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CARDIODEPRESSOR ACTION OF BLOOD SERUM FROM PATIENTS WITH SEVERE SUPPURATIVE INFECTIONS

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Surgical sepsis is accompanied as a rule by disturbances of myocardial contractility, with clinical manifestations of septic myocarditis [5, 6]. Previous investigations [4] showed the presence of toxic myocardial damage in 83% of patients with surgical sepsis, which developed in association with acute suppurative infection or with extensive post-traumatic purulent wounds. In patients with sepsis the infectious process sometimes develops so rapidly that it leads to toxic (septic) shock, a key factor in which is the direct toxic action on the heart [7]. The blood plasma of animals with experimental septic shock has been shown to depress contractility of the intact myocardium significantly [9]. Data in the literature on the study of the central hemodynamics of patients with sepsis are very contradictory, and both a decrease and an increase in their cardiac output have been reported [1, 8, 11].

The aim of this investigation was to study the direct action of blood serum from patients with severe suppurative infection (septicemia, febrile respective pyemia) on contractility and intracellular potentials of isolated fragments of guinea pig myocardium.

EXPERIMENTAL METHOD

Isometric contractions and intracellular transmembrane potentials in response to electrical stimulation of the isolated auricles of guinea pig atria were studied in three series of experiments (Table 1). In series I each myocardial preparation was perfused with Tyrode solution, during stimulation at constant frequency, followed by replacement of the solution by blood serum from healthy donors or from patients with sepsis. In the experiments of series II, the action of serum from healthy blood donors and patients on the same myocardial preparation was compared. In the experiments of series III the frequency-force relationship was investigated during a change in the frequencies of stimulation: 0.1, 0.2, 0.5, 1, and 2 Hz.

Blood from patients with sepsis was taken immediately after admission to the clinic and before treatment had been instituted. The serum used for perfusion in all series of experiments was diluted with Tyrode solution in the ratio of 1:1, oxygenated with carbogen (95% O_2 + 5% CO_2) for 15 min, and the pH stabilized at 7.2-7.25. Next, with the aid of ion-selective electrodes (Radiometer, Denmark) activity of free Ca^{2+} ions was measured, and in the event of disparity, PCA was adjusted in the donors' and patients' sera to the level in Tyrode solution (2 mM). To prevent the serum from frothing during oxygenation, antifoam was used.

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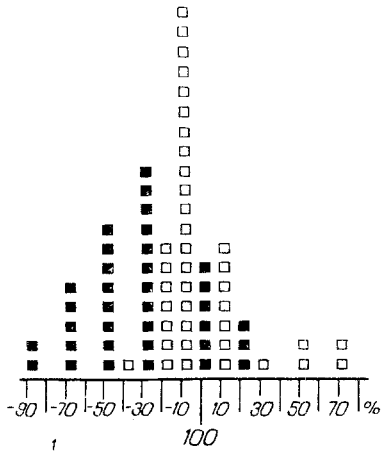

