against the background of the action of ACS on the heart the decrease in MAP disappeared and this was accompanied by a fall of LVP (Fig. 2); distinct tachycardia (Table 1) appeared instead of the bradycardia usually observed after the development of the inotropic action of adrenomimetics. The ionotropic action of adrenalin and IP, judging by the response of the index of myocardial contractility (P'_{max}/P_d) was unchanged after injection of ACS and, as a rule, consisted of two positive phases (Fig. 2). The marked increase in heart rate (HR) during the second phase of an increase in the P'_{max}/P_d index in response to injection of adrenalin and IP after ACS (Table 1), with their positive inotropic action, may to some extent explain the absence of any decrease in the response of P'_{max}/P_d and P'_{max} to adrenergic stimulation of the heart, and even the small increase observed in the response of P'_{max} to injection of IP, despite the cytotoxic action of ACS on the myocardium: P'_{max}/P_d was reduced by the action of ACS from 41.8 ± 3.3 to 35.4 ± 2.7 sec^{-1} ($P < 0.05$). However, the reactivity of the myocardium to adrenomimetics also evidently was not significantly worsened, as is shown by the absence of any significant changes in the response of P'_{max}/P_d and P'_{max} in the first phase of the inotropic action of adrenalin and IP, which evidently corresponded to their primary (without reflex modulation) action on the heart. Under the influence of IC the response of HR to adrenalin did not change significantly, the response of MAP remained depressor, although it was reduced by 53 ± 11%, and changes also were absent in the responses of P'_{max}/P_d and P'_{max} to adrenalin. Meanwhile it must be noted that changes in the cardio- and hemodynamics in response to injection of IC were not weaker than those in response to ACS [8, 7]. After injection of IC, in the present experiments MAP fell from 127 ± 8 to 78 ± 9 mm Hg, and after injection of ACS it fell from 118 ± 9 to 86 ± 10 mm Hg, followed by some recovery, P'_{max} fell equally after injection of IC (from 4019 ± 317 to 3016 ± 319 mm Hg/sec, i.e., by 25%), and in response to injection of ACS (from 3848 ± 230 to 2781 ± 176 mm Hg/sec., i.e., by 26%). Differences in the action of ACS on the coronary and myocardial effects of adrenomimetics (disappearance of the cardiogenic depressor reflex and the depressor response of the coronary vessels) are evidently associated with the specific cytotoxic action of ACS on the heart tissues. A decrease in the depressor coronary response to adrenomimetics and replacement of its pressor response in combination with the unchanged or increased functional load on the myocardium (an increase in the after-load and HR), observed after injection of ACS and IC, suggest that the action of these immune agents on the heart may lead to the appearance of coronary insufficiency in stress situations.

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EFFECT OF GEOMAGNETIC STORMS ON THE STATE OF THE MYOCARDIAL MITOCHONDRIA AND THEIR ROLE IN ENERGY SUPPLY FOR CARDIAC CONTRACTIONS

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Helio-geomagnetic disturbances have a significant influence both on biological rhythms [2] and on the course of some pathological processes, including the development of myocardial infarction and its complications, among them sudden death [1, 4, 8]. However, the subcellular and molecular mechanisms of this effect have not been adequately studied.

The aim of this investigation was to study the state of ultrastructures of the intact heart (with the aid of scanning electron microscopy) and to assess its contractility under conditions of geomagnetic storms.

EXPERIMENTAL METHODS

Experiments were carried out on 120 mature male Chinchilla rabbits weighing 2.5-3.5 kg. For 3 days (from midnight on September 20, 1984, to 9 p.m. on September 23, 1984) every 3 h the highest value of the intraventricular pressure attained (IVP_{max}) in the left ventricle, determined during occlusion of the ascending aorta for 5 sec, was recorded electromanometrically in five rabbits in the acute experimental group under superficial hexobarbital anesthesia. Pieces of papillary muscles from the left ventricle were then rinsed in Hanks' solution, frozen in liquid nitrogen, sheared, and placed in 2% glutaraldehyde solution. The material was then dehydrated in acetone, dried by taking through the critical point from liquid carbon dioxide (Balzers Union, Liechtenstein), and sputtered with gold-palladium alloy by means of ionic bombardment, using a cold "Sputter" apparatus (Poliron, England). The IsI-60 scanning electron microscope used had a resolving power of 6 nm (magnification 1000-20,000). The volume of the mitochondria (MC) was calculated on electron micrographs by appropriate equations for similar geometric shapes. Simultaneously with the study of cardiac function, the concentration of free fatty acids (FFA) in the arterial blood of the experimental animals was determined spectrophotometrically. The intensity of geomagnetic activity was characterized by the Ap and Cp indices, values of which were obtained at the International Data Center (IDC-2, Moscow). During statistical analysis of the results, besides calculating the mean values of the parameters studied and determining the significance of the difference between the means by Student's test, correlation analysis for the presence or absence of correlation between values recorded during the experiment was undertaken on the "Iskra-1256" minicomputer (correlation was considered to be strong when $r \geqslant 0.7$, moderately strong when $r = 0.3-0.69$, and as weak when $r \leqslant 0.29$).

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