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RESTORATION OF MYOCARDIAL CONTRACTILITY DURING GRADUAL REPERFUSION AFTER TOTAL ISCHEMIA

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KEY WORDS: heart; ischemia; reperfusion; purine bases.

Restoration of myocardial contractility during reperfusion depends not only on the reversibility of the disturbances induced by ischemia, but also on the damaging action of reperfusion itself on metabolism, ultrastructure, and function [8, 10]. The principal factors damaging the myocardium during reperfusion are excessive reoxygenation and accumulation of cytoplasmic calcium [6]. The addition of antioxidants and calcium antagonists to the reperfusion solution, therefore, improves the restoration of the contractile function and metabolism of the ischemic myocardium [4, 7, 9]. Another approach was used in the present investigation, conducted on isolated guinea pigs' hearts, namely gradual restoration of the reperfusion rate to its initial level. Two versions of gradual reperfusion were used: circulating, when the perfusion fluid passed once through the heart, and recirculating, when the perfusion fluid passed through the coronary vessels several times.

EXPERIMENTAL METHOD

Experiments were carried out on isolated hearts of guinea pigs weighing 200-300 g, anesthetized with urethane (1.25-1.50 g/kg). The heart was perfused in the retrograde direction by Langendorff's method with Krebs' solution (37°C) in a constant volume velocity of 10-12 ml/min/g. A small latex balloon, filled with liquid, was introduced into the left ventricle. The pressure in the left ventricle, and also the perfusion pressure in the aorta, were recorded by means of Gould Statham P23Db strain-guage transducers on a Gould Brush 2200 instrument. The contractile function was calculated as the product of the developed pressure and heart rate (HR), and the coronary resistance (CR) as the ratio of perfusion pressure to specific volume velocity perfusion.

After a period of stabilization of the contractile function (20-30 min) perfusion of the heart was completely stopped for 25 min, creating total ischemia, and this was followed by reperfusion for 30 min. In the control series (n = 12) reperfusion was carried out with the initial volume velocity. In the series of gradual circulating reperfusion (n = 8) the the initial volume velocity was 13 ± 1% of the initial value, and it increased by the same amount every 4 min of reperfusion, to reach the initial value by the end of reperfusion. In

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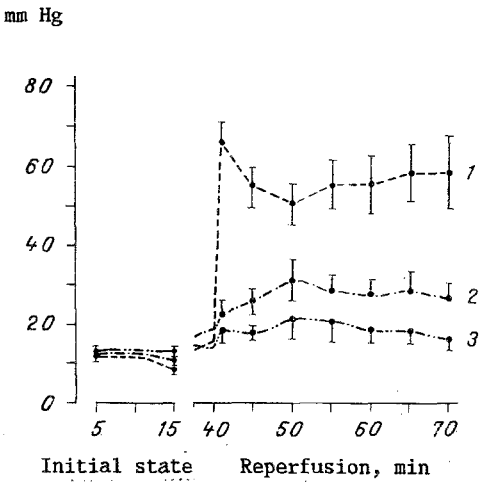

Fig. 1. Changes in diastolic pressure during control (1), gradual circulating (2), and gradual recirculating (3) perfusion after ischemia (M ± m).

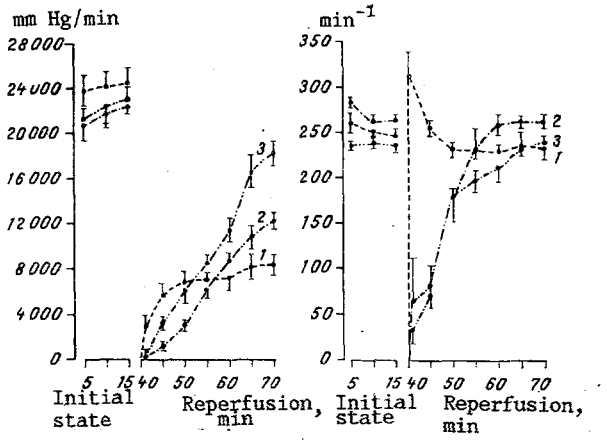

Fig. 2. Restoration of CF (a) and HR (b) during control (1), gradual circulating (2), and gradual recirculating (3) reperfusion after ischemia (M ± m).

series III (n = 7) gradual reperfusion was supplemented by recirculation, during which the solution passed through the coronary vessels several times. In the series with control and gradual circulating reperfusion, samples of perfusion fluid draining from the heart were collected in order to determine concentrations of breakdown products of adenine nucleotides by high-performance liquid chromatography [3].

The results were subjected to statistical analysis by Student's t test.