Fig. 1

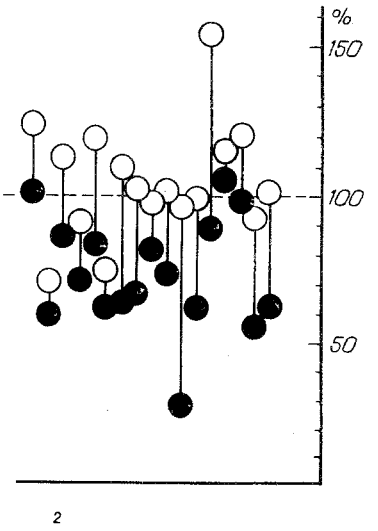

Fig. 2

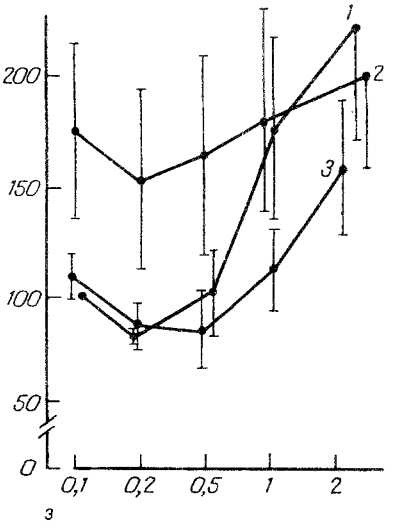

Fig. 3

Fig. 1. Action of blood serum from healthy blood donors (empty squares) and from patients with sepsis (filled squares) on amplitude of contraction of isolated fragments of guinea pig myocardium. Horizontal axis, amplitude of contractions (in % of response to Tyrode solution, taken as 100%). Each square represents a separate experiment.

Fig. 2. Comparison of cardiotropic action of serum from healthy blood donors (empty circles) and of patients with severe suppurative infection (filled circles) on the same myocardial preparation. Vertical axis, amplitude of contractions (in % of amplitude of contractions in Tyrode solution, taken as 100%), with a frequency of stimulation of 1 Hz.

Fig. 3. Changes in frequency versus amplitude of contraction plots in isolated guinea pig auricles under the influence of blood serum from patients with sepsis. Abscissa, frequency of stimulation (in Hz); ordinate, amplitude of contractions (in % relative to amplitude of contractions in Tyrode solution, taken as 100%), with frequency of stimulation of 0.1 Hz.

TABLE 1. Distribution of Experimental Material

Series of experiments	Number of experiments	Frequency of stimulation, Hz	Order of perfusion	Duration of action, min
I	39	1	Tyrode solution	20
			Healthy human serum	20
	35	1	Tyrode solution	20
		1	Patients' serum	20
II	17	1	Healthy human serum	20
			Patients' serum	20
III	10	0,1—2	Healthy human serum	20
			Patients' serum	20

The method of isolation of the myocardial fragments, their arrangement in the working chamber (volume 2 ml, continuous closed-circuit perfusion), the experimental conditions, the apparatus used, and the composition of the Tyrode solution were all described previously [2].

EXPERIMENTAL RESULTS

The distribution of amplitudes of auricular contractions of the guinea pig hearts perfused with blood serum from 39 healthy blood donors and 35 patients with a clinical diagnosis of sepsis or of febrile resorptive pyemia is shown in Fig. 1. During constant stimulation of the preparations with a frequency of 1 Hz, healthy human serum (empty squares) in most cases caused virtually no change in the amplitude of contractions, or depressed it very slightly, compared with the amplitude in Tyrode solution, which was taken to be 100%. In individual experiments healthy human serum led to the development of a positive inotropic effect. Unlike

TABLE 2. Action of Blood Serum from Healthy Donors and Patients (sepsis, febrile resorptive pyemia) on Intracellular Potentials of Guinea Pig Atrium (M ± m)

Perfusion fluid	RP	AP	Duration of AP, msec		
	mV		Level of repolarization, %		
			20	50	80
Tyrode solution (n = 5)	74,5±1,93	94,8±5,81	40,8±8,8	66,2±7,7	80,1±7,4
Healthy human serum (n = 5)	78,7±3,94	94,8±4,7	34,2±9,4*	57,2±7,4*	74,6±7,8*
Patients' serum (n = 5)	78,5±7,28	98,7±4,5	16,0±4,7*	34,8±4,9*	53±7,2*

Legend. *$p < 0.05$.

healthy human serum, the patients' serum (filled squares) reduced the amplitude of contractions in most preparations tested. The black squares in Fig. 1 are shifted to the left on the amplitude scale, signifying the development of a negative inotropic effect in the myocardium under the influence of the patients' sera. The percentage of depression of the amplitude of contractions of the myocardial preparations under the influence of the patients' serum varied from 30 to 90. After rinsing to remove the cardiodepressor action of the patients' serum the amplitude of isometric contractions in Tyrode's solution was 90.5 ± 3.54%.