EXPERIMENTAL RESULTS

In the control series a sharp increase of distolic pressure (DP) was observed at the beginning of reperfusion, and it continued until its end (Fig. 1); the degree of recovery of contractile function (CF) after 30 min of reperfusion was 34 ± 4% of the initial value. In experiments with gradual circulating reperfusion the increase in DP was small, and by the end of reperfusion DP was approximately half the control value (Fig. 1), but restoration of CF was better than in the control, for it amounted to 54 ± 3% of the initial value. Restoration of CF was even better (up to 80 ± 5% of the initial value) in the experiments with gradual recirculating reperfusion, in which there was virtually no increase of DP (Fig. 1). During the first 5 min of control reperfusion CF was significantly higher than in the experiments with gradual reperfusion (Fig. 2a), due to an increase in HR up to 126 ± 13% of the initial value (Fig. 2b). The onset of tachyarrhythmias during rapid reperfusion was observed also in other in-

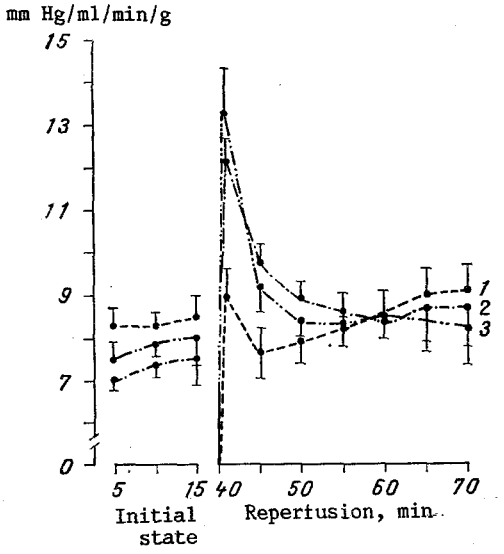

Fig. 3. CR during control (1), gradual circulating (2), and gradual recirculating (3) reperfusion after ischemia (M ± m).

vestigations [2, 15]. During gradual reperfusion no tachysystoles occurred, and HR after 5 min was 30% of its initial value, and it rose gradually, returning to normal after 20 min.

Determination of the principal breakdown products of adenine nucleotides showed that in the control series the heart lost 641 ± 71 nmoles/g inosine and 181 ± 21 nmoles/g hypoxanthine. In the series with gradual circulating reperfusion of loss of hypoxanthine was the same as in the control (228 ± 31 nmoles/g), but the loss of inosine was 458 ± 45 nmoles/g, i.e., 28% less ($p < 0.05$) than in the control series.

The favorable action of gradual circulating reperfusion, observed in these experiments, agrees with the results of other investigators who observed better recovery of contractile function during reperfusion at reduced perfusion pressure [1], with gradual restoration of the reperfusion rate [15], or with hemodilution during reperfusion [12]. The improvement of metabolism and of the function of the ischemic myocardium, observed in the studies cited, was evidently connected with diminution of the damaging action of reoxygenation, reduced by different methods. This conclusion is supported by our own data on an increase in CR in both series with gradual reperfusion (Fig. 3). Since with a stable perfusion rate CR reflects changes in coronary vascular tone, which depends basically on the degree of oxygenation of the myocardium [5], it can be postulated that during gradual reperfusion the coronary vessels remain capable of reducing excessive reoxygenation of the myocardium, and thereby reducing its damaging action [11].

Reduction of the loss of breakdown products of adenine nucleotides, observed in the present experiments with gradual circulating reperfusion, suggests that the more complete restoration of contractile function is associated with improvement of the energy status of the cells. This is helped by the low intensity of the contraactile function, observed in the initial period of gradual reperfusion, and also, possibly, by reutilization of catabolites of purine bases. The results of the experiments with gradual recirculating reperfusion are in good agreement with this hypothesis. The considerable improvement of restoration of CF in this series may be connected, not only with reutilization of breakdown products of adenine nucleotides, but also with gradual normalization of the extracellular medium, the composition of which by the end of ischemia had an inhibitory action on CF. Another factor may also have an increase in the oncotic pressure of the reperfusion solution and the reduction of cellular edema associated with it [13], as a result of the appearance of enzymes released from the cells into it at the beginning of reperfusion.

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EFFECT OF ADENOSINE ON HEMODYNAMIC CHANGES DURING DEVELOPMENT OF NEUROGENIC MYOCARDIAL DAMAGE

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More and more importance is currently being attached to nervous factors in the development of cardiovascular pathology. External stimulation of the hypothalamic region or of the reflexogenic zone in the arch of the aorta under experimental conditions is accompanied by disturbance of energy metabolism of the heart muscle, by disorders of cardiac function and, finally, by the development of diffuse-focal necrosis of the myocardial tissue [4]. These processes are based on reactions that are common to all stress-induced damage [4, 5]. Massive release of catecholamines from the tissue depots and associated disturbances of the hemodynamics and metabolism [4] are particularly important.

Among the stress-limiting systems of the body an important role is ascribed to the system of adenosine and adenine nucleotides [5]. Besides its positive effect on energy metabolism [7], adenosine also inhibits sympathetic neurotransmission [8] and has an antiadrenergic action [1], which is accompanied by normalization of the hemodynamics [3]. The aim of this investigation was to study the action of adenosine on hemodynamic changes induced by electrical stimulation of the reflexogenic zone of the arch of the aorta.

EXPERIMENTAL METHOD

Experiments were carried out on male rabbits weighing 2.5-3 kg. The immobilized animals were anesthetized by intravenous injection of pentobarbital (50 mg/kg body weight). A nichrome electrode 120 μ in diameter, in polyethylene insulation, was introduced through the right common carotid artery into the arch of the aorta; the electrode tip, 0.3-0.5 mm long,

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