The serum of some patients had no cardiodepressor action, even if the disease proved fatal. One possible reason for the absence of a cardiodepressor action of the patients' serum could be the dose-dependent action of staphylococcal α-toxin, which, as the writers showed previously, in low concentrations strengthens myocardial contractility [3]. The results of comparison of the action of the donors' and patients' serum on the same myocardial preparations are given in Fig. 2. These data show that even when healthy human serum (empty circles) induced an exceedingly small decrease in amplitude of the contractions, the patients' serum (filled circles) had always a much stronger depressant effect.

Replacement of the Tyrode solution perfusing the myocardial preparation by healthy human blood serum led to an increase in amplitude of isometric contractions at low frequencies of stimulation: 0.1-0.5 Hz (Fig. 3). Subsequent replacement of normal serum by patients' serum led to a marked decrease in the amplitude of myocardial contractions at all frequencies of stimulation. In the same series of experiments, with a frequency of stimulation of 1 Hz, parallel with a study of the contractile responses of the myocardium, intracellular potentials were recorded. Data showing the effect of healthy human and patients' sera on intracellular resting (RP) and action potentials (AP) are given in Table 2. Serum from healthy blood donors affected neither the initial RP nor the amplitude of AP, but significantly shortened the duration of AP, measured at 20, 50, and 80% levels of repolarization. Similar shortening of the duration of plateau phase of AP was found by the writers previously [3] when studying the action of normal blood plasma on the myocardium of intact animals.

The patients' serum, like that of healthy blood donors, did not significantly change the amplitude of the intracellular potentials, but shortened the duration of AP even more. Shortening of AP by the action of the patients' serum relative to that of healthy serum, was significant ($p < 0.05$).

These results thus show that in most cases the blood serum from patients with sepsis and with febrile resorptive pyemia has a marked cardiodepressor action compared with healthy human serum. The cardiodepressor effect of the patients' serum is reversible in character, for subsequent perfusion with Tyrode solution leads to restoration of contractility, but far more complete recovery of the amplitude of contractions takes place when the myocardial preparation is perfused with healthy human serum. One cause of inhibition of myocardial contractility in septic shock is known to be a fall of the Ca^{2+} ion concentration in blood of the affected animals [10]. The results of the present investigation were obtained when the free Ca^{2+} level in the patients' serum was raised up to values recorded in healthy human serum. Under these conditions also, the cardiotoxicity of the patients' serum was exhibited very clearly.

The fact that changes in the duration of the plateau phase under the influence of staphylococcal α-toxin, which increases the duration of AP [2] and under the influence of patients' serum, which shortens the duration of AP, are in opposite directions is evidence

that the cause of the reduction in myocardial contractility under the influence of serum from patients with severe suppurative infection is multifactorial in nature, including not only microbial toxins, but also factors not directly related to the agents of suppurative infection.

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EFFECT OF STRESS AND THE ANTIOXIDANT IONOL ON CATECHOLAMINE SYNTHESIS AND THE DOPAMINE CONCENTRATION IN THE HEART AND ADRENALS

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Activation of the antioxidant systems of the body during adaptation to stress [6] or administration of extrinsic synthetic antioxidants is known to limit the elevation of the blood corticosterone level and exhaustion of brain catecholamines during long-term stress [4] and, at the same time, to prevent stress-induced damage to various internal organs – from the heart and stomach on the one hand, to the brain and retina, on the other [5]. The problem of the role played in the protective effect of antioxidants in stress by their influence on catecholamine metabolism still remains unsolved.

The aim of this investigation was to assess the effect of the antioxidant ionol (dibunol) on synthesis of catecholamines and their concentration in the adrenals and heart during emotional stress.

EXPERIMENTAL METHOD

Experiments were carried out on male Wistar rats weighing 200-220 g. Emotional-painful stress was induced by the method in [10] for 6 h. The animals were killed by decapitation 2 h after the end of exposure to stress. The synthetic antioxidant ionol (2,6-di-tert-butyl-4-methylphenol) was injected intraperitoneally in a dose of 60 mg/kg daily during the 3 days before stress. The catecholamine concentrations in the heart and adrenals of the animals

